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Metabolic Targets and Physical Activity in Breast Cancer

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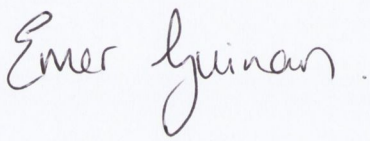
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Summary

Breast cancer is the most common female cancer diagnosed in Ireland and worldwide. Breast cancer risk and outcome may be managed through modifiable risk factors including body weight and physical activity. Physical activity is hypothesised to protect against breast cancer occurrence and recurrence through alterations in several obesity-related metabolic pathways. The aim of this thesis was to examine the presentation of and relationships between metabolic dysfunction and habitual physical activity in two high risk groups; breast cancer survivors and unaffected carriers of mutations in the *BRCA* genes. Study I and II involve breast cancer survivor cohorts while in Study III unaffected *BRCA* mutation carriers are examined.

Work for this thesis commenced with a systematic review of exercise interventions examining the effect of exercise training on metabolic outcomes in breast cancer survivors. While some decreases in anthropometric measures and insulin-like growth factors were reported, overall trials demonstrated little effect. The first study presented in this thesis (Study I) was an eight-week aerobic exercise intervention designed to further investigate the effect of exercise on metabolic and inflammatory biomarkers in breast cancer survivors 2-6 months post chemotherapy. The intervention was designed as an ancillary study to a larger ongoing randomised controlled trial named the PEACH trial. The results from the PEACH trial demonstrated no change in anthropometric, metabolic or inflammatory biomarkers. Moreover, no changes were reported in physical activity levels, including sedentary time. Analysis of those with highest adherence to the prescribed protocol (>90%) demonstrated a significant decrease in waist circumference ($p<0.05$) and a significant increase in subjectively reported weekly physical activity ($p=0.005$).

Adjuvant breast cancer treatment is associated with numerous side-effects including altered body composition, reduced physical activity levels and early menopause, which may lead to metabolic decline. Therefore, Study II in this thesis was undertaken to investigate the presentation of dysmetabolism and the relationship with energy expenditure in a group of breast cancer survivors who had previously completed metabolic screening on the morning of breast cancer surgery. In Study IIa, changes in anthropometric and metabolic biomakers from the time of breast cancer surgery to completion of adjuvant treatment (2-5 years post diagnosis) were examined. Significant deteriorations in measures of glucose metabolism

characterised by increases in fasting insulin ($p<0.001$), insulin resistance ($p<0.001$) and HBA_{1c} ($p=0.001$) were demonstrated. These changes occurred in the absence of change in BMI or the proportion of participants classed as centrally obese (waist circumference >80cm).

In Study IIb, despite a predominance of overweight, obesity and central obesity, there was minimal evidence of dysmetabolism. Resting metabolic rate, adjusted for fat free mass, correlated with a number of metabolic outcomes. Physical activity did not correlate with any anthropometric or metabolic measure. It was noted however that participants spent the majority of waking hours sedentary (49%) and showed poor adherence to physical activity guidelines. A secondary analysis, subdividing the group by central obesity and insulin resistance suggested that participants who were both centrally obese (waist circumference >80cm) and insulin resistant, showed evidence of dyslipidemia, low-grade inflammation and glucose dysregulation. Resting metabolic rate was higher in participants with insulin resistance versus those who were centrally obese only. Metabolic profiles of those who were centrally obese in the absence of insulin resistance were not significantly different from lean subjects.

Study III in this thesis examined the anthropometric, physical activity and metabolic traits of *BRCA*-mutation carriers who were unaffected by breast cancer. A systematic review of previous literature in this area highlighted several limitations relating to retrospective study design and subjective data collection methods. A prospective study was designed to investigate the relationship between modifiable risk factors and breast cancer risk in this cohort. Baseline assessments revealed several modifiable breast cancer risk factors including obesity and physical inactivity. The results of the prospective study will examine if these risk factors influence future cancer occurrence in this cohort.

The studies in this thesis investigate the potential for physical activity to be used as an adjunct to traditional breast cancer management and treatment strategies. The results from Study I and II may be used to inform future exercise interventions which aim to modify metabolic markers of breast cancer risk in breast cancer survivors. It is hoped that the long-term results from Study III will be used to inform the potential for modifiable risk factors to manage breast cancer risk in *BRCA*-mutation carriers.

Acknowledgements

I am eternally grateful to so many who have been there for me throughout this process.

To the staff at St. James's hospital. I would particularly like to thank Ms. Elizabeth Connolly, who co-supervised this work, and Dr. John Kennedy, for their constant support and guidance. I would also like to thank Mr. Terry Boyle, Dr. David Gallagher, Dr. Dearbhaile O'Donnell and their teams for their help with recruitment. Thank you to the nursing staff in the oncology, genetics and breast care departments for all your help. To the breast care nurses in particular, I thank you for your kindness and friendship. I would like to thank the physiotherapy manager Niamh Murphy and the staff in the physiotherapy department for always facilitating me. Finally, I owe a huge debt of gratitude to the phlebotomy staff working in outpatients. Thank you all so much for all the help with "difficult veins" and for always greeting me with a smile.

To my colleagues at Trinity College. I would particularly like to thank my supervisor Dr. Juliette Hussey who has been an incredible support to me over the past three years. Thank you for all your help and for always being so approachable and encouraging. I would like to thank all of my colleagues who I have worked with closely, particularly Dr. John Gormley, Dr. Julie Broderick, Dr. Laura Healy, Dr. Paul Carroll, Dr. Joanne Lysaght, Dr. Sarah McGarrigle, Dr. Fiona Lithander and Dr. Kathleen Bennett. To all the physiotherapists who have been through the research room during my time there - thank you for your friendship and for all the inspirational chats over a cup of tea and some chocolate from the vending machine!

To all the wonderful ladies who participated in the studies. Thank you for giving your time so generously and for being such a pleasure to work with.

Finally, to my family and friends. To my parents, Ann and Seamus who have supported and loved me unconditionally throughout the years. I owe so much to you. To my beloved grandmother Nellie, who is an inspiration. To my fantastic friends, particularly to Linda and Cuisle for proof-reading and deleting so many unnecessary commas! And finally to John who came into my life just as this process was starting. Thank you for your love and encouragement throughout it all - I couldn't have done it without you.

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Publications from the work in this Thesis

Published papers

Guinan, E.M., Connolly, E.M., Healy, L.A., Carroll, P.A., Kennedy, M.J, Hussey, J. (2013) "The Development of the Metabolic Syndrome and Insulin Resistance following Adjuvant Treatment for Breast Cancer" *Cancer Nursing* Epub ahead of print.

Guinan, E.M., Connolly, E.M., Kennedy, M.J, Hussey, J. (2013) The Presentation of Metabolic Dysfunction and the Relationship with Energy Output in Breast Cancer Survivors: A Cross-Sectional Study. *Nutrition Journal* **12**: 99

Guinan, E.M., Connolly, E.M., Hussey, J. Response to commentary: "Exercise to improve obesity-related biomarkers in breast cancer survivors. A commentary on: "Exercise Training in Breast Cancer Survivors – A Review of Trials Examining Anthropometric and Obesity-Related Biomarkers of Breast Cancer Risk"" *Physical Therapy Reviews* **18**(3)229-231

Guinan E., Hussey J., McGarrigle S.A., Healy L.A., O'Sullivan J.N., Bennett K., Connolly E.M.A Prospective Investigation of Predictive and Modifiable Risk Factors for Breast Cancer in Unaffected BRCA1 and BRCA2 Gene Carriers (2013). *BMC Cancer* 13 (138), DOI: 10.1186/1471-2407-13-138

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Guinan E., Hussey J., Broderick J.M., Lithander F.E., O'Donnell D., Kennedy M.J., Connolly E.M. (2013) The Effect of Aerobic Exercise on Metabolic and Inflammatory Markers in Breast Cancer Survivors – A Pilot Study. *Support Care Cancer* DOI: 10.1007/s00520-013-1743-5

Walsh JM, Hussey J, Guinan E, O'Donnell D (2010) Pragmatic randomized controlled trial of individually prescribed exercise versus usual care in a heterogeneous cancer survivor population: a feasibility study PEACH trial: prescribed exercise after chemotherapy. *BMC Cancer* 10:42.

Published abstracts

Guinan, E.M., Hussey, J.M., Walsh, J.M., Kennedy, M.J., Connolly, E.M. (2011) The metabolic risk profile of breast cancer survivors 2 to 6 months post-chemotherapy. *J Clin Oncol* 29 (15 Supplement): e19612

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Submitted papers

Guinan, E.M., Connolly, E.M., Hussey J The Influence of Modifiable Breast Cancer Risk Factors on BRCA-related Cancer Risk: a review of the current literature. *Manuscript under review at Women and Health*

List of Abbreviations

%BF	Percentage body fat
95% CI	95% Confidence interval
AC	Doxorubicin and cyclophosphamide (chemotherapy regimen)
ACSM	American College of Sports Medicine
ADA	American Diabetes Association
AI	Aromatase inhibitor
AMPK	AMP-activated kinase
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BSO	Bilateral Salpingo-Oophorectomy
CG	Control group
CRP	C-reactive protein
CVD	Cardiovascular disease
DCIS	Ductal carcinoma in situ
DEXA	Dual energy x-ray absorptiometry
DLW	Doubly labelled water
DNA	Deoxyribonucleic acid
EG	Exercise group
ER	Estrogen receptor
FFM	Fat free mass
FFQ	Food frequency questionnaire
FMP	Final menstrual period
GLUT-4	Glucose isoform 4
HBA_{1c}	Glycated haemoglobin A_{1c}
HDL-C	High-density lipoprotein cholesterol
HEAL	Healthy Eating Activity and Lifestyle Study

HER-2	Human epidermal growth factor receptor 2/*neu*
HOMA-IR	Homeostatic model assessment index - Insulin resistance
HR	Hazard ratio
HRmax	Maximum heart rate
HRR	Heart rate reserve
HRT	Hormone replacement therapy
ICC	Inter-class correlation coefficients
IGF	Insulin-like growth factor
IGFBP	Insulin-like growth factor binding protein
IL-6	Interleukin-6
LCIS	Lobular carcinoma in situ
LDL-C	Low-density lipoprotein cholesterol
LVEF	Left ventricular ejection fraction
MET	Metabolic equivalent
MET-h.week^{-1}	Metabolic equivalent hours per week
MET-min.week^{-1}	Metabolic equivalent minutes per week
MetSyn	Metabolic syndrome
MHO	Metabolically healthy but obese
MRI	Magnetic resonance imaging
MUGA	Multi gated acquisition
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
PARQ	Physical activity readiness questionnaire
PPMCC	Pearson product moment correlation coefficients
PR	Progesterone receptor
RCT	Randomised controlled trial
RMR	Resting metabolic rate

RQ	Respiratory quotient
RR	Relative risk
SAA	Serum amyloid A
SHBG	Sex hormone binding globulin
SLÁN	Survey of Lifestyle, Attitudes and Nutrition
T2DM	Type II diabetes mellitus
TC	Docetaxel and cyclophosphamide (chemotherapy regimen)
TC	Total cholesterol
TG	Triglycerides
TLS	Total leisure score
TNF-α	Tumor necrosis factor-α
VCO_2	Carbon dioxide produced
VM	Vector magnitude
VO_2	Oxygen consumed
VO_2max	Maximum oxygen consumption
VO_{2peak}	Peak oxygen consumption
WC	Waist circumference
WCRF/AICR	World Cancer Research Fund / American Institute for Cancer Research
WHO	World Health Organisation
WHR	Waist to hip ratio

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Chapter 1 Introduction

1.1 Breast Cancer Worldwide and in Ireland

Breast cancer is the most common form of malignancy diagnosed in women worldwide and the leading cause of female cancer death (Parkin et al., 2005). On average 2,518 women are diagnosed with invasive breast cancer in Ireland every year (mean age of 59.6 years) (National Cancer Registry, 2012). The numbers presenting with early stage disease has been steadily increasing, in line with the roll-out in 2000 of the breast screening programme *BreastCheck*. A steady improvement in five-year relative survival has been observed, increasing from 71.8% in the period 1994-1998 to 81% in the present day. Despite this, breast cancer survival in Ireland is lower than the European average, representing the 4th highest breast cancer mortality of 30 European countries.

1.1.1 Definition of Cancer

Cancer defines a group of over 100 diseases characterised by the abnormal, uncontrolled growth of previously normal cells arising from accumulated alterations in deoxyribonucleic acid (DNA) (Almeida and Barry, 2010a). Normally, cell division, replication and death are controlled at a number of tightly regulated checkpoints during the cell cycle. Cancer cells divide rapidly due to dysregulation of this process, resulting in tumour formation. Tumours may be benign or malignant, but only the latter invade and infiltrate surrounding tissues. Damage to the DNA can arise from endogenous influences, for example inheriting a genetic defect (10-15% of cancer), inflammation or oxidative stress, or exogenous / environmental influences such as nutrition, obesity or physical inactivity (WCRF/AICR 2007)[1].

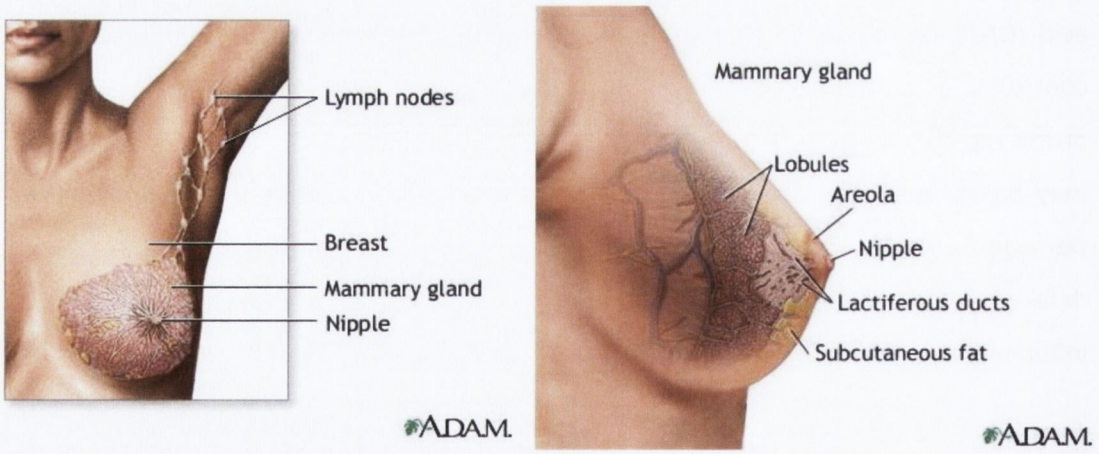
Sub-categories of cancer include carcinomas, which describes cancers arising in the epithelium of internal organs (85% of solid cancers), sarcomas which arise in the connective tissue such as the muscle or fat and haematological malignancies including lymphomas which arise in the bone marrow and lymphatic system. Breast cancer, an adenocarcinoma, arises from the epithelium of the mammary glands in the breast. Metastases occur when cancer cells break free from the primary tumour and travel via the circulatory or lymphatic systems to other

[1] WCRF/AICR = World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washing DC: AICR, 2007

locations in the body where they divide and form secondary tumours. The most common sites for metastases from the breast are the bone, lungs, liver and brain.

The normal female breast comprises adipose tissue, mammary glands (the duct-lobular unit) and connective tissue (Figure 1). The duct-lobular unit functions as a modified apocrine gland comprising clusters of milk-producing alveoli termed lobules, which become lobes and terminate as ducts at the nipple-areolar complex on the anterior surface of the breast (Nawaz, 2011, Almeida and Barry, 2010b). Epithelial cell growth on the lining of the ducts and lobes is controlled by the sex hormones estrogen and progesterone. At puberty, the lobular system develops due to increases in estrogen and progesterone. After the menopause, the duct-lobular units (mammary gland) atrophy due to decreased hormone levels resulting in less dense, more fatty breast tissue. Lymphatic drainage of the breast is via the axillary, supraclavicular and mediastinal lymph nodes.

Figure 1 The Normal Female Breast



The majority of breast cancers arise in the epithelial linings of the lobes and ducts. *In situ* cancer is an early form of cancer that has not invaded surrounding tissue, termed as either ductal carcinoma *in situ* (DCIS) or lobular carcinoma *in situ* (LCIS). Invasive ductal carcinoma and invasive lobular carcinomas infiltrate the epithelium and invade surrounding tissue. In Ireland 75% of breast cancers diagnosed are ductal in origin and 15% are lobular (National Cancer Registry, 2012).

Tumour grade refers to the extent to which the cancer cell resembles a normal cell, thus indicating the speed at which the tumour is likely to grow. Low-grade tumours (grade I and II) are well differentiated and tend to grow at a slow rate while high grade tumours (grade III) are poorly differentiated, growing and spreading rapidly. The American Joint Committee on Cancer staging system (Singletary et al., 2002) (Table 1) categorises cancer according to expected prognosis by considering tumour size (T0-T4), the presence and extent of regional lymph node involvement (N0-N3) and the presence of distant metastasis (M0-M1), therefore roughly corresponding low (stage I), moderate (stage II) and high (stage III) risk. In Ireland, the most common stage of diagnosis is stage II (42% of breast cancers), followed by stage I (29%), stage III (12%) and stage IV (7%) (National Cancer Registry, 2012).

Table 1 American Joint Committee on Cancer Staging System for Breast Cancer

Stage	Size of Tumour	Spread	TNM Classification
0	DCIS or LCIS	N/A	T*is*, N0, M0
I	<2cm diameter	Nil	T1, N0, M0
IIA	2-5cm <2cm	Nil Axillary lymph nodes	T0, N1, M0; T1, N1, M0 T2, N0, M0
IIB	>5cm 2-5cm	Nil Axillary lymph nodes	T2, N1, M0 T3, N0, M0
IIIA	<5cm >5cm	Axillary lymph nodes that are attach to each other or other structures. Axillary lymph nodes	T0, N2, M0 T1, N2, M0 T2, N2, M0 T3, N1, M0 T3, N2, M0
IIIB	Penetrate breast to the skin and chest wall	Lymph nodes inside the chest wall along the sternum	T4, N0-3, M0 T0-4, N3, M0
IV	Any size	Spread to other organs	T0-4, N0-3, M1

Abb: DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; N/A = not applicable

Breast tumours are classified histologically according to the presence or absence of estrogen receptors (ER), progesterone receptors (PR) and the human epidermal growth factor receptor 2/*neu* (Her-2) receptor (Almeida and Barry, 2010b). The binding of estrogen to ER, and of progesterone to PR, can stimulate cell growth and therefore inhibition of this binding process is the target for adjuvant hormonal treatments (Elias et al., 2011). Approximately 70-80% of breast tumours express ER. Triple negative breast cancer (ER-, PR-, and HER-2-) is associated with poorer prognosis and reduced survival (Curigliano and Goldhirsch, 2011).

1.1.2 Risk Factors for Breast Cancer

There are numerous established modifiable and non-modifiable risk factors for breast cancer development. Non-modifiable risk factors include increasing age, female gender, family history and genetic predisposition. The majority of breast cancers are sporadic in nature, and are therefore attributed to modifiable causes including reproductive influences, obesity and physical inactivity (WCRF/AICR 2007). Obesity and physical inactivity will be discussed in detail sections 1.2 and 1.4. The following sections will discuss two key determinants of breast cancer risk - lifetime exposure to estrogen and inherence of a mutation in the *BRCA* gene.

1.1.2.1 Lifetime Exposure to Estrogen

Breast cancer is considered as a hormone-sensitive cancer due to the proliferative effects of estrogen on the epithelial duct cells in the mammary glands. Therefore lifetime exposure to estrogens is a significant determinant of breast cancer risk (Almeida and Barry, 2010b). Exposure to estrogen is determined by a number of key reproductive events in the woman's lifetime; age at menarche, number of pregnancies, age at menopause, use of estrogen therapies including hormone replacement therapy (HRT) or the oral contraceptive pill (Nelson et al., 2012). Menarche before the age of 12 is associated with a 10-20% higher risk of breast cancer compared to menstruation after age 14 (Goldstein and Ziegfeld, 2011). In contrast, for every year that menopause is delayed after the age of 50, a woman's risk of breast cancer increases by 3% due to an increase in the number of menstrual cycles and thus increased exposure to estrogen. Prophylactic oophorectomy, before the age of 50, avoids this increase in estrogen exposure and is a management strategy for decreasing breast cancer risk in high-risk women (Pruthi et al., 2010). A greater number of pregnancies, particularly in women <30 years at first pregnancy, and breastfeeding are associated with reduced risk (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). Landmark results from the Women's Health Initiative indicated that HRT significantly increased postmenopausal breast cancer risk and delayed breast cancer detection (Chlebowski and Anderson, 2012). Oral contraceptive use is also associated with increased risk, however only for the duration of use (Nelson et al., 2012).

1.1.2.2 Genetic Breast Cancer – the BRCA Gene

While the majority of breast cancers are sporadic in nature, up to 10% arise from inherited genetic mutations (National Cancer Registry, 2012). Mutations in the breast cancer (*BRCA*) genes, (*BRCA1* and *BRCA2*) account for up to 60% of hereditary breast cancers. (Pruthi et al., 2010). Less common mutations include the TP53 mutation, which is associated with Li-Fraumeni syndrome and the PTEN mutation associated with Cowden syndrome. Women with mutations in the *BRCA* genes have up to an 80% risk of developing breast cancer and up to a 60% risk of ovarian cancer (Axilbund et al., 2011, Almeida and Barry, 2010b). This compares to 12.5% breast cancer risk for women in the general population (Howlader et al., 2010). *BRCA1/2* mutation carriers are also at increased risk of cancer of the fallopian tubes, pancreas, male breast cancer, prostate, lymphoma, melanoma, larynx and colorectal cancer (Nkondjock and Ghadirian, 2004, Ford et al., 1994, http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/HealthProfessional (accessed 21.02.2013)).

Autosomal dominant mutations in the *BRCA* gene can be passed to both men and women in the next generation. Management of individuals who have been identified as carriers of *BRCA1/2* mutations, but who are unaffected by breast cancer, includes intensive surveillance involving yearly mammograms, breast magnetic resonance imaging (MRI) and clinical examination for the early breast cancer detection, prophylactic risk-reducing surgeries including bilateral salpingo-oophorectomy or bilateral mastectomy, and pharmacological interventions using Tamoxifen (Paradiso and Formenti, 2011, Pruthi et al., 2010, Nkondjock and Ghadirian, 2004). Prophylactic mastectomy reduces breast cancer risk by 90-95%. Oophorectomy reduces breast cancer risk by 40-50%, although this can be as high as 73% in *BRCA2* mutation carriers if completed prior to the onset of natural menopause (Pruthi et al., 2010). Prophylactic oophorectomy reduces the risk of ovarian cancer by 80-90% however the resultant early-onset of menopause and estrogen deficiency leads to issues with bone health (Challberg et al., 2011) and increased risk of the metabolic syndrome (MetSyn) and cardiovascular disease (CVD) (Michelsen et al., 2009). Annual ovarian screening has not been shown to be of risk-reducing benefit (Nobbenhuis et al., 2011). A systematic review of the current evidence regarding the role of lifestyle risk factors on breast cancer risk in this specific cohort is presented in Chapter 6, section 6.3.

Tumours arising from *BRCA1* and *BRCA2* mutation are characterised by a number of histological and pathological features. Breast cancers arising from *BRCA1* mutations tend to be high grade, ER-negative or often triple negative and are associated with a younger age of onset, with risk typically increasing at age 40 (Pruthi et al., 2010, Mavaddat et al., 2012). The proportion of ER-positive breast cancers increases with increasing age. (Mavaddat et al., 2012, Tung et al., 2010). Breast cancers arising from *BRCA2* mutations are also of high histological grade but are similar to sporadic breast cancer due to the tendency to present as hormone sensitive tumours (Mavaddat et al., 2012). In contrast to *BRCA1*-related breast cancer the proportion of ER-negative and triple negative tumours increases with increasing age in *BRCA2*-related breast cancer (Mavaddat et al., 2012). Greater ER-negativity is associated with an increase in histological tumour grade (Foulkes et al., 2004). Age of onset for *BRCA2*-related breast cancer is slightly older than observed in *BRCA1* carriers (age 45 years onwards) (Pruthi et al., 2010). Due to the younger age of onset in both *BRCA1* and *BRCA2*-related breast cancer compared to non-carriers, the features of *BRCA*-related breast cancer are consistent with those associated with breast cancer in younger women. The proportion of both ER- and triple negative tumours is higher in both *BRCA1* and *BRCA2* carriers compared to age-matched sporadic breast cancers (Mavaddat et al., 2012, Foulkes et al., 2004).

There are many different mutations of *BRCA1* and *BRCA2* genes. Within ethnically defined groups the diversity of mutations can be restricted and founder effects occur whereby frequent mutations are observed within a geographically isolated, ethically restricted population (Liede et al., 2000). There are three well described founder *BRCA1/2* effects in Ashkenazi Jewish populations, which account for up to 99% of mutations in this cohort (*BRCA1* 185delAG and 5382insC mutations; *BRCA2* 6174delT mutation) (Janavicius, 2010). In Scotland and Northern Ireland there is evidence of a *BRCA1* 2800delAA founder mutation (Liede et al., 2000). The prevalence of *BRCA2* mutations appears to be higher in Scotland and Northern Ireland compared to other parts of Europe (The Scottish/Northern Irish BRCA1/BRCA2 Consortium, 2003). In the Republic of Ireland it is reported that the *BRCA1* E143X mutation accounts for up to 22% of hereditary breast cancers (Janavicius, 2010, McDevitt et al., 2010).

1.1.3 Treatment for Breast Cancer

Treatments for breast cancer often involve a multi-modal approach that can include surgery, chemotherapy, radiotherapy, hormonal therapy and targeted-therapies. The most common treatment combinations in Ireland are surgery, radiotherapy and chemotherapy (18%), surgery, radiotherapy, chemotherapy and hormones (17%) and surgery, radiotherapy and hormones (14%) (National Cancer Registry, 2012). Individualised, tumour-specific treatment regimens are selected according to a number of factors including the patients' age and menopausal status, disease stage, tumour grade and histological characteristics including ER/PR/HER2 status.

Surgical resection is the most common form of treatment for breast cancer in Ireland, with 45% of women undergoing breast conserving surgery (lumpectomy (wide local excision) or quadrantectomy) and 39% undergoing mastectomy (National Cancer Registry, 2012). Management of the axilla in the presence of positive axillary nodes may involve either a complete sential node biopsy, whereby only the node draining the tumour is removed or an axillary node dissection. The latter is associated with considerable arm and shoulder morbidity and complications such as lymphoedema (Duff et al., 2001).

Radiotherapy, the second most commonly used treatment for breast cancer in Ireland (National Cancer Registry, 2012), is targeted directly at the area that has cancer, using ionizing radiation to damage the DNA of malignant cells (Zellars et al., 2011). In the treatment of breast cancer, radiotherapy is delivered externally to the chest wall, daily over a 5-6 week period. Radiotherapy is advised after all breast conserving surgeries, sometimes following mastectomy and in the case of cancer spread to the lymph nodes to reduce risk of recurrence. The addition of radiotherapy following breast conserving surgery reduces the risk of local recurrence to 6-15% (Zellars et al., 2011). Side-effects include fatigue, skin reactions and, specifically following breast radiation, arm swelling and reduced upper limb mobility (Shapiro and Recht, 2001).

Chemotherapy is a cytotoxic treatment, destroying both healthy and malignant cells, used to treat approximately 50% of breast cancers patients in Ireland (National Cancer Registry, 2012).

Treatment may be delivered either neo-adjuvantly (prior to surgery to shrink the tumour size to facilitate surgery), adjuvantly (following surgery to reduce risk of recurrence) or in metastatic disease to ease symptoms and prolong life (Elias et al., 2011). The standard adjuvant chemotherapy regimens for primary breast cancer are doxorubicin and cyclophosphamide (AC) and docetaxel and cyclophosphamide (TC). These regimens, delivered every 2-3 weeks for 4-8 cycles, are associated with similar degrees of toxicity however toxicity is increased in more dose-dense protocols. Dosage schemes for chemotherapy are prescribed based on total body surface area, giving rise to the ongoing debate regarding dosage guidelines for obese patients, as more dose-dense treatments will result in greater toxicity, however an inadequate dose is ineffective in terms of cancer treatment (Griggs et al., 2012).

Due to the cytotoxic nature of chemotherapy, there are a wide range of associated side-effects including ovarian failure in premenopausal women, weight gain, myelosuppression, nausea and vomiting and cardiac toxicity (Shapiro and Recht, 2001, Theodoulou and Seidman, 2003). Taxanes (paclitaxel and docetaxel) are particularly associated with hypersensitivity reactions, peripheral neuropathy, myalgia and arthralgia, while the AC regimen is most likely to cause alopecia and vomiting (Shapiro and Recht, 2001). Anthracyclines (e.g. doxorubicin) are associated with significant cardiotoxicity resulting in cardiomyopathy and reduced left ventricular ejection fraction (LVEF) (Theodoulou and Seidman, 2003).

Hormonal therapy is used to treat ER- and/or PR- positive tumours. There are two types - selective estrogen-receptor modulators (SERMS) (Tamoxifen) and aromatase inhibitors (AIs) (including but not exclusive to letrozole (Femara™), anastrozole (Arimidex™) and exemestane (Aromasin™)). Tamoxifen, which can be prescribed in both pre- and postmenopausal women, works by blocking the binding of estrogen to ER binding site on breast tumours. In contrast, AIs prevent the peripheral conversation of androgens to estrogens in adipose tissue and therefore is only used in the treatment of postmenopausal breast cancer (Elias et al., 2011). Hormonal therapy is taken in tablet form for a standard prescription of five years, however due to side-effects compliance is often poor. As tamoxifen mimics the action of estrogen it is associated with certain beneficial effects including preservation of bone quality and improved lipid profiles, however adverse effects include increased risk of thrombosis, increased endometrial cancer risk, menopausal symptoms (hot flushes, vaginal discharge, irregular

menses), depression and weight gain. In contrast, AIs are associated with bone and joint issues including decreased bone density and arthralgia, alterations in lipid metabolism and musculoskeletal complications (Shapiro and Recht, 2001, Elias et al., 2011, Mouridsen, 2006).

Biological therapies (biological response modifiers) are developed in the laboratory setting to mimic immune defences that occur naturally in the body including interferons, interleukins and monoclonal antibodies. The development of the monoclonal antibody trastuzumab (Herceptin™) as an adjuvant treatment that specifically targets the HER-2 receptor has significantly improved treatment of this defined group (Seal et al., 2012). Treatment can be delivered in combination with adjuvant chemotherapy. While the development of biological response modifiers is the most significant recent advancement in the treatment of breast cancer, both trastuzumab (Herceptin™) and bevacizumab (Avastin™), which are currently at clinical trials stage in the treatment of primary breast cancer, are associated with significant cardiotoxicity characterised by a reduced LVEF, hypertension and cardiovascular dysfunction (Bear et al., 2012, Criscitiello et al., 2012).

1.1.4 Breast Cancer Treatment and the Menopause

The menopause is a normal part of aging, representing the time when normal ovarian function and monthly menstruation stops and marks the end of reproductive phase of a woman's life Soules et al., 2001, Hulka and Meririk,1996). The mean age for onset of natural menopause is 51 years (range 42-58 years) (Soules et al., 2001, Torino et al., 2012). Menopause starts at the final menstrual period (FMP), which can only be identified in retrospect following 12 consecutive months of amenorrhoea (Soules et al., 2001). Perimenopause refers to the events leading up to the FMP, when the hormonal environ of the body is changing, and the 12 months following the FMP. Induced menopause follows either surgical removal of the ovaries or results from ovarian ablation induced as a side-effect of treatments such as chemotherapy or radiotherapy.

Ovarian failure due to chemotoxicity on the ovaries may result in either transient or permanent amenorrhoea. The risk of ovarian failure increases with increasing age, particularly in those ≥40 years, and greater cumulative dose of treatments is associated with greater

ovarian damage (Torino et al., 2012, Goodwin et al., 1999b). The type of chemotherapy used is also predictive, with regimens including docetaxel associated with greater degree of reversible amenorrhea than others (Berliere et al., 2008, Minton and Munster, 2002, Sukumvanich et al., 2010). Both amenorrhoea and menopause resulting from chemotherapy are associated with improved clinical outcomes for premenopausal patients with breast cancer (Swain et al., 2010, Torino et al., 2012), however there are numerous side-effects including adverse effects on sexual function, bone health, cardiac health and psychological issues (Rostom, 2001).

There is no clear definition of chemotherapy-induced ovarian failure. Molina and colleagues (2005) cite amenorrhoea lasting for >12 months following chemotherapy and a follicle stimulating hormone level of ≥30 $MIU.mL^{-1}$ as appropriate cut-points while Clemons and Simmons (2007) argue that even the prolonged absence of menstrual cycles does not imply ovarian failure and that adjuvant hormonal therapy results in unpredictable hormone levels. Clinically, a combination of clinical signs including age, presence of menopause-related symptoms including hot flushes, night sweats or interruption of sexual function, and likelihood of ovarian toxicity from chemotherapy are considered (Torino et al., 2012).

1.2 Obesity and Breast Cancer

1.2.1 Obesity – A Global Epidemic

Overweight and obesity describe a state of abnormal and excess accumulation of body fat which may impair health (WHO, 2000). Overweight and obesity are classified using body mass index (BMI), calculated as a ratio of weight (kg) to height (m^2). Healthy BMI ranges from 18kg.m^{-2} to 24.9kg.m^{-2}. A BMI <18kg.m^{-2} is deemed underweight and BMI between 25kg.m^{-2} and 29.9kg.m^{-2} is classed as overweight. Obesity is defined as a BMI ≥30kg.m^{-2} and is further subdivided as obese class I (BMI 30 kg.m^{-2} - 34.9kg.m^{-2}), obese class II (35kg.m^{-2} - 39.9kg.m^{-2}) and obese class III (≥40kg.m^{-2}).

The World Health Organization (WHO) have termed the growing rates of overweight and obesity worldwide as a "global epidemic" (WHO, 2000). In 2008, 35% of adults worldwide were overweight and 12% were obese, representing a 50% increase in the prevalence of obesity between 1980 and 2008. Obesity was most prevalent in some regions of America where 62% of the population were overweight and 26% obese, and in Europe where over 50% of women were overweight, 23% of whom were obese (2008). In Ireland, the Survey of Lifestyle, Attitudes and Nutrition (SLÁN) in 2007 reported that 39% of adults (45% of men and 33% of women) were overweight and 25% (24% of men and 26% of women) were obese (Morgan et al., 2008).

The health consequences of overweight and obesity are well established. Obesity is a major risk factor for a number of chronic diseases such as CVD including coronary artery disease and cerebrovascular disease (Reaven et al., 2004), type II diabetes mellitus (T2DM) (Reaven et al., 2004), musculoskeletal disorders including osteoarthritis (Sridhar et al., 2012) and certain cancers (WCRF/AICR 2007). Obesity, characterised by both total body fatness and abdominal fatness, increases the risk of numerous cancers including oesophageal adenocarcinoma, pancreatic, colorectal, postmenopausal breast, endometrium and kidney cancers (WCRF/AICR 2007).

1.2.2 Obesity and Breast Cancer Risk

The relationship between obesity and breast cancer varies by menopausal status (Friedenreich, 2001, Ballard-Barbash, 1994, Han et al., 2006, Ursin et al., 1995). Body fatness, as measured by BMI is associated with increased postmenopausal breast cancer risk, such that every $5kg.m^{-2}$ gain in BMI increases risk of cancer development by 8% (WCRF/AICR, 2007, Ballard-Barbash, 1994). Other anthropometric measures including adult weight gain and increased abdominal adiposity are also associated with increased breast cancer risk (Friedenreich, 2001, Huang et al., 1999, Huang et al., 1997, Han et al., 2006), particularly in postmenopausal women who have never used HRT (Huang et al., 1997, Huang et al., 1999). Conversely, there is a suggestion of a protective relationship between high BMI and premenopausal breast cancer risk, whereby a $5kg.m^{-2}$ increase in BMI, decreases breast cancer risk by 15% (WCRF/AICR, 2007). There is a lack of consensus regarding the role of other anthropometrics in this regards with the results from the Nurses' Health Study reporting that neither BMI at aged 10-20, adult weight gain nor central adiposity are associated with increased breast cancer risk (Huang et al., 1997, Huang et al., 1999, Han et al., 2006).

The contrasting relationship described above is largely due to differing sources of sex hormones pre and post the menopausal transition. In premenopausal women, estrogen is produced almost exclusively by the ovaries and circulating levels are controlled through feedback loops involving the hypothalamus and the anterior pituitary (Key et al., 2001). Conversely, in postmenopausal women oestrogens are produced by aromatisation of precursor androgen to estradiol in the adipose tissue, a process that is largely unregulated. Sex hormone binding globulin (SHBG) is the primary binding site for oestrogens and testosterones and therefore concentrations of free circulating estrogens and androgens are influenced by the availability of SHBG. SHBG levels are decreased with rising levels of obesity (Verkasalo et al., 2001, McTiernan et al., 2003). In obese premenopausal women, levels of free estradiol remain relatively constant due to the regulation by the feedback loop. Clinically obese premenopausal women, (BMI $>30kg.m^{-2}$) experience frequent anovular menstrual cycles, leading to a marked reduction in both oestrogen and progesterone production. In contrast, obese postmenopausal women, with increasing adipose tissue experience a reduction in SHBG levels leading to increased concentrations of free estradiol due to unregulated estrogen production (Ballard-Barbash, 1994, Key et al., 2001). As discussed in

section 1.1.2 above, estrogen is a major determinant of breast cancer risk, particularly of hormone sensitive tumours.

1.2.3 Obesity and Breast Cancer Prognosis

Obesity at diagnosis is associated with more advanced tumour presentation characterised by larger tumour size, greater nodal involvement and higher incidence of lymphovascular invasions compared to lean patients (Healy et al., 2010b, Daling et al., 2001, Cui et al., 2002, Abe et al., 1976). Subsequently obesity (BMI ≥30 $kg.m^{-2}$) at breast cancer diagnosis is associated with poorer breast cancer outcomes (Ligibel, 2011, Protani et al., 2010, Patterson et al., 2010, Emaus et al., 2010). A recent meta-analysis cited a 33% increased risk of both breast cancer specific (hazard ratio (HR) 1.33, 95% confidence interval (95% CI), 1.19 to 1.50) and total mortality (HR 1.33, 95% CI, 1.21 to 1.47) particularly in premenopausal women (HR 1.47 versus HR 1.22 pre versus postmenopausal) (Protani et al., 2010). Increased abdominal adiposity has been associated with mortality in both premenopausal women (Abrahamson et al., 2006) and postmenopausal women with ER-positive tumours (Borugian et al., 2003). The effect of an elevated waist circumference, particularly if >88cm, in combination with increased BMI is associated with a considerably worse prognosis (Abrahamson et al., 2006).

Weight gain and changes in body composition during adjuvant treatment may also impact negatively on survival. Weight gain is a commonly reported side-effect of treatment, with typical gains of 2.5 to 6.2kg although up to 10kg are also feasible (Demark-Wahnefried et al., 1993). Women who remain weight stable during adjuvant treatment may experience changes in body composition characterised by increases in body fat with concurrent decreases in lean body mass (muscle mass) leading to the development of sarcopenia (Campbell et al., 2007, Demark-Wahnefried et al., 2001a, Del Rio et al., 2002), a condition most commonly associated with aging (Karakelides and Nair, 2005). Weight gain and changes in body composition most commonly occur in premenopausal women (Goodwin et al., 1999a), associated with early-onset of menopause (Goodwin et al., 1999b), hormonal therapy (Redig and Munshi, 2010) and in those who receive lengthy, multi-agent chemotherapeutic regimens (Rock et al., 1999, Camoriano et al., 1990, Del Rio et al., 2002). Changes in energy output including altered metabolic rate (Del Rio et al., 2002, Harvie et al., 2004, Demark-Wahnefried et al., 1997) and

decreased physical activity levels following diagnosis (Demark-Wahnefried et al., 1997, Irwin et al., 2005a, Demark-Wahnefried et al., 2001a) are also hypothesised to cause weight gain.

There is evidence of a U-shaped relationship between weight change and breast cancer outcome, whereby both weight gain and weight loss lead to increased mortality (Nichols et al., 2009, Thivat et al., 2010, Caan et al., 2012). The largest of these analyses, the After Breast Cancer Pooling Project (n=12,915), reported increased mortality in American women who both lost weight of ≥10% (11.64kg) (HR 1.41, 95% CI, 1.14 to 1.75) and in women who gained weight of ≥10% (10.5kg) during treatment (HR 1.15, 95% CI, 0.98 to 1.35) (Caan et al., 2012). An increase in CVD mortality has also been reported with treatment-related weight gain (Nichols et al., 2009). Consequently to improve breast specific and all-cause mortality following breast cancer, weight maintenance is recommended during adjuvant treatment.

1.2.4 Management of Obesity

Long-term obesity occurs due to a positive energy imbalance resulting from excessive intake of energy-dense food and inadequate energy expenditure (Nguyen and El-Serag, 2010) and therefore management of obesity involves a combination of diet and exercise considerations. While calorie restriction ≥500kcal.day^{-1} is required for meaningful weight loss (Dietary Guidelines for Americans, 2005) aerobic exercise, either alone or in combination with diet, is a more effective strategy than diet-alone for reducing visceral adipose tissue (Kay and Fiatarone Singh, 2006, Ross et al., 2004, McTiernan, 2004, Ismail et al., 2012). Energy expenditure comprises three components, resting metabolic rate (RMR), diet-induced thermogenesis and physical activity (Groff and Gropper, 1999, Astrup and Tremblay, 2009). RMR refers to the energy required to fuel the body's basic physiological needs, accounting for 60-75% of energy expenditure in sedentary adults (Bandini and Flynn, 2003, Donahoo et al., 2004, Marra et al., 2007) but this can vary up to 25% between individuals (Astrup and Tremblay, 2009). Due to the large contribution of RMR to energy balance, even small alterations may have a significant impact on weight management (Bandini and Flynn, 2003). A reduced RMR increases risk of weight gain. Physical activity, or activity thermogenesis, accounts for 10-15% of total daily energy expenditure (Donahoo et al., 2004). The direct impact of physical activity on breast cancer risk and survival will be discussed sections 1.4.2 and 1.4.3 below. In addition, physical activity may indirectly increase breast cancer risk through reductions in obesity and abdominal

adiposity (WCRF/AICR, 2007). In this thesis, obesity will be considered in the context of energy expenditure, primarily in relation to physical activity, although RMR and aerobic fitness will also be explored.

The metabolic consequences of obesity are well described (Despres and Lemieux, 2006, Galic et al., 2010). Breast cancer survivors may be at a further disadvantage due to a number of adverse lifestyle changes that are described following diagnosis including physical inactivity and sedentariness (section 1.4.5), early menopause (section 1.1.4) and sarcopenia. The menopausal transition and sarcopenia are both associated with the development of metabolic abnormalities including insulin resistance, chronic inflammation and abdominal adiposity (Dominguez and Barbagallo, 2007, Stenholm et al., 2008, Aubertin-Leheudre et al., 2006, Carr, 2003, Lovejoy et al., 2008). The management of dysmetabolism is a key therapeutic strategy in the treatment of obesity-related chronic disease such as CVD and cancer. The therapeutic influences of physical activity are hypothesised to be mediated via positive alterations in these pathways and therefore a thorough understanding of the inter-relationship between obesity, physical activity and metabolic presentation is essential for the development of targeted management strategies for chronic disease and breast cancer control. The following sections will describe the key metabolic pathways involved in carcinogenesis, the role of physical activity in cancer control and the evidence exploring the potential influence of physical activity on metabolic biomarkers of breast cancer risk.

Obesity and Breast Cancer Summary

Obesity increases the risk of postmenopausal breast cancer but demonstrates an inverse relationship with premenopausal breast cancer.

Obesity at diagnosis is a negative prognostic indicator for both pre- and postmenopausal outcomes following breast cancer.

Women are recommended to remain weight stable during adjuvant treatment to optimise breast cancer specific and all-cause mortality.

Weight gain and/or sarcopenia is a common side-effect of adjuvant treatment associated with menopausal transition, physical inactivity, long chemotherapeutic regimens and hormonal treatment.

The management of obesity requires consideration of both energy intake and energy expenditure. Understanding the relationships between obesity, dysmetabolism and physical activity is required for targeted management.

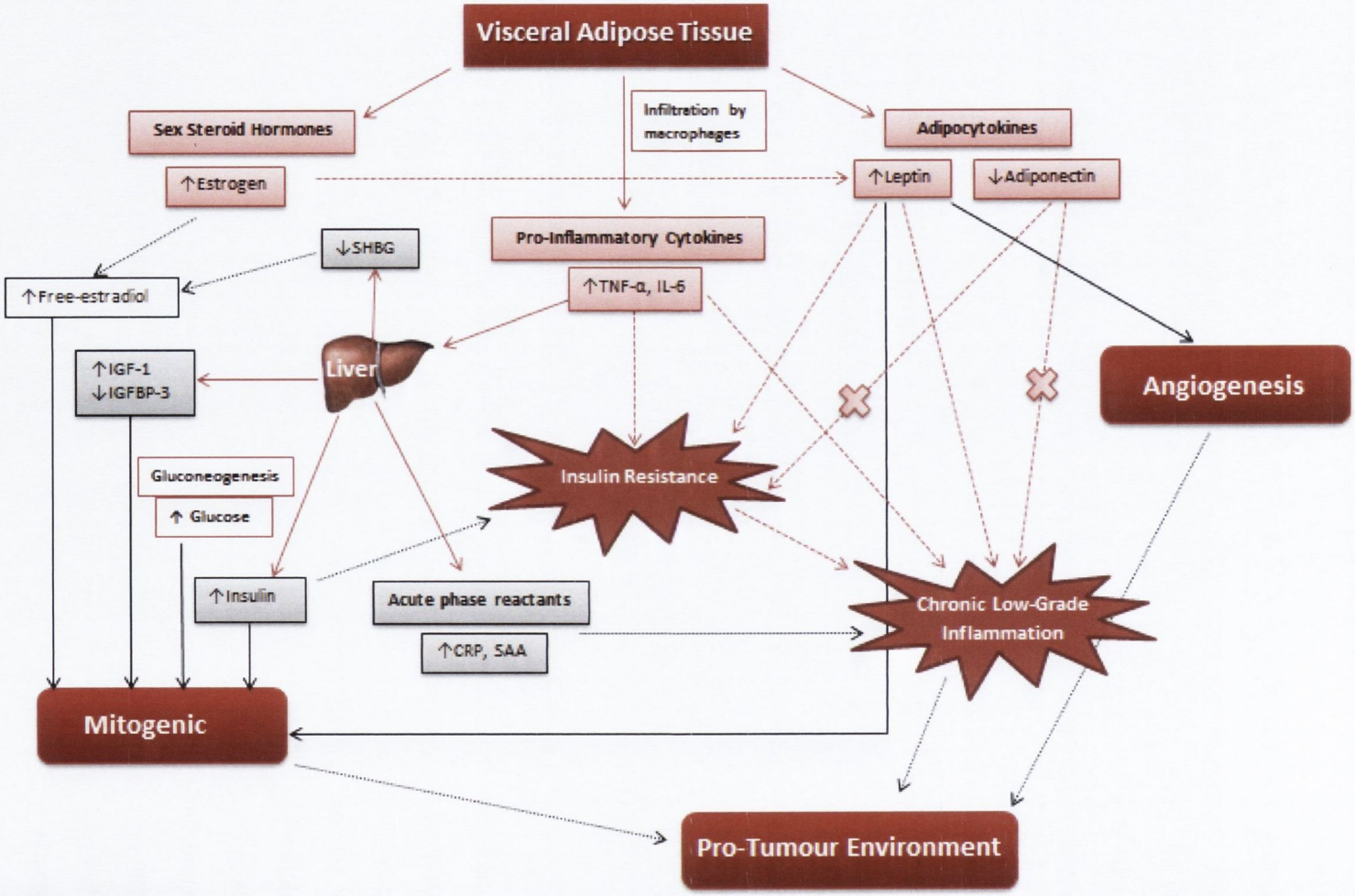
1.3 Metabolic Pathways Linking Obesity to Breast Cancer

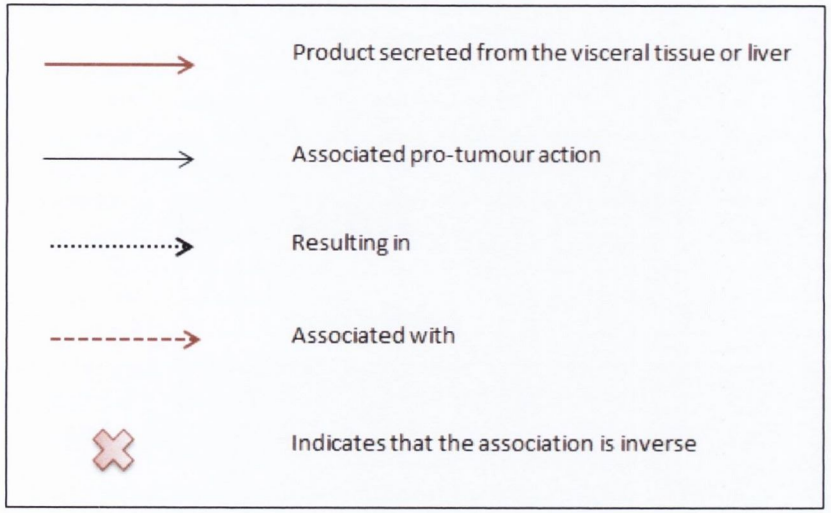
1.3.1 The Adipose Tissue as an Endocrine Organ

The adipose tissue, while originally viewed as passive, inert tissue, for energy storage, is now known as a complex, multifunctional endocrine organ producing a range of proteins, inflammatory markers and adipocytokines (Hauner, 2005, Kershaw and Flier, 2004, Galic et al., 2010). The metabolic activity of adipose tissue is dependent on the regional distribution of body fat. Upper body fat accumulation, also known as "android" or "male-type obesity", is associated with a greater degree of metabolic dysfunction compared to lower body fat accumulation or "gynoid" / "female fat distribution". Upper body fat accumulates centrally (abdominally), and is composed of both subcutaneous and intra-abdominal (visceral) fat. Visceral fat surrounds the abdominal organs and is composed of omental, mesenteric and retroperitoneal fat deposits (Wajchenberg, 2000). In contrast lower body fat deposits in the gluteo-femoral region, over the buttocks and thighs. In premenopausal women, estrogen promotes the accumulation of gluteo-femoral fat. Resultant estrogen deficiency following menopause causes central fat accumulation, dyslipidemia and an increase in insulin resistance, which is one of the key links between obesity and increased breast cancer risk in postmenopausal women (Carr, 2003, Lovejoy et al., 2008).

Visceral adipose tissue, is the most metabolically active adipose tissue, displaying multiple endocrine, metabolic and immunological properties central to the pathogenesis of disorders of metabolic dysfunction (Despres and Lemieux, 2006). Anthropometric measures of visceral obesity (waist circumference) are therefore considered a core component of the MetSyn and may account for differences in the presentation of dysmetabolism in those with obesity (Wajchenberg, 2000). Products secreted from the adipose tissue include pro-inflammatory cytokines, adipokines and sex steroid hormones, resulting in a pro-inflammatory, insulin-resistant environment (Figure 2), many of which contribute directly and indirectly to breast cancer carcinogenesis. The following sections will describe the role of the MetSyn, insulin-related parameters, chronic low-grade inflammation and adipokines in breast cancer risk and prognosis.

Figure 2 Secretary Factors from the Adipose Tissue





Visceral adipose tissue secrets sex hormones (estrogen), pro-inflammatory cytokines (TNF-α, IL-6) and adipokines (leptin, adiponectin). Pro-inflammatory cytokines cause increased gluconeogenesis at the liver, resulting in increased glucose production and consequently pancreatic insulin secretion, resulting in insulin resistance. The liver also controls the secretion of IGF-1, IGFBP-3 and SHBG. Reduced SHBG, combined with increased estrogen from the adipose tissues results in increased concentrations of free-estradiol. Concentrations of insulin resistance are directly related to leptin and indirectly related to adiponectin. Both adipokines display similar relationships to measures of chronic low-grade inflammation. Chronic low grade inflammation occurs as a results of increased acute-phase reactants (secreted from the liver) and pro-inflammatory cytokines. These products combine to exert mitogenic and angiogenic effects, which coupled with inflammation, create a pro-tumour environment. (Despres and Lemieux, 2006, Galic et al., 2010, Hauner, 2005)

1.3.2 The Metabolic Syndrome

The MetSyn describes a clustering of risk factors for CVD and T2DM that includes abdominal obesity, hypertension, atherogenic dyslipidemia and elevated fasting glucose (Alberti et al., 2009, Grundy et al., 2005). While individually each component is associated with increased risk of CVD and T2DM, the combination of typically three or more factors is associated with a much more powerful disease risk (Alberti and Zimmet, 1998). The MetSyn was originally described in 1988 by Reaven and colleagues (Reaven, 1988) as "Syndrome X" and since then several terms have been used to describe this clustering of interrelated risk factors for CVD and T2DM including the "deadly quartet", the "insulin-resistance syndrome" and the "metabolic syndrome" (Grundy et al., 2005).

The criteria used to define the presence of the MetSyn have been subject of debate and several sets of criteria have been developed (Table 2). Earlier definitions of the MetSyn cite insulin resistance as the central component and as an obligatory requirement in addition to two or more risk factors (Alberti and Zimmet, 1998, Balkau and Charles, 1999, Einhorn et al., 2003). Subsequent definitions dropped the insulin resistance as a requirement, stating instead that insulin resistance was the predominant underlying cause of the syndrome (Grundy et al., 2005, Alberti et al., 2009). This variety of definitions has resulted in inconsistencies in protocols regarding the defining criteria for the MetSyn, therefore limiting comparisons between studies.

While excess abdominal adiposity is considered one of the core components of the MetSyn (Alberti et al., 2009) there has been considerable debate regarding the most appropriate cut-points to use to define central adiposity. Waist circumference cut-off points for males and females have been described as ≥94cm and ≥80cm (Balkau and Charles, 1999, Alberti et al., 2005) and also as ≥102cm and ≥88cm respectively (2002b, Grundy et al., 2005). The most recent definition of the MetSyn, which was developed as part of a consensus statement by the International Diabetes Federation Task Force on Epidemiology and Prevention, the National Heart, Lung, and Blood Institute, the American Heart Association, the World Heart Federation, the International Atherosclerosis Society and International Association for the Study of Obesity (Alberti et al., 2009), has recommended the use of population-specific and ethnic-specific cut-points.

Table 2 Definitions of the Metabolic Syndrome

Institute	Authors	Criteria	Obesity	Fasting Glucose	HDL-C	TG	HTN	Micro-albuminuria
WHO (1998)	Alberti and Zimmet (1998)	IGT, T2DM +/or hyperinsulinemia and 2 or more of:	Men: WHR ≥0.9; Women: WHR >0.85 +/or BMI ≥30 $kg.m^{2}$	≥6.1 $mmol.L^{-1}$ or 2h post-glucose load ≥7.8 $mmol.L^{-1}$	Men: <0.9 $mmol.L^{-1}$ Women: <1.0 $mmol.L^{-1}$	≥1.7 $mmol.L^{-1}$	≥160/90 mmHg	Urinary albumin excretion rate ≥20 $\mu g.min^{-1}$ or albumin/ creatinine ratio ≥20 $mg.g^{-1}$
EGIR (1999)	Balkau and Charles, (1999)	Insulin resistance +/or fasting hyperinsulinemia (nonT2DM patients) and 2 of:	Men: WC ≥94 cm Women: WC ≥80cm	≥6.1 $mmol.L^{-1}$	HDL < 1.0 $mmol.L^{-1*}$	≥2.0 $mmol.L^{-1*}$	≥140/90 mmHg †	N/A
NCEP ATP III (2001)	NCEP ATP III (2002b)	3 or more of:	Men: WC ≥102cm Women: WC ≥88cm	≥6.2 $mmol.L^{-1}$ or T2DM	Men: <1.03 $mmol.L^{-1}$, Women: <1.3 $mmol.L^{-1}$	≥1.7 $mmol.L^{-1}$	≥130/85 mmHg	N/A
AACE (2003)	Einhorn et al., (2003)	IGT or IFG or other features of insulin resistance and any of the following based on clinical judgement:	BMI ≥25$kg.m^{-2}$	IGT or IFG (not T2DM)	Men: <1.03 $mmol.L^{-1}$, Women <1.29 $mmol.L^{-1}$	>1.7 $mmol.L^{-1}$	≥130/85 mmHg	N/A
IDF (2005)	Alberti et al., (2005)	Elevated WC and 2 or more of:	Ethnic specific cut-points +/or BMI ≥30 $kg.m^{2}$	≥5.6 $mmol.L^{-1}$ or T2DM	Men: <1.03 $mmol.L^{-1}$, Women <1.29 $mmol.L^{-1*}$	>1.7 $mmol.L^{-1*}$	Systolic ≥130 +/or diastolic ≥85 mmHg †	N/A

Institute	Authors	Criteria	Central Obesity	Fasting Glucose	HDL-C	TG	HTN	Micro-albuminuria
AHA/ NHLBI (2005)	Grundy et al., (2005)	3 or more of:	Men: WC ≥102cm Women: WC ≥88cm	≥5.6 $mmol.L^{-1}$‡	Men: <1.03 $mmol.L^{-1}$, Women <1.29 $mmol.L^{-1}$*	>1.7 $mmol.L^{-1}$*	Systolic ≥130 +/or diastolic ≥85 mmHg †	N/A
Consensus Statement (2009)	Alberti et al., (2009)	3 or more of:	Population specific cut-points	≥5.6 $mmol.L^{-1}$ or T2DM‡	Men <1.03 $mmol.L^{-1}$, Women <1.3 $mmol.L^{-1}$*	≥1.7 $mmol.L^{-1}$*	Systolic: ≥130 and/or diastolic: ≥85 mmHg †	N/A

** Drug treatment for dyslipidemia is an alternate indicator; † Drug treatment for hypertension is an alternate indicator; ‡ Drug treatment for fasting glucose is an alternate indicator*

Abb: HDL-C = high density lipoprotein cholesterol; TG = triglycerides; HTN = hypertension; WHO = World Health Organisation; IGT = impaired glucose tolerance; T2DM = type II diabetes mellitus; WHR = waist-to-hip ratio; BMI = body mass index; EGIR = European Group for Study of Insulin Resistance; WC = waist circumference; N/A = not applicable; NCEP = National Cholesterol Education Program; ATP = adult treatment panel; AACE = American Association of Clinical Endocrinologists; IFG = impaired fasting glucose; IDF = International Diabetes Federation; AHA = American Heart Association; NHLBI = National Heart, Lung, and Blood Institute;

The association between the MetSyn and cancer risk is well established. Initial results from the Metabolic Syndrome and Cancer (Me-Can) Project, the largest (n=600,000) prospective cohort study of its kind (Bjorge et al., 2010a), have found that the presence of the MetSyn is associated with an increased risk of colorectal cancer (men: relative risk (RR) 1.25, 95% CI, 1.18 to 1.32; women: RR 1.14, 95% CI, 1.06 to 1.22, (Stocks et al., 2010)), endometrial cancer (RR 1.37, 95% CI, 1.28 to 1.46, (Bjorge et al., 2010b)) and pancreatic cancer (RR 1.58, 95% CI, 1.34 to 1.87, (Johansen et al., 2010)). In relation to breast cancer, the relationship is similar to that observed with obesity in that the MetSyn is associated with increased risk of postmenopausal (>60 years old) (RR 1.23, 95% CI, 1.04 to 1.45) and a decreased risk of premenopausal (<50 years) breast cancer (RR 0.83, 95% CI, 0.76 to 0.90) (Bjorge et al., 2010a). These results are consistent with other case-control studies reporting increased postmenopausal breast cancer risk in the presence of the MetSyn at any point over the lifetime (Porto et al., 2011, Rosato et al., 2011, Agnoli et al., 2010). Results from the Women's Health Initiative reported that evidence of the MetSyn specifically 3-5 years prior to breast cancer diagnosis was associated with increased risk of both total (*In situ* plus invasive cancer) (HR 1.84 95% CI, 1.12 to 3.01) and invasive breast cancer (HR 1.77, 95% CI, 1.01 to 3.12) (Kabat et al., 2009).

The reported prevalence of the MetSyn among newly diagnosed postmenopausal patients with breast cancer ranges from 15% to 39%, depending on the MetSyn criteria used (Healy et al., 2010a, Capasso et al., 2011, Pasanisi et al., 2006). This is characterised by a significant prevalence of central obesity ranging from 33-53% (when waist circumference is classed as <88cm) to 87% (when waist circumference is classed as <80cm). Postmenopausal patients with breast cancer are more likely to have the MetSyn (OR 0.30, 95% CI, 0.24 to 0.35) than healthy postmenopausal controls (OR 0.19, 95% CI, 0.15 to 0.22) (Capasso et al., 2011). The presence of the MetSyn at diagnosis is associated with increased all-cause mortality (HR 1.41, 95% CI, 1.09 to 1.83) (Emaus et al., 2010) and a greater risk of breast cancer recurrence (HR 3.0, 95% CI, 1.2 to 2.7) (Pasanisi et al., 2006) in postmenopausal women. Premenopausal patients with breast cancer display similar prevalence of MetSyn to their healthy counterparts (Capasso et al., 2011) and there is a lack of consensus regarding the associations between the MetSyn and premenopausal breast cancer risk, particularly in relation to ER-negative and triple negative breast cancer (Maiti et al., 2010, Colonna et al., 2012).

The MetSyn and metabolic dysfunction is a long-term complication of curative treatment for many cancers such as testicular (Strumberg et al., 2002), prostate (Shahani et al., 2008), survivors of childhood cancers (Talvensaari et al., 1996) and haematological malignancies including leukaemia and lymphoma (Jung et al., 2012), with prevalence rates of MetSyn ranging from 26% for testicular cancer survivors following platinum-based chemotherapy regimens to 55% for prostate cancer survivors on androgen deprivation therapy (de Haas et al., 2010). Among survivors of female breast cancer, prevalence rates are reported at 54.8% in women receiving adjuvant hormone therapy, with 96% of participants reported as being centrally obese (waist circumference >88cm) (Thomson et al., 2009). Early onset of the menopause, which occurs in approximately 50% of patients with breast cancer as a side-effect of adjuvant chemotherapy, is proposed as one of the mechanisms leading to the development of MetSyn in breast cancer survivors (de Haas et al., 2010), however there may be a significant contribution from a range of other factors such as weight gain, sarcopenia and sedentariness.

1.3.3 Insulin, Glucose and Insulin Resistance

Insulin is a polypeptide hormone secreted from pancreatic beta (β) cells in response to raised glucose concentrations. The main targets for insulin are skeletal muscle, adipose tissue and the liver, however many other tissues, including healthy breast tissue and breast cancer cells express insulin receptors, the binding site for insulin (Wolf et al., 2005). The primary function of insulin is to maintain homeostasis through the glucose regulation primarily in the liver, muscle and fat. Insulin action is controlled by interaction with insulin receptors located on cell membranes. This binding of insulin with its associated receptor results in activation of tyrosine kinase and a cascade of intracellular responses. In the liver, insulin inhibits glucose production and metabolism through the inhibition of gluconeogenesis and glycogenolysis. In the muscle and fat, insulin stimulates glucose uptake, storage and usage. Insulin also plays a role in protein and lipid regulation (Moller and Flier, 1991). The number and function of insulin receptors can be altered by numerous physiologic factors such as hyperinsulinemia, exercise, diet and certain endocrine hormones including growth hormone and glucocorticoids.

Insulin resistance is defined as the subnormal biologic response to a given concentration of insulin (American Diabetes Association (ADA), 2012) and refers to impaired action of insulin on glucose homeostasis. The clinical consequences of insulin resistance can be described as those that arise from deficient insulin action, such as impaired glucose tolerance or diabetes, and those that result from hyperinsulinemia. Hyperinsulinemia is a significant risk factor for CVD (Reaven, 2005), while it is also associated with increased risk for cancer at several sites including colon (Giovannucci, 2007), pancreas (Stolzenberg-Solomon et al., 2005) and prostate (Albanes et al., 2009).

In vitro, insulin is shown to be a powerful mitogenic agent in mammary tissues through promotion of proliferation of malignant breast cells due to over-expression of the insulin receptor(Hursting et al., 2007, Eliassen et al., 2007, Wolf et al., 2005). Hyperinsulinemia can also influence breast cancer risk indirectly by stimulating downregulation of SHBG and consequential increased expression of free oestrogen (Wolf et al., 2005, Hursting et al., 2007). There is however conflicting evidence from case-control and epidemiological studies regarding the contribution of insulin-related parameters to breast cancer risk. While associations between hyperinsulinemia and both premenopausal (OR 2.23, 95.CI, 1.22 to 6.58) (Del Giudice et al., 1998) and postmenopausal (HR 1.46, 95% CI, 1.00 to 2.13) (Gunter et al., 2009) breast cancer risk have been reported, several studies have reported no relationship in predominantly premenopausal breast cancer (Eliassen et al., 2007, Muti et al., 2002). In postmenopausal women there is a suggestion that hyperinsulinemia may only increase breast cancer risk in those who have never used HRT (Gunter et al., 2009). Only one study has reported an association between fasting glucose levels and premenopausal breast cancer risk (RR 2.8, 95% CI, 1.2 to 6.5) (Muti et al., 2002). Similarly, fasting C-peptide, a peripheral marker of insulin secretion, have been associated with breast cancer risk in some (Bruning et al., 1992) but not all studies (Eliassen et al., 2007, Keinan-Boker et al., 2003).

The prognostic influences of insulin-related variables have been investigated by a small number of prospective cohort studies. Goodwin and colleagues (2012) collected fasting blood samples 4-12 weeks following primary surgery and reported increased breast cancer recurrence and mortality in those with hyperinsulinemia (HR $_{\text{Recurrence}}$ 2.32, 95% CI, 1.39 to 3.86; HR $_{\text{Mortality}}$ 2.85, 95% CI, 1.48 to 5.50), hyperglycaemia (HR $_{\text{Recurrence}}$ 1.74, 95% CI, 1.08 to

2.82; HR $_{Mortality}$ 1.97, 95% CI, 1.07 to 3.63), insulin resistance (HR $_{Recurrence}$ 2.62, 95% CI, 1.54 to 4.48 ; HR $_{Mortality}$ 3.23, 95% CI, 1.62 to 6.42) and elevated C-peptide (HR $_{Recurrence}$ 1.86, 95% CI, 1.02 to 3.40; HR $_{Mortality}$ 2.90, 95% CI, 1.31 to 6.4). In contrast, the Healthy Eating Activity and Lifestyle (HEAL) study collected samples 3 years post diagnosis and also reported increased mortality outcomes with elevated C-peptide (breast cancer specific mortality HR 2.39, 95% CI, 1.00 to 7.5) (Irwin et al., 2011a) and insulin resistance (breast cancer specific mortality HR 1.12, 95% CI, 1.05 to 1.20; all-cause mortality HR 1.09, 95% CI, 1.02 to 1.15) (Duggan et al., 2011). Chronic hyperglycaemia (glycated haemoglobin A_{1c} (HbA_{1c}) ≥6.5%) is associated with increased all-cause mortality compared to women with normal glycaemic control (HR 2.35, 95% CI, 1.56 to 3.54) (Erickson et al., 2011)

The insulin pathway also consists of the insulin-like growth factor (IGF) axis which includes the polypeptide hormones IGF-1 and IGF2, the associated insulin-like growth factor binding proteins (IGFBP), and the IGF receptor (Wolf et al., 2005, Hursting et al., 2007). In breast cancer, increased bioavailability of IGF-1 is one of the key regulatory pathways linking obesity to breast cancer risk (Keinan-Boker et al., 2003, Hursting et al., 2007). IGF-1 is secreted by the liver in response to growth hormone and when it binds to the IGF-receptor it stimulates cell proliferation in both normal and neoplastic breast cells (Rosen et al., 1991). The availability of IGF-1 is regulated by a number of processes including the presence of growth factors, hormonal influences, the availability of binding proteins, particularly IGFBP-3, and circulating levels of insulin (Hursting et al., 2007). Elevated insulin levels reduce the bioavailability of IGFBP-3, therefore increasing levels of IGF-1. Case-control studies have reported a significant association between increased availability of IGF-1 and IGFBP-3 with premenopausal (Muti et al., 2002, Del Giudice et al., 1998) but not with postmenopausal breast cancer risk (Keinan-Boker et al., 2003, Gunter et al., 2009).

1.3.4 Chronic Low Grade Inflammation

Obesity is characterised by expansion of adipose tissue, leading to infiltration by macrophages, stimulating secretion of pro-inflammatory cytokines including tumor necrosis factor (TNF)-α and interleukin (IL)-6 from the adipose tissue (Galic et al., 2010, Kershaw and Flier, 2004). These inflammatory cytokines contribute to the development of insulin resistance, induce disturbances in glucose and lipid metabolism, promote the development of

atherosclerotic plaques by increasing the aggregability of thrombocytes and stimulating fibrinogen production, and stimulate secretion of non-specific, acute-phase reactants including C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen (Hauner, 2005, Kershaw and Flier, 2004). This cascade of events contributes to the pro-inflammatory, pro-thrombotic environment, characteristic of the MetSyn (Alberti et al., 2009, Grundy et al., 2005).

Inflammation plays an important role in carcinogenesis (Biasucci, 2004) and is one of the key components of cancer development and progression (Coussens and Werb, 2002). Inflammation is defined as a physiological response of an organism to harmful stimuli, which can be chemical, physical or biological and occurs with the aim of restabilising homeostasis (Sherwood, 2010). Certain neoplasms develop as a result of infection (e.g. Epstein-Barr virus is associated with certain types of lymphoma), or arise from chronic inflammatory disorders (e.g. reflux oesophagitis and Barrett's oesophagus are associated with oesophageal adenocarcinoma) (Coussens and Werb, 2002).

In contrast, the inflammatory state accompanying obesity does not occur in response to infection or disease, characterising a set of unique biological mechanisms. Chronic inflammation contributes to the local tumor microenvironment and promotes proliferation, survival and migration of neoplastic cells (Coussens and Werb, 2002). Raised CRP is a feature in many patients diagnosed with cancer, including gastro-oesophageal (Crumley et al., 2006), colorectal (McMillan et al., 2003) and pancreatic (Falconer et al., 1995) cancers. CRP is most widely used in clinical studies and is one of the best markers of inflammation as it is highly correlated with concentrations of TNF-α and IL-6 (Schultz and Arnold, 1990) and has been proposed as core feature of the MetSyn (Devaraj et al., 2010). CRP levels >3mg $mg.L^{-1}$ define a state of chronic low-grade inflammation in the absence of another identifiable cause (Grundy et al., 2005). In breast cancer, higher levels of CRP are related to higher stage of disease, with highest values in those with metastatic disease (O'Hanlon et al., 2002, Robertson et al., 1991, Albuquerque et al., 1995). There is a lack of consensus regarding the prognostic significance of CRP at breast cancer diagnosis with one study showing no association (Al Murri et al., 2007) and another showing decreased survival rates for elderly women with elevated inflammatory markers in women with and without primary cancer (Heikkila et al., 2007).

In long-term breast cancer survivors on adjuvant hormone therapy, mean high-sensitivity CRP levels of 5.1 (5.3) $mg.L^{-1}$, characteristic of chronic inflammation, have been reported (Thomson et al., 2009). CRP and SAA both correlate with a number of anthropometric and lifestyle related prognostic indicators in breast cancer survivors including increasing BMI, increasing waist circumference and decreasing physical activity levels (Pierce et al., 2009b). CRP is also elevated in women who are smokers and in those with a history of heart failure, but is reduced in Tamoxifen users (Pierce et al., 2009b). Elevated inflammatory status is associated with overall survival even following adjustment for other prognostic indicators (tumor stage, age, BMI) as measured by CRP (HR 2.27, 95% CI, 1.27 to 4.08) and SAA (HR 3.15, 95% CI, 1.73 to 5.65) (HR of highest versus lowest quartile) (Pierce et al., 2009a).

1.3.5 Adipokines

Adipokines, or adipocytokines, are a group of polypeptides secreted almost exclusively from the adipose tissue (Rose et al., 2004, Vona-Davis et al., 2007). Adipokines encompass a range of hormones and cytokines including the pro-inflammatory cytokines discussed above (TNF-α and IL-6), vascular endothelial growth factor, heparin-binding epidermal growth factor-like growth factor, leptin and adiponectin. The following section will focus on the latter two hormones, leptin and adiponectin.

Leptin is produced by the obesity gene (ob gene) and secreted from the pre-adipocytes and adipocytes of the adipose tissue and also the mammary epithelial cells (Rose et al., 2004, Vona-Davis et al., 2007). The primary function of leptin is to act as a neurohormone, regulating energy balance and food intake through appetite regulation in the hypothalamus (Rose et al., 2004, Garofalo et al., 2006). In the breast, leptin promotes normal mammary gland development and lactation and therefore dysregulation of leptin may contribute to tumorgenesis (Ray and Cleary, 2010). Levels of circulating leptin are correlated with increasing obesity and are directly related to insulin resistance and pro-inflammatory cytokines (Cirillo et al., 2008). Normal circulating levels range from 5-50$ng.mL^{-1}$, however they can be as high as 100 $ng.mL^{-1}$ in obese individuals (Grossmann et al., 2010). Leptin expression is upregulated by estrogen and downregulated by testosterone, leading to higher circulating levels in women than in men (Ray and Cleary, 2010). Leptin is considered as one of the key variables in the MetSyn, displaying strong relationships with other MetSyn features including waist

circumference, blood pressure, dyslipidemia and hyperglycaemia (de Courten et al., 1997). In obese individuals, hyperleptinaemia characterises a resistance of the body to the hormone due to insensitivity of leptin receptors (Cirillo et al., 2008). In breast cancer survivors, higher leptin levels correlate with increasing BMI and low physical activity levels (Irwin et al., 2005b).

Leptin is thought to promote tumorgenesis through several different actions in breast cell lines including cell growth, proliferation, migration, invasion and angiogenesis (Cirillo et al., 2008, Grossmann et al., 2010). *In vitro* studies on animal models have shown that leptin stimulates proliferation of ER-positive breast cell lines (Ray and Cleary, 2010) and may also enhance tumor growth by promoting aromatase action in breast cells (Grossmann et al., 2010). Clinical studies investigating the role of leptin in breast cancer risk have yielded conflicting results. Petridou et al., (2000) reported a significant association between leptin concentrations at diagnosis, and pre- but not postmenopausal breast cancer risk and while Ozet et al., (2001) reported high leptin levels in patients with breast cancer compared to controls, results were confounded by tamoxifen use in the cancer cohort. Two other studies reported no association between leptin and either pre- or postmenopausal breast cancer risk (Mantzoros et al., 1999, Stattin et al., 2004). The relationship with prognosis remains to be established with only one study demonstrating no association between leptin as measured at diagnosis with breast cancer outcome (Goodwin et al., 2005).

Adiponectin is produced exclusively by the adipocytes and is the most abundant gene product in the adipose tissue, with a normal range of 2-20 $\mu g.mL^{-1}$ (Rose et al., 2004, Grossmann et al., 2010). Unlike leptin, adiponectin is inversely correlated with body fat, leptin and insulin and demonstrates anti-inflammatory, anti-diabetic, anti-atherogenic properties (Vona-Davis et al., 2007, Grossmann et al., 2010). Therefore, low levels of adiponectin are associated with increased risk of CVD, T2DM and certain cancers (Barb et al., 2006, Giannessi et al., 2007). Studies haves shown that the adiponectin receptors (AdipoR1 and AdipoR2) are expressed in breast tumor tissue and breast cell lines and *in vitro* studies have demonstrated anti-proliferative effects of adiponectin in healthy breast tissue (Grossmann et al., 2010, Jarde et al., 2009). Like leptin, adiponectin represents a key feature of the MetSyn, demonstrating an inverse relationship with hypertension, dyslipidemia, CRP and with increasing number of MetSyn components (Vona-Davis et al., 2007). In addition, the leptin:adiponectin ratio

demonstrates a significant correlation with insulin resistance, with some suggestion of it being a more accurate measure than the homeostatic model assessment index (HOMA-IR), in patients with and without T2DM (Inoue et al., 2005, Inoue et al., 2006) and is inversely associated with more advanced breast cancer presentation (Chen et al., 2006).

A number of case-control studies have reported an association between low circulating levels of adiponectin and increased risk of both pre- and postmenopausal breast cancer (Mantzoros et al., 2004, Miyoshi et al., 2003, Chen et al., 2006). Data from the Nurses' Health Study, the only prospective investigation of the association between adiponectin and breast cancer risk, suggested an association between low adiponectin concentrations and postmenopausal (RR 0.73, 95% CI, 0.55 to 0.98) but not premenopausal (RR 1.30, 95% CI, 0.8 to 2.1) breast cancer (Tworoger et al., 2007a). Associations were strongest for postmenopausal women who had never used HRT and in those with the lowest levels of circulating estrogen. Only one study has investigated the association between adiponectin and breast cancer survival, reporting that reduced adiponectin levels were associated with reduced breast cancer-specific and all-cause mortality in postmenopausal breast cancer survivors (HR 0.39, 95% CI, 0.15 to 0.95) (Duggan et al., 2011).

Metabolic Pathways Linking Obesity to Breast Cancer - Summary

Adipose tissue, in particular visceral adipose tissue, is an active endocrine organ secreting numerous proteins and hormones contributing to carcinogenesis.

The metabolic syndrome is a clustering of risk factors for cardiovascular disease and diabetes that is thought to provide one of the vital links between obesity and cancer.

The metabolic syndrome is associated with an increased risk of post- but not pre-menopausal breast cancer development.

Insulin resistance is one of the core features of the metabolic syndrome and is associated with increased breast cancer risk largely due to mitogenic effects of insulin of mammary cells.

Hyperinsulinemia at breast cancer diagnosis is associated with a greater than two-fold increase in risk of breast cancer recurrence and a three-fold increase in all-cause mortality, particularly in the first five years post diagnosis.

Obesity also results in chronic low-grade inflammation, characterised by pro-inflammatory cytokines (TNF-α, IL-6) and acute-phase reactants (CRP, SAA), creating a pro-tumor inflammatory micro-environment that is ideal for neoplastic cells to proliferate, grow and develop.

Raised markers of inflammation (CRP, SAA) are associated with greater mortality following breast cancer.

Adipokines, such as leptin and adiponectin, are secreted directly from the adipose tissue may also contribute to carcinogenesis.

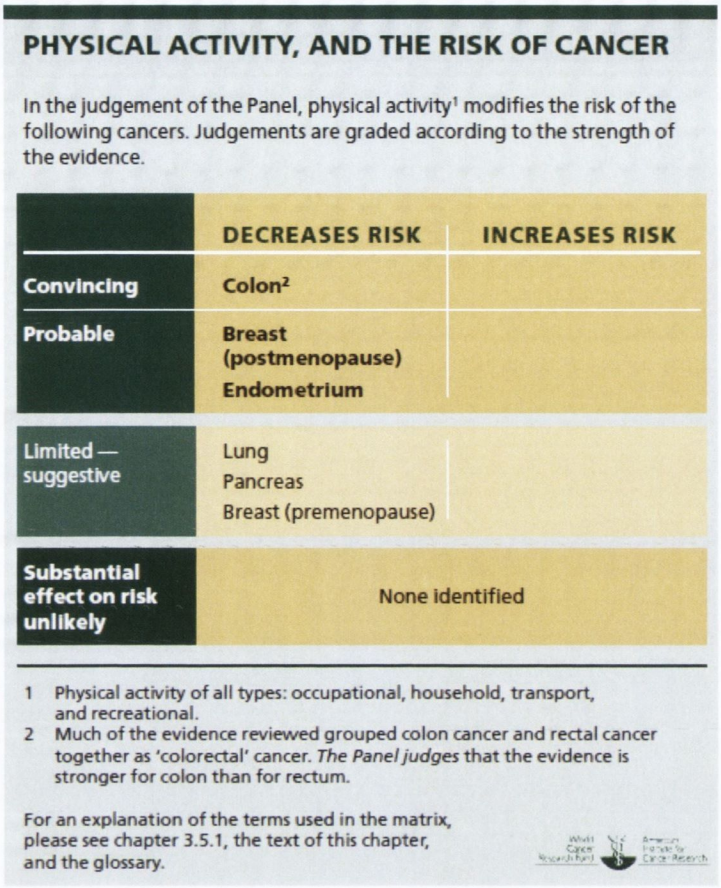
1.4 Physical Activity and Breast Cancer

1.4.1 Physical Inactivity: A Risk Factor for Non-communicable Diseases

Physical activity is defined as any body movement, produced by skeletal muscles and resulting in energy expenditure that exceeds resting levels (Caspersen et al., 1985). Exercise is defined as a form of leisure-time physical activity that is performed repeatedly over an extended period of time with the intention of maintaining fitness. Moderate-to-vigorous intensity physical activity is known to improve health outcomes and reduce the risk of several diseases including CVD (Shephard and Balady, 1999), T2DM (Thomas et al., 2006), osteoporosis (Sinaki et al., 2010) and cancer (WCRF/AICR, 2007). In contrast, physical inactivity is associated with increased disease burden, increasing the risk of T2DM, CVD, and certain cancers (particularly colon and breast) (Thorp et al., 2011, Lee et al., 2012). Physical inactivity is identified as the fourth leading global risk for non-communicable diseases, responsible for 6% of mortality worldwide (Lee et al., 2012, WHO, 2009). In Ireland, the burden of disease risk associated with physical inactivity is estimated to be 8.8% for coronary heart disease (95% CI, 2.0 to 17.4%), 10.9% for T2DM (95% CI, 2.9 to 20.2%), 15.2% for breast cancer (95% CI, 3.5 to 27.3%), 15.7% for colon cancer (95% CI, 4.1 to 27.6%) and 14.2% for all-cause mortality (95% CI, 6.0 to 22.9%) (Lee et al., 2012). While these percentages are lower than those estimated for the United Kingdom, they are higher across all categories when compared to the United States of America and to the median value across all Europe countries. Individuals with the MetSyn (or an equivalent clustering of CVD risk factors) are more likely to be physically inactive and demonstrate low cardiorespiratory fitness levels (Lakka et al., 2003, Carroll et al., 2000, Rennie et al., 2003).

The strongest evidence of a protective influence of physical activity on cancer is in relation to colon cancer (Lee et al., 2012, WCRF/AICR, 2007) (Figure 3). There is also evidence of a protective role of physical activity over breast (postmenopausal more than premenopausal) cancer development (discussed in sections 1.4.3 and 1.4.4), endometrial cancer (Cust, 2011) and to a lesser extent lung, pancreatic and prostate cancers (Miles, 2007) (Figure 3).

Figure 3 Summary of Physical Activity Evidence from WCRF/AICR Second Expert Report



PHYSICAL ACTIVITY, AND THE RISK OF CANCER

In the judgement of the Panel, physical activity[1] modifies the risk of the following cancers. Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
Convincing	**Colon[2]**	
Probable	**Breast (postmenopause)** **Endometrium**	
Limited — suggestive	Lung Pancreas Breast (premenopause)	
Substantial effect on risk unlikely	None identified	

1 Physical activity of all types: occupational, household, transport, and recreational.
2 Much of the evidence reviewed grouped colon cancer and rectal cancer together as 'colorectal' cancer. *The Panel judges* that the evidence is stronger for colon than for rectum.

For an explanation of the terms used in the matrix, please see chapter 3.5.1, the text of this chapter, and the glossary.

The WCRF/AICR Second Expert Report on Food, Nutrition, Physical Activity, and the Prevention of Cancer is the largest, most comprehensive report on the influence of diet, physical activity and body fatness on cancer risk. Systematic literature reviews of the evidence in each area were completed and recommendations on food, nutrition, physical activity and body composition were generated. The above table is taken from Chapter 5 of the report and summarises the judgements of the panel on the level of evidence available in relation to physical activity and cancer risk (www.dietandcancerreport.org).

1.4.2 Physical Activity in the General Population

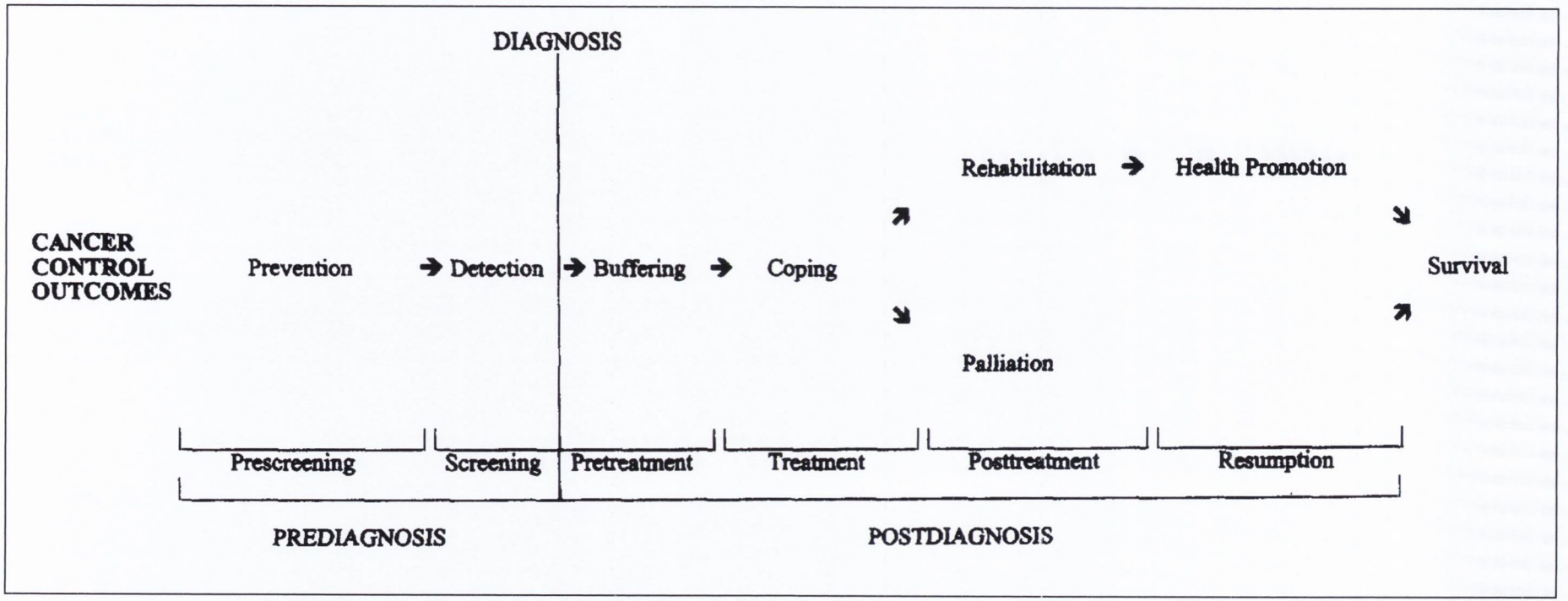
Despite the known health benefits of physical activity, inactivity levels worldwide are worryingly high. In the first global survey of physical activity levels, 31.1% (95% CI, 30.9% to 31.2%) of adults worldwide were classed as inactive (Hallal et al., 2012).[2] Inactivity levels were highest in Europe (34.8% (95% CI, 34.5 to 35.1%) and in the Americas (43.2% (95% CI, 42.8% to 43.6%), greater in women (33.9%) than in men (27.9%) and increase with increasing age. Percentage time spent engaging in sedentary behaviour, defined as spending >4 hours.day^{-1} sitting, was 41.5% (95% CI, 41.3 to 41.7%) worldwide, with highest rates observed in Europe (64.1%, 95% CI, 63.5 to 64.7%). Conversely, the amount of time in vigorous intensity activity on ≥3 days.week^{-1}, was 31.4% (95% CI, 31.2 to 31.4%) for adults worldwide, with lowest values recorded in the Americas (24.6%, 95% CI, 24.3 to 24.9%) and Europe (25.4%, 95% CI, 250 to 25.8%).

Physical inactivity and sedentariness are attributed to changing lifestyle patterns and reliance on technology and motorised transport and increased leisure-time being sedentary based including television watching and use of computers. Those who commute to work by walking or cycling experience health benefits in terms of all-cause mortality and reduced disease risk (de Nazelle et al., 2011). Walking is the most affordable, accessible and common activity people perform. In the SLÁN survey of lifestyle habits in an Irish population, 55% of adults report engaging in regular physical activity that is sufficient to meet recommended activity guidelines, with only 22% reporting that they are inactive (Morgan et al., 2008). The most frequent reason provided by respondents for physical inactivity was a "lack of time". Reported time engaging in moderate-to-vigorous intensity activity, ≥3 times.week^{-1} was 41%, which was not significantly different from SLÁN surveys completed in 1998 (38%) or 2002 (41%).

Physical activity is recommended at all stages throughout the cancer trajectory as illustrated in the The Physical Exercise Across the Cancer Experience (PEACE) Framework by Courneya and Friedenreich (2001) in (Figure 4). Courneya and Friedenreich refer to cancer prevention and survival as "cancer control outcomes". The following sections will discuss the role of physical activity in breast cancer prevention and survival.

[2] Inactive implies that an individual is not achieving physical activity guidelines. In contrast, sedentary behaviour characterises activity that involves little or no movement or physical activity, requiring an energy expenditure of ≤1.5 METs such as prolonged sitting or lying.

Figure 4: Framework PEACE



The Physical Exercise Across the Cancer Experience (PEACE) Framework, devised by Courneya and Friedenreich, (2001), defines a role for physical exercise pre-diagnosis (prevention), at diagnosis, during treatment, survivorship and end of life. In this thesis, the role of physical activity is examined at two time-points along this trajectory; prevention and survival. The studies described in Chapters 3, 4 and 5 examine the role of exercise in cancer survivorship in terms of the influence of an structured exercise intervention on biomarkers of breast cancer risk and the relationships between physical activity and metabolic outcomes of interest. In Chapter 6 modifiable lifestyle risk factors for breast cancer are examined. Habitual physical activity levels and the relationships with metabolic variables of interest are presented.

1.4.3 Physical Activity and Breast Cancer Prevention

Research in the area of exercise and physical activity in cancer has increased considerably in the last 20 years. Prevention is most studied of all cancer control outcomes. The most recent and comprehensive systematic review, published by Lynch and colleagues (2011b), identified 33 cohort studies and 40 case-control studies examining this association. Of the 73 studies reviewed, 51 reported a reduction in breast cancer risk in physically active women (29 papers reported a statistically significant reduction), with an average risk reduction of 25% observed across all studies. There was some evidence of a dose-dependent response. Moderate (15% decreased risk) and vigorous (18%) intensity activity conveyed greatest benefits. Similarly, 6.5 hours.week^{-1} of moderate-to-vigorous intensity activity was associated with greater benefits (30%) than engaging in 2-3 hours.week^{-1} of similar activity (9%). In terms of activity type, highest reductions were observed for recreational and household activity (21%) followed by walking/cycling (18%) and occupational related activity (13%).

Lynch and colleagues (2011b) identified a number of population sub groups who appeared to experience greatest benefits including postmenopausal women (31% risk reduction versus 27% in premenopausal women), those with a lower BMI (BMI <22 kg.m^{-2}: 27% reduced risk; BMI 22-25 kg.m^{-2}: 24% reduced risk; BMI ≥25 kg.m^{-2}: 18% reduced risk; BMI ≥30 kg.m^{-2}:<1% reduced risk), women without a family history of breast cancer (21% risk reduction for those without a family history of breast cancer versus <1% reduction for women with a family history) and parous women (38% risk reduction versus 18% in nulliparous women). Risk was not modified by ER status while there was some evidence to suggest a higher effect for PR-positive versus PR-negative tumours. The average risk reduction was lower in white women (20%) compared to black (41%), Hispanic (28%), Indian (38%) and Asian (41%) women.

Other systematic reviews have also reported a strong protective effect of physical activity on postmenopausal breast cancer development that doesn't appear to exist in premenopausal women (Miles, 2007, Friedenreich and Orenstein, 2002, Friedenreich and Cust, 2008). The WCRF/AICR reported a stronger relationship between physical activity and postmenopausal breast cancer risk than that observed with premenopausal breast cancer, citing the evidence as "limited" (WCRF/AICR, 2007) (Figure 3). The panel also concluded that a sedentary lifestyle conveys increased risk of breast cancer. While the protective effect of physical activity is

independent of confounding factors such as body fat, physical activity also protects against overweight and obesity and hence indirectly contributes to reduced risk. The majority of studies examined breast cancer risk in relation to lifetime physical patterns, however, there is some evidence to suggest that physical activity undertaken specifically during adolescence and early adulthood may also reduce the risk of future breast cancer development (RR 0.81, 95% CI, 0.73 to 0.89) (Lagerros et al., 2004) and therefore physical activity and exercise should be encouraged from an early age. The menopause transition has also been identified as a critical time. The Nurses' Health Study reported that sedentary women who increased activity levels (from < 9 metabolic equivalent hours (MET-h).week^{-1} to > 9MET-h.week^{-1}) at the time of menopause transition had a reduced breast cancer risk compared to women who remained inactive (HR 0.9, 95% CI, 0.82 to 0.98) (Eliassen et al., 2010).

1.4.4 Physical Activity and Breast Cancer Survival

Physical activity plays two roles in breast cancer survival. Firstly, physical activity has a role in improving breast cancer outcome by reducing the risk of breast cancer recurrence and breast cancer specific mortality. Secondly, physical activity may reduce the risk of all-cause mortality following breast cancer by reducing morbidity and mortality resulting from secondary consequences of adjuvant therapy. In particular, physical activity may decrease CVD risk factors, thus targeting the most significant contributor to all-cause mortality following breast cancer (Nichols et al., 2009, Chapman et al., 2008, Patnaik et al., 2011).

A person is considered a cancer survivor from the time of diagnosis through the balance of his or her life (http://www.canceradvocacy.org (accessed 31.07.2012)). Therefore, exercise prescription models, such as the one proposed by Schmitz, (2011) advocate the commencement of exercise shortly after diagnosis, with a view to continuing programmes throughout treatment and into survivorship. Observational studies have examined both exercise undertaken prior to diagnosis and exercise commenced following-diagnosis in relation to secondary prevention (Ibrahim and Al-Homaidh, 2011, Ballard-Barbash et al., 2012). Moderate-to-vigorous intensity activity completed prior to diagnosis is associated with a 29% reduction in all-cause mortality (HR 0.71, 95% CI, 0.53 to 0.94, p=0.02) with no effect observed for breast cancer specific mortality. As physical activity levels reduce significantly following breast cancer diagnosis (discussed in section 1.4.5 below), it may be more clinically

relevant to examine post-diagnosis physical activity levels in relation to breast cancer outcome.

A protective effect of post-diagnosis physical activity (highest versus lowest activity group) on all-cause mortality has been shown by a number of large epidemiological studies including the Nurses' Health Study (RR 0.65 (95% CI, 0.48 to 0.88), p=0.003) (Holmes et al., 2005),the HEAL study (HR 0.33, 95% CI, 0.15 to 0.73) (Irwin et al., 2008), the Life after Cancer Epidemiology study (HR 0.66 (95% CI, 0.42 to 1.03), p=0.04) (Sternfeld et al., 2009) the Collaborative Women's Longevity Study (HR 0.44, 95% CI, 0.32 to 0.60) (Holick et al., 2008) and the Shanghai Breast Cancer Survival Study (HR 0.65 (95% CI, 0.51 to 0.84) p<0.001) (Chen et al., 2011). The Women's Healthy Eating and Living study reported a 35% reduction in mortality among patients with breast cancer who adhered to recommended physical activity guidelines following diagnosis (HR 0.65 (95% CI, 0.47 to 0.91), p<0.01) (Bertram et al., 2011). Recently data from the Women's Health Initiative reported a 33% reduction in all-cause mortality in survivors exercising to ≥9 metabolic equivalent–hours (MET-h).week^{-1}, even if they were sedentary pre-diagnosis (Irwin et al., 2011b). Worryingly, the HEAL study reported almost a four-fold increase in mortality risk among women who reduced activity levels at diagnosis (HR 3.95, 95% CI, 1.45 to 10.5).

Holick and colleagues (2008) reported a dose dependent relationship between physical activity and breast cancer specific mortality whereby exercising at 2.8-7.9 MET-h.week^{-1} reduced mortality risk by 35%, exercising at 8.0-20.9 MET-h.week^{-1} reduced risk by 41% and engaging in >21 MET-h.week^{-1} of activity reduced risk by 49%. Similarly, Chen and colleagues reported a 41% reduction in breast cancer specific mortality (HR 0.59 (95% CI, 0.45 to 0.76) p=0.006) with ≥8.3 MET-h.week^{-1} of activity in the first three years post diagnosis (Chen et al., 2011). The Nurses' Health Study reported a 26% reduction in breast cancer recurrence (RR 0.74 (95% CI, 0.5 to 1.1), p=0.05) for ≥24 versus <3 MET-h.week^{-1} activity (Holmes et al., 2005). A systematic review by Ballard-Barbash and colleagues (2012) reported little evidence of an effect for confounding factors such as menopausal status, BMI, tumour stage, hormone receptor status, comorbidities, race or ethnicity, on the relationship between physical activity and secondary breast cancer prevention.

1.4.5 Physical Activity Levels among Breast Cancer Survivors

Exercise guidance for the prevention of, and survival following, breast cancer are largely based on public health recommendations. The American College for Sports Medicine (ASCM) physical activity guidelines for healthy adults recommend 30-60 minutes.day^{-1} (150 minutes.week^{-1}) of moderate intensity exercise, or 20-60 minutes.day^{-1} of vigorous intensity exercise or a combination or both, ≥5 days.week^{-1} if moderate intensity activity and ≥3 days.week^{-1} if vigorous activity (Garber et al., 2011). Specific exercise guidelines for cancer control have been published by both the AICR (WCRF/AICR, 2007) and the American College of Sports Medicine (ACSM) (Schmitz et al., 2010). For cancer prevention, the WCRF/AICR recommend 30 minutes of moderate intensity activity on every day of the week. The ACSM recommend that cancer survivors adhere to public health recommendations as able but that exercise prescription be individualised according to the cancer survivors' needs, taking into account cancer site-specific and treatment related contraindications to exercise. In patients with breast cancer, upper limb arm and shoulder morbidity should be assessed prior to commencing an upper limb exercise programme, and individuals should be monitored for changes in arm/shoulder symptoms such as decreased range of motion or increased arm swelling. Additionally, decreased bone density is a side effect of AIs (hormonal therapy) and therefore awareness of fracture risk is important. Overall, cancer survivors should avoid prolonged inactivity and be as physically active as their condition allows, with a view to achieving recommended physical activity guidelines for healthy adults as normal life resumes (WCRF/AICR, 2007, Garber et al., 2011).

Despite these recommendations, patients with breast cancer experience a decrease in physical activity of approximately two hours per week ($p<0.05$) at the time of diagnosis (Irwin et al., 2003a). Furthermore functional status can remain low for a prolonged period in certain breast cancer survivors subgroups including the elderly (Sweeney et al., 2006) and socially isolated women (Michael et al., 2000). Low habitual activity levels are reported across a range of cancer survivors particularly female colorectal cancer survivors (13.8%), female breast cancer survivors (16.6%) and female melanoma skin cancer survivors (19.1%) (Courneya et al., 2008b). Reductions in physical activity levels are most pronounced in obese women (Irwin et al., 2003a, Irwin et al., 2004). Obese breast cancer survivors less likely to be physically active than their obese, non-breast cancer counterparts (Adjusted OR 0.51, 95% CI 0.27 to 0.94) (Courneya et al., 2008b). These results support the suggestion by Demark-Wahnefried and

colleagues (1997) that reduced physical activity levels following breast cancer diagnosis contributes to weight gain in this group. Decreases in recreational physical activity levels are also greater in those who received combined regimens of adjuvant treatment (chemotherapy and radiotherapy) versus those who underwent surgery or radiotherapy only ($p<0.05$) (Irwin et al., 2003a).

Objective reports of physical activity[3] levels in breast cancer survivors report a predominance of sedentary behaviour (66% of waking hours) and light intensity activity (33%) (Lynch et al., 2010). Objectively measured sedentary time is significantly associated with markers of adiposity (BMI and waist circumference) while moderate-to-vigorous intensity activity was inversely associated with BMI, waist circumference and serum insulin levels in both postmenopausal breast cancer survivors (Lynch et al., 2010) and healthy postmenopausal women (Lynch et al., 2011a). These associations emphasise the therapeutic targets for increasing physical activity for the purpose of cancer control.

Several observational studies show that physical activity levels among cancer survivor cohorts are similar to the general population in terms of sedentary time (Eakin et al., 2007), participation in moderate-to-vigorous intensity activity (Kwon et al., 2012, Coups and Ostroff, 2005) and adherence to physical activity guidelines (Kwon et al., 2012, Courneya et al., 2008b). There are some reports to suggest that cancer survivors are more active than the general population, engaging in up to twice the frequency of exercise (Bellizzi et al., 2005, Demark-Wahnefried et al., 2000) and greater regular participation ($\geq$5 days.week^{-1}) in moderate-to-vigorous intensity activity (Pinto et al., 2002, Demark-Wahnefried et al., 2000). Studies measuring physical activity by self-report have found between 20% and 32% of breast cancer survivors adhere to recommended physical activity guidelines ($\geq$150 minutes.week^{-1}), with middle-aged women (40-64 year olds) most likely to be less active (Coups and Ostroff, 2005, Bellizzi et al., 2005, Irwin et al., 2004). Self-report estimates of adherence to physical activity guidelines suggest that up to 64% of healthy adults exercise to recommended levels, however this is as low as 10% when activity is measured using accelerometry (Tucker et al., 2011).

[3] Objective physical activity refers to physical activity that is measured using objective methods such as accelerometry. In contrast, subjective methods rely on recall questionnaires and self-report. The measurement of physical activity is discussed in Chapter 2 (section 2.3.1).

Physical Activity and Breast Cancer - Summary

Physical activity has a role across the entire cancer trajectory, from pre-diagnosis to survival.

Physical activity to the equivalent of ≥9 MET-h.week^{-1} is associated with a 25% reduction in postmenopausal breast cancer risk.

Women who are physically active after a breast cancer diagnosis have up to a 35% reduction in all-cause mortality as well as reduced risk of breast cancer recurrence and breast cancer-specific mortality.

Breast cancer survivors significantly reduce physical activity levels upon breast cancer diagnosis and rarely return to pre-diagnostic activity levels when treatment is complete, with less than 35% achieving recommended physical activity guidelines.

Women who are obese and those who undergo multimodal adjuvant treatment regimens show the greatest reductions in physical activity.

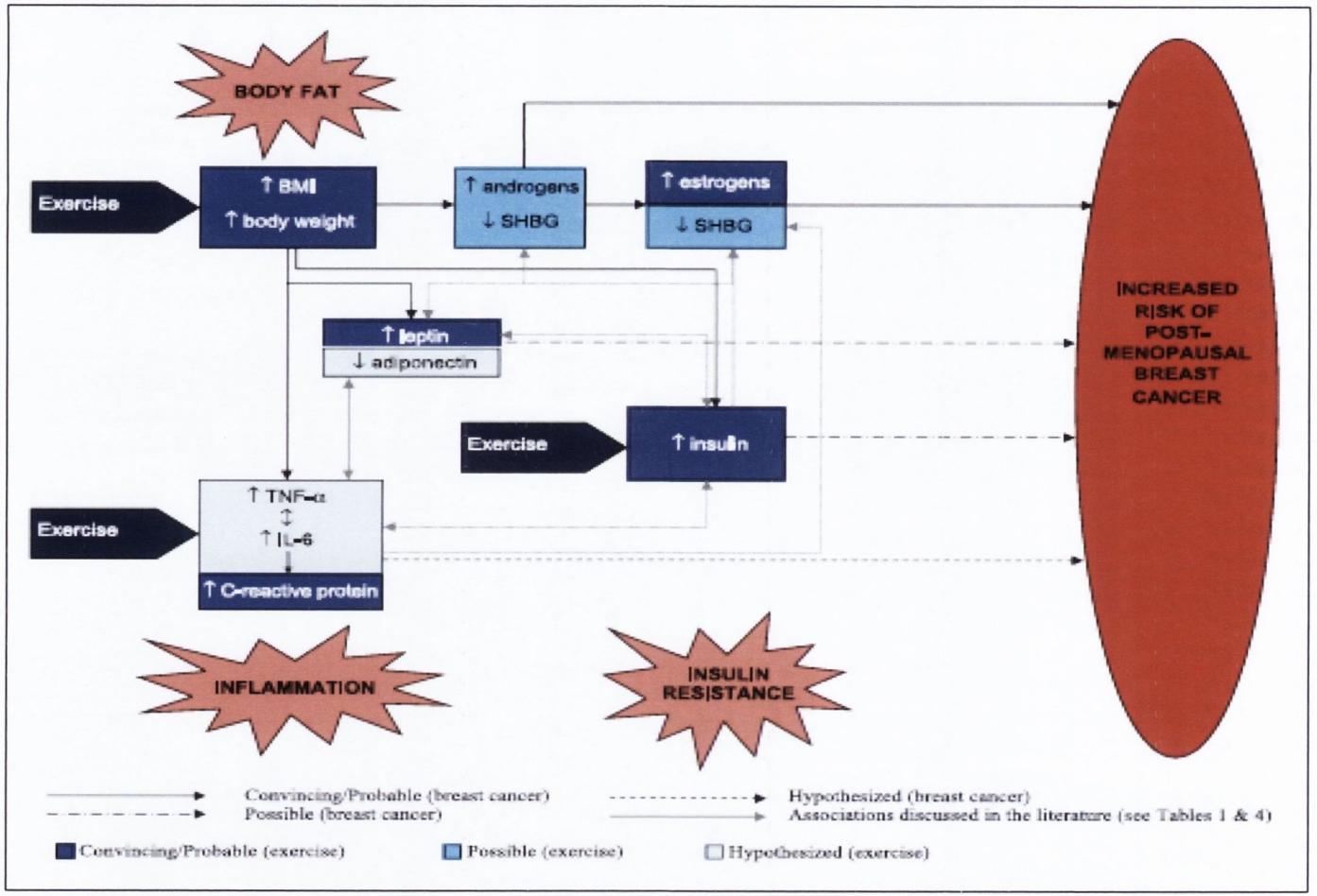
An excess of physical inactivity and sedentary behaviour is observed at population level and therefore despite the evidence that breast cancer survivors are physically active to population levels, this is likely to be insufficient for health benefits.

1.5 Biological Mechanisms Linking Physical Activity to Breast Cancer

A number of key pathways, hypothesised to explain the link between physical activity and breast cancer have been proposed, many of which are inter-related with obesity and associated biomarkers. Neilson and colleagues (2009) proposed a model, identifying a number of key metabolic pathway of breast cancer risk which may be influenced by long-term exercise (Figure 5). These pathways are anthropometrics (BMI, body weight), sex hormones (estrogens, androgens, SHBG), adipocytokines (leptin, adiponectin), markers of insulin resistance (insulin, glucose, c-peptide, HbA_{1c}) and inflammatory markers (TNF-α, IL-6 and CRP).While the IGF-axis was not included in this model, other authors have proposed this pathway as one that physical activity may influence to decrease breast cancer risk (Friedenreich and Orenstein, 2002, McTiernan et al., 1998).

Observational studies in breast cancer survivors, particularly the HEAL study and the National Health and Nutrition Examination Survey (NHANES) have reported significant associations between high amounts of physical activity and favourable levels of selected biomarkers in postmenopausal breast cancer survivors. Such biomarkers include low c-peptide (Irwin et al., 2005b), low leptin (Irwin et al., 2005b), low waist circumference (Lynch et al., 2010), decreasing BMI (Lynch et al., 2010, Irwin et al., 2004), lower insulin (Lynch et al., 2010) and increased IGF-1 and IGFBP-3 (Irwin et al., 2005b). Conversely, physical inactivity is associated with increasing waist circumference (Lynch et al., 2010), high BMI (Lynch et al., 2010), high insulin (Lynch et al., 2010) and high markers of inflammation (Pierce et al., 2009b). Such relationships have also been observed in healthy postmenopausal women (Lynch et al., 2011a).

Figure 5 Biological Model Relating Breast Cancer Biomarkers to Long-term Exercise



The proposed model by Neilson et al., (2009) relates proposed breast cancer biomarkers to long-term exercise in relation to postmenopausal breast cancer risk.

Physical activity can be subdivided into a number of categories namely cardiorespiratory (aerobic) fitness, muscle fitness, body composition, flexibility and neuromotor fitness (Garber et al., 2011). In cancer research, "physical activity" generally refers to the effects of aerobic exercise. Aerobic exercise is defined as any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature (Church et al., 2010). During aerobic exercise the body has adequate oxygen to meet metabolic needs. In contrast anaerobic exercise requires short periods of high intensity exercise which requires energy generated in the absence of oxygen (Katch et al., 2011e). Aerobic exercise is recommended as a first-line approach to the prevention and treatment of cardiometabolic disease risk factor. Benefits can be gained in anthropometric and cardiometabolic factors, cardiorespiratory fitness and quality of life (WHO, 2009). The greatest health benefits are observed in sedentary individuals who commence a moderate intensity (70% maximum heart rate (HRmax)) continuous aerobic programme (Katch et al., 2011e).

Aerobic exercise is recommended in addition to calorie restriction for long-term maintenance of weight loss and to prevent weight regain (Donnelly et al., 2009, Curioni and Lourenco, 2005). Aerobic exercise, either alone or in combination with diet, is the most effective strategy for reducing visceral adipose tissue (Kay and Fiatarone Singh, 2006, Ross et al., 2004, McTiernan, 2004, Ismail et al., 2012). A recent systematic review and meta-analysis by Ismail and colleagues (2012) reported an effect size of -0.23 (95% CI, -0.35 to -0.12, $p<0.001$) for the effect of aerobic exercise on visceral fat. Reducing body fat, particularly metabolically active visceral adipose tissue is identified as one of the key mechanisms through which aerobic exercise leads to a reduction in low grade chronic inflammation, reduced insulin resistance and lower levels of circulating sex hormones, particularly among postmenopausal women (Neilson et al., 2009, McTiernan, 2004).

A number of randomised controlled trials (RCTs) have reported significant changes in body weight, visceral fat and components of abdominal fat following 4-12 months of moderate-to-vigorous intensity aerobic exercise, in sedentary, overweight adults (Slentz et al., 2005, Irwin et al., 2003b, Irving et al., 2008). There is evidence of a dose-response relationship across all studies with greater benefits observed with higher volumes of exercise. The volume of exercise completed takes into account exercise intensity and duration (i.e. occasions per week

exercising and length of activity programme). Slentz et al., (2005) and Irving et al., (2008) both reported significant decreases in total abdominal fat visceral fat and subcutaneous abdominal fat following 4-9 months of vigorous intensity exercise (65-80% peak oxygen consumption (VO_{2peak}) that were not observed in the comparative moderate intensity (40-55% VO_{2peak}) aerobic groups. Moderate intensity exercise performed of longer duration (12 months) was associated with significant decreases in body weight, total body fat, visceral fat and subcutaneous abdominal fat (Irwin et al., 2003b). Exercise induced weight loss is associated with a greater reduction in total abdominal fat than equivalent diet associated weight loss (Ross et al., 2004). Reductions in abdominal fat can even occur in the absence of weight loss with vigorous intensity aerobic activity (~80% HRmax) fat (Ross et al., 2004). Slentz and colleagues (2005), reported a significant increase in total abdominal fat, visceral fat and body weight following six months of inactivity in a control group, highlighting the ill-effects of sedentary behaviour over a relatively short period of time.

Aerobic exercise is also associated with improvements in cardiometabolic biomarkers in the absence of weight loss, most notability in insulin sensitivity. Skeletal muscle is the primary site for glucose disposal in the body. Two key pathways are involved in stimulating glucose transport to the skeletal muscle; the phosphatidylinositol 3 kinase pathway, which is stimulated by insulin and IGFs, and the 5'AMP-activated kinase (AMPK) pathway which is activated in response to muscle contraction or hypoxia (Golbidi et al., 2012, Henriksen, 2002). This latter pathway describes the effects of an acute bout of aerobic exercise on insulin action (Lakka and Laaksonen, 2007). Ultimately, both the phosphatidylinositol 3 kinase and the 5'AMPK pathways result in increased translocation of the glucose isoform 4 (GLUT-4) protein from within the skeletal muscle cell to the plasma membrane. The GLUT-4 protein is one of the key enzymes involved in glucose metabolism, and the translocation to the cell surface characterises one of the key regulatory steps in glucose uptake in skeletal muscle (Henriksen, 2002, Golbidi et al., 2012). Translocation of GLUT-4 occurs in response to peroxisome proliferator-activated receptor *y* coactivator-1, which is expressed in skeletal muscle in response to exercise (Golbidi et al., 2012, Goodyear and Kahn, 1998). In this way, acute aerobic exercise can improve glucose disposal and uptake through pathways that are independent of insulin. This is of particular importance in individuals with impaired insulin-action due to obesity (Goodpaster et al., 2003), those with T2DM (Dela et al., 1995) or

impaired glucose tolerance (Hughes et al., 1993) and can also protect against the development of T2DM (Goodyear and Kahn, 1998).

Despite the strong physiological background, trials examining the effect of continuous aerobic training on insulin sensitivity have yielded mixed results. Frank and colleagues (2005) reported a significant reduction in fasting insulin and insulin resistance (HOMA-IR) following 12 months moderate intensity (60-75% HRmax) aerobic training. These changes occurred in conjunction with significant decreases in total abdominal fat, visceral fat and subcutaneous abdominal fat. In contrast, others have reported no change in insulin, glucose or insulin resistance despite significant changes in anthropometric variables, including abdominal adiposity, following moderate-to-vigorous training in overweight sedentary women (Ross et al., 2004, Arsenault et al., 2009, Polak et al., 2006). Similar results are reported for other cardiometabolic markers. Decreases in inflammatory markers (mainly CRP) are reported in some (Friedenreich et al., 2012, Campbell et al., 2009) but not all (Arsenault et al., 2009, Devries et al., 2008) aerobic interventions in overweight sedentary women. While all interventions prescribed moderate intensity aerobic exercise, only those of 12 month duration yielded significant results, supporting the suggestion that total volume of exercise is critical. Equally aerobic interventions of longer duration (12 months) appear necessary to stimulate change in adipokines (leptin and adiponectin), with shorter duration interventions having little effect (Frank et al., 2005, Devries et al., 2008, Arsenault et al., 2009).

Over the past decade there has been increasing evidence that resistance training (strength training) is associated with a lower incidence of the MetSyn (Jurca et al., 2005) and reduced all-cause mortality (Ruiz et al., 2008). Resistance exercise is associated with improvements in body composition such as increased muscle mass (Benton et al., 2011a, Olson et al., 2007), increased muscle strength (Rabelo et al., 2011) and a loss of body fat (Bryner et al., 1999, Schmitz et al., 2002) and therefore is recommended for the management of sarcopenia (Benton et al., 2011b). Isometric muscle contraction stimulates activation of the 5'AMPK pathway as observed with aerobic training and thus can enhance insulin sensitivity (Henriksen, 2002). In addition, muscle hypertrophy creates a greater area within the body for glucose disposal (LeBrasseur et al., 2011). Resistance training also results in an increase in RMR (Bryner et al., 1999). Despite this, interventions based solely on resistance training in

overweight sedentary women have not yielded positive alterations in markers of insulin resistance, despite favourable increases in muscle mass and reductions in body fat (Olson et al., 2007, Schmitz et al., 2002). Combined resistance and aerobic training programmes have demonstrated superior improvements in glycaemic control in individuals with T2DM when compared to either aerobic or resistance training alone (Sigal et al., 2007, Church et al., 2010). While resistance training has not been examined in relation to breast cancer risk and prognosis it may be a useful adjuvant to aerobic programmes targeting biomarkers of breast cancer risk.

1.5.1 Systematic Literature Review

Statement of Author's Contribution

The idea for this review was developed by the student Emer Guinan (EG) and supervisor Dr. Juliette Hussey (JH). The search protocol was developed by EG. The search was completed initially by EG and verified by JH. Data analysis and interpretation was completed by EG. Co-supervisor Ms. Elizabeth Connolly (EC) provided medical advice regarding interpretation of the data. EG was responsible for drafting section 1.5.1 and the subsequent published manuscript and invited response to expert commentary. All authors approved the final version of the published manuscript.

The following section provides a systematic review of the literature examining the impact of exercise training on the above discussed metabolic biomarkers of breast cancer risk specifically in breast cancer survivors.

This literature review has been published in Physical Therapy Reviews (Appendix II).

Guinan, E.M., Connolly, E.M., Hussey (2013). Exercise training in breast cancer survivors: a review of trials examining anthropometric and obesity-related biomarkers of breast cancer risk. Physical Therapy Reviews, 18 (2), 79-89

A commentary on the review by Campbell and Neil (2013)and an invited response to this commentary have also been published in Physical Therapy Reviews (Appendix II).

While there is strong epidemiological evidence to support a role for physical activity in improving breast cancer-related outcomes (section 1.4.4) and also evidence of associations between physical activity and a number of recognised biomarkers of breast cancer risk (section 1.5), exercise interventions with biomarkers as end-points are required to fully elucidate the role of physical activity in modifying these variables and establish information on dose-response. Should such interventions be effective, they may convey the benefits of improved survival and reduced risk of recurrence. Exercise interventions have been shown to improve many recognised biomarkers of breast cancer risk in similar of populations (section 1.5) however the value of such interventions in breast cancer survivors is not fully understood.

Breast cancer survivors are a unique group and face challenges to exercise, which may not be applicable to other cohorts, including weight gain and changes in body composition following adjuvant therapy (Demark-Wahnefried et al., 2001b), low physical activity levels (Irwin et al., 2004, Courneya et al., 2008b), side-effects of ongoing hormone therapy including joint pain or menopausal symptoms (Mouridsen et al., 2003), early menopause (Goodwin et al., 1999b), persistent cancer-related fatigue (Berger et al., 2012), reduced arm/shoulder mobility (Hayes et al., 2010) and psychological challenges related to alterations in body image (Hormes et al., 2008). A recent systematic review by Ballard-Barbash and colleagues (2012) concluded that physical activity was associated with reduced all-cause and breast cancer specific mortality and that exercise interventions may have a role in improving biomarkers of cancer risk among a range of cancer survivor populations, with particular emphasis on disease outcome. The current systematic review aims to expand on the conclusions of Ballard-Barbash et al., (2012) by focusing on the physical activity parameters prescribed by exercise interventions to stimulate changes in cancer risk biomarkers and anthropometric variables, specifically in breast cancer survivors.

1.5.1.1 Methods

Eligibility Criteria

Studies which examined the effects of exercise interventions in patients with breast cancer who had completed all adjuvant treatment and were showing no signs of recurrent or progressive disease were reviewed. Studies where participants continued to take endocrine therapy during the intervention period were included. Studies were considered if they included a structured exercise programme based on aerobic and/or resistance exercise, fully-supervised, partially supervised or non-supervised. Interventions where another intervention

type such as diet or pharmacological interventions were combined with exercise were excluded. Exercise interventions which included non-specific exercise protocols based on stretching, Tai Chi, yoga or dance were excluded. Due to the small number of published studies both randomised and non-randomised trials of exercise training were included.

Studies evaluating the effect of exercise on obesity-related biomarkers of breast cancer risk were considered for inclusion. This included anthropometric measures (BMI, percentage body fat (%BF), waist circumference), inflammatory markers and adipokines (CRP, IL-6, TNF-α, leptin, adiponectin) and markers of insulin resistance (insulin, glucose, insulin resistance, IGFs, IGFBPs). These biomarkers were chosen because as discussed above (section 1.5), they have been identified as being involved in the biological mechanisms linking physical activity to breast cancer development and progression. Markers of immune function such as natural killer cells, macrophages and neutrophils were not included for review. Although these biomarkers are associated with long-term breast prognosis, immunosuppression in cancer survivors results as a direct effect of anti-cancer therapies and is therefore not considered an obesity-related biomarker (Fairey et al., 2002).

Search Strategy

The preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines were adhered to when conducting this review. Studies were identified through a comprehensive electronic search using the databases PubMed, Embase, SciVerse, the Cochrane Library, AMED and PEDro.

The following search algorithm was used to identify potentially suitable articles: ((("breast cancer" [Title/Abstract] OR "breast cancer patient" [Title/Abstract] OR "breast cancer survivor" [Title/Abstract] OR "cancer survivor" [Title/Abstract] OR "cancer survival" [Title/Abstract]) AND ("biomarker" [Title/Abstract] OR "body mass index" [Title/Abstract] OR "body fat" [Title/Abstract] OR "waist circumference" [Title/Abstract] OR "waist to hip ratio" [Title/Abstract] OR "glucose" [Title/Abstract] OR "insulin" [Title/Abstract] OR "insulin-like growth factor" [Title/Abstract] OR "insulin resistance" [Title/Abstract] OR "c-reactive protein" [Title/Abstract] OR "tumor necrosis factor" [Title/Abstract] OR "interleukin" [Title/Abstract]

OR "adipokine" [Title/Abstract] OR "adiponectin" [Title/Abstract] OR "leptin" [Title/Abstract] OR "inflammation"[Title/Abstract]) AND ("exercise training" [Title/Abstract] OR "aerobic exercise" [Title/Abstract] OR "aerobic training" [Title/Abstract] OR "resistance training" [Title/Abstract] OR "resistance exercise" [Title/Abstract] OR "endurance training" [Title/Abstract] OR "endurance exercise" [Title/Abstract] OR "physical activity" [Title/Abstract] OR "intervention" [Title/Abstract])))). Sex hormones including estrogens, androgens and sex hormone binding globulin were included in the initial search, however as no interventions were identified these terms were removed from the algorithm. In addition, a manual search of the reference lists of associated reviews and relevant articles was conducted (Ballard-Barbash et al., 2012, Neilson et al., 2009). All applicable articles published in the English language up until March 2013 were considered for inclusion. Searches were carried out by one reviewer (Emer Guinan) who assessed potential studies against inclusion criteria. The search strategy was repeated and verified by a second reviewer (Juliette Hussey).

Quality Assessment

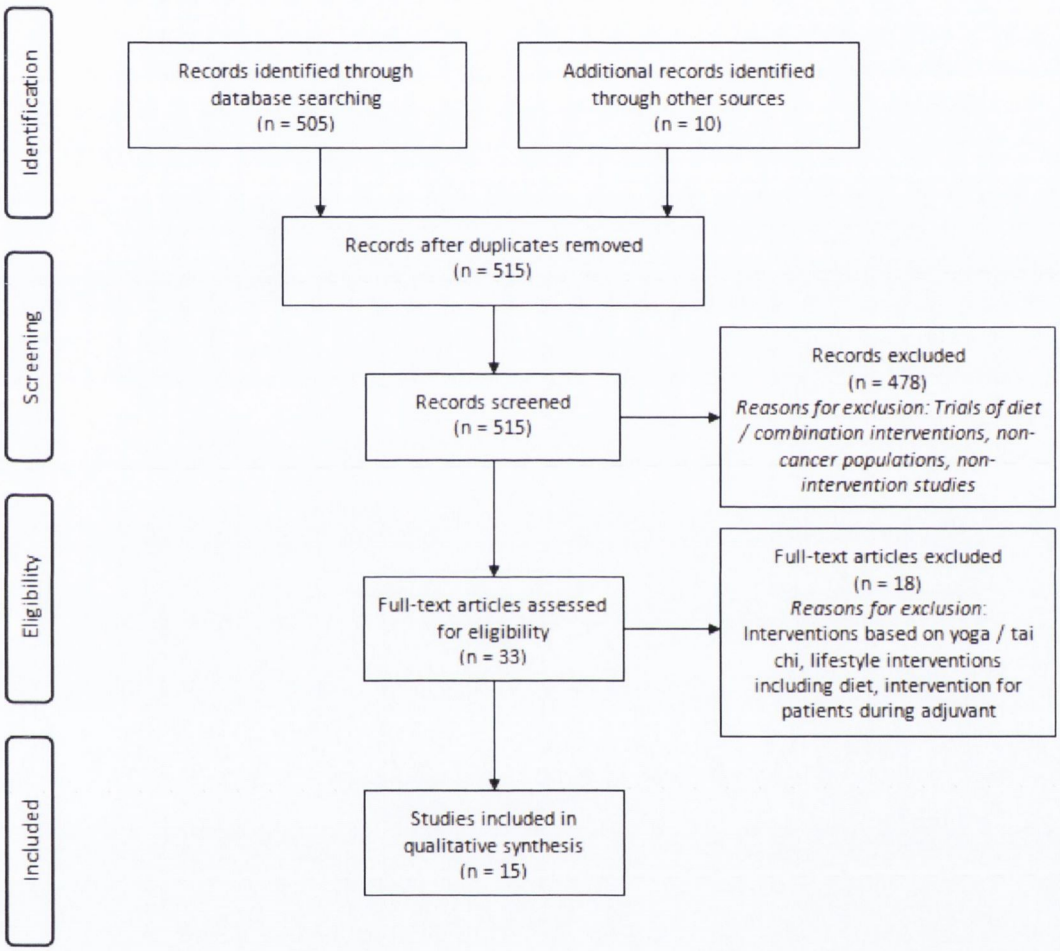
The methodological quality of RCTs included for review was assessed using the PEDro scale, a valid measure of methodological quality used for clinical trials (de Morton, 2009). The scale, which is based on the Delphi list, contains 11 criteria for quality assessment. Two criteria relating to blinding subjects and therapists were not considered for this review as it is impossible to blind these groups to treatment provided in this area of research. Therefore nine of the eleven criteria were evaluated. A score >6 indicates good methodological quality and a score >9 indicated excellent methodological quality.

1.5.1.2 Results

The search strategy identified 515 potentially suitable articles. When inclusion and exclusion criteria were applied a total of fifteen articles representing nine interventions remained for inclusion, including seven RCTs (Courneya et al., 2003, Fairey et al., 2003, Fairey et al., 2005a, Fairey et al., 2005b, Schmitz et al., 2005, Herrero et al., 2006, Payne et al., 2008, Ligibel et al., 2008, Ligibel et al., 2009b, Irwin et al., 2009a, Irwin et al., 2009b, Rahnama et al., 2010, Nuri et al., 2012) and two non-randomized trials (Cheema and Gaul, 2006, Knobf et al., 2008) (Figure 6). Four RCTs had multiple publications included for review: The *Rehabilitation Exercise for Health after Breast Cancer* (REHAB) trial had four (Courneya et al., 2003, Fairey et al., 2003, Fairey et al., 2005b, Fairey et al., 2005a) and The *Yale Exercise and Survivorship* (YES) study

(Irwin et al., 2009a, Irwin et al., 2009b, Jones et al., 2013) had three and the RCT by Ligibel and colleagues (Ligibel et al., 2008, Ligibel et al., 2009b) had two. Publications by Rahnama et al., (2009) and Nuri et al., (2012) both refer to the same intervention.

Figure 6 PRISMA Diagram



Methodological Quality

Quality scores are presented in Table 3. The mean quality score for the seven RCTs was 7.1, with two studies adhering to all nine criteria (Courneya et al., 2003, Irwin et al., 2009a). The main shortcomings were follow-up assessments completed on <85% of participants, and subsequently a failure to use intention-to-treat analysis.

Table 3 Methodological Quality of Randomised Controlled Trials Reviewed (PEDro Scale)

	Eligibility	Random Allocation	Concealed Allocation	Similar at Baseline	Blinding of Assessors	Measures from >85%	Intention-to-treat analysis	Between group comparison	Measures of variability	Total Items reported
REHAB Trial Courneya et al., (2003) Fairey et al., (2003) Fairey et al., (2005a) Fairey et al., (2005b)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9**
Schmitz et al., (2005)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	**8**
Herrero et al., (2006)	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	**7**
Payne et al., (2008)	Yes	Yes	No	Not reported	No	Yes	No	Yes	Yes	**5**
Ligibel et al., (2008) Ligibel et al., **(2009a)**	Yes	Yes	No	Yes	No	No	No	Yes	Yes	**5**
YES Study Irwin et al., (2009a) Irwin (2009b) Jones et al., (2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9**
Rahnama (2010) Nuri et al., (2012)	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	**7**

Study Designs and Participants

All seven RCT's compared an exercise group (EG) to a non-exercising control group (CG). Non-randomized trials included an EG only. Results were reported from pre- and post-treatment assessments. No trial included long-term follow-up. Breast cancer stage was reported in all trials and ranged from *In Situ* cancer (stage 0) to stage IIIb. All participants were post adjuvant treatment including chemotherapy and/or radiotherapy. In two studies all participants were taking hormone therapy during the interventions (Payne et al., 2008, Rahnama et al., 2010, Nuri et al., 2012) while in seven other studies (Knobf et al., 2008, Cheema and Gaul, 2006, Schmitz et al., 2005, Ligibel et al., 2008, Irwin et al., 2009a, Courneya et al., 2003, Fairey et al., 2003, Fairey et al., 2005a, Fairey et al., 2005b, Ligibel et al., 2009b) varying percentages of participants were taking hormone therapy. Herrero et al., (2006) did not describe endocrine therapy use. While the majority of studies included participants who were within five years of diagnosis, this ranged from 0.8 to 22.0 years post diagnosis (Cheema and Gaul, 2006) and 0.45 to 28.5 years post diagnosis (Ligibel et al., 2009b) in two studies. Mean time since diagnosis or treatment was not described by two studies (Rahnama et al., 2010, Payne et al., 2008).

Menopausal status was described by all studies. Six studies included postmenopausal women only (Courneya et al., 2003, Irwin et al., 2009a, Herrero et al., 2006, Knobf et al., 2008, Rahnama et al., 2010, Payne et al., 2008, Fairey et al., 2003, Fairey et al., 2005a, Fairey et al., 2005b, Irwin et al., 2009b, Nuri et al., 2012) while in the remaining trials the majority [81.5% (Schmitz et al., 2005), 92.6% (Cheema and Gaul, 2006), 85% (Ligibel et al., 2008, Ligibel et al., 2009b)] of participants were postmenopausal. Baseline BMI was reported in seven trials (Herrero et al., 2006, Knobf et al., 2008, Rahnama et al., 2010, Courneya et al., 2003, Ligibel et al., 2008, Schmitz et al., 2005, Irwin et al., 2009a, Fairey et al., 2003, Fairey et al., 2005a, Fairey et al., 2005b, Ligibel et al., 2009b, Irwin et al., 2009b, Nuri et al., 2012). In these trials the majority of participants were overweight (BMI 25-29.4 $kg.m^{-2}$) or obese (BMI $\geq$30 $kg.m^{-2}$).

Baseline physical activity levels were described in six studies (Courneya et al., 2003, Ligibel et al., 2008, Schmitz et al., 2005, Herrero et al., 2006, Irwin et al., 2009a, Irwin et al., 2009b, Fairey et al., 2003, Fairey et al., 2005a, Fairey et al., 2005b, Ligibel et al., 2009b) with three studies stating sedentary behaviour as an inclusion criterion (Ligibel et al., 2008, Herrero et al., 2006, Irwin et al., 2009a, Ligibel et al., 2009b, Irwin et al., 2009b). In all other studies,

participants spent the majority of time in sedentary or light intensity activity prior to study entry. One study recruited participants from an all-breast cancer survivor dragon boat team (Cheema and Gaul, 2006). While baseline physical activity levels were not reported, it is reasonable to assume that this cohort was more physically conditioned than other groups reviewed.

Exercise Interventions

Exercise interventions are described in Table 4. Nine of the ten programmes involved aerobic exercise, either alone or in combination with resistance training (Knobf et al., 2008, Rahnama et al., 2010, Courneya et al., 2003, Ligibel et al., 2008, Cheema and Gaul, 2006, Herrero et al., 2006, Irwin et al., 2009a, Nuri et al., 2012). Schmitz et al., (2005) prescribed resistance training only. At least one element of exercise training was supervised in all programmes with the exception of that by Payne et al., (2008), who prescribed a home-based walking programme. Home-based aerobic programmes were also prescribed by Cheema and Gaul (2006), Ligibel and colleagues (Ligibel et al., 2008, Ligibel et al., 2009b) and Irwin and colleagues (Irwin et al., 2009a, Irwin et al., 2009b). Adherence was monitored using heart rate monitors (Irwin et al., 2009a, Ligibel et al., 2008), pedometers (Ligibel et al., 2008), exercise logs (Ligibel et al., 2008, Irwin et al., 2009a, Payne et al., 2008) and manual pulse (Cheema and Gaul, 2006).

Exercise intensity increased progressively throughout each aerobic intervention to a moderate-to-vigorous aerobic intensity (80% HRmax)[4] with the exception of one study with an upper limit of 65% HRmax (Nuri et al., 2012, Rahnama et al., 2010). Aerobic intensity in the walking programme by Payne et al., (2008) was described as "moderate", however no specific intensity was described. Unsupervised home programmes required participants to exercise at an intensity equivalent to that in the supervised class (Irwin et al., 2009a) or to prescribed target heart rate zones (Cheema and Gaul, 2006, Ligibel et al., 2008). Resistance training progressed similarly throughout sessions, with arm lymphedema dictating progression of upper limb exercises (Schmitz et al., 2005). Participants trained at either 80% or 100% 1RM over 10-14 repetitions (Cheema and Gaul, 2006, Schmitz et al., 2005, Herrero et al., 2006, Ligibel et al., 2008, Rahnama et al., 2010, Ligibel et al., 2009b, Nuri et al., 2012).

[4] See Table 4 for individual programme aerobic intensity prescription and progression

Table 4 Description of Exercise Interventions

Authors	Design	Participants	Description of Intervention	Outcomes	Adherence	Results
REHAB Trial Courneya et al., (2003) Fairey et al., (2003) Fairey et al., (2005a) Fairey et al., (2005b)	RCT	Overall: n=53 EG: n=25, mean age 59(5) years CG: n=28, mean age 58.6(6) years. Time post rx: 14(6) months.	15-week , three times weekly supervised aerobic intervention. Exercise intensity set at 70-75% VO_2max. Class duration commenced at 15 minutes (weeks 1-3), increasing by 5 minutes every 3 weeks to 35 minutes (weeks 13-15). CG received usual care	BMI %BF Insulin Glucose HOMA-IR IGFs IGFBPs CRP IL-6 TNF-α	EG completed 44.3/45 (98.4%) of prescribed sessions.	Significant decrease in IGF-I (p=0.05), increase in IGFBP-3 (p=0.02) and decrease in the IGFI:IGFBP3 molar ratio (p=0.02). No other significant findings; BMI (p=0.33), %BF (p=0.095), insulin (p=0.94), glucose (p=0.82), HOMA-IR (p=0.25), IGF-II (p =0.10), IGFBP-1 (p =0.77), CRP (p=0.07), IL-6 (p-value NR) or TNF-α (p-value NR)
Schmitz et al., (2005)	RCT	Overall: n=85 EG: n=42, mean age 53.3(8.7) years, CG: n=43, mean age 52.8(7.6) years. Time post rx: 18-24 months.	6 month, twice weekly, progressive resistance programme; months 1-3 supervised and months 3-6 unsupervised. Upper body exercises started with no weight or 0.5lb and progressed as symptoms allowed. Lower limb exercises were prescribed at 8-10 repetitions of 1RM, building up to three sets before progressing. Sessions lasted 60 minutes. CG served as a delayed treatment group.	BMI %BF WC Glucose Insulin HOMA-IR IGFs	EG completed 92% of supervised classes and adhered to 66% of HEP	Significant decrease IGF-II (p=0.02) and %BF (DEXA) (p=0.03) and significant increase in lean body mass (p=0.008). No other significant findings groups; BMI (p=0.77), WC (p=0.22), glucose (p=0.17), insulin (p=0.46), HOMA-IR (p=0.78), IGF-I (p=0.64), IGFBP-1 (p=0.47), IGFBP-2 (p=0.89), IGFBP-3 (p=0.32).
Cheema and Gaul, (2006)	Non-RCT	n=27, Mean age 57.7(7.2) years, Mean time post rx: 5.2 (range 0.8-21 years).	8-week aerobic and resistance programme. Supervised resistance training weeks 1-2 and weeks 5-8. 8-12 repetition of 1RM to a max of 3 sets. Unsupervised aerobic sessions at an intensity of 65-85% HRmax. Duration progressed from 15 minutes (weeks 1-2) to 30 minutes (weeks 7-8).	%BF WC	99.1 (2.9)% to resistance training, 97.1±6.5% to aerobic training.	Significant decrease in %BF (skinfolds) (p<0.01) and WC (p<0.01). There was no change in body weight (p-value NR).

Authors	Design	Participants	Description of Intervention	Outcomes	Adherence	Results
Herrero et al., (2006)	RCT	Overall: n=16 EG: n=8, mean age50(5) years CG: n=8, mean age 51(10) years. Time post rx: EG: 36(13); CG: 35(12) months	Supervised 8-week, three times weekly, aerobic and resistance programme. Resistance training incorporated 11 exercises at 12-15 repetition of 1RM, to a maximum of 3 sets. Aerobic training was performed for 20 minutes at 70% HRmax progressing to 30 minutes at 80% HRmax. CG received usual care	BMI %BF	Mean adherence in the EG was 91.1 (6.9)%	Significant decrease in %BF (skinfolds) between groups ($p<0.05$). No change in BMI (p-value NR).
Knobf et al., (2008)	Non-RCT	n=26 Mean age 51.3(6.2) years. Time post rx: NR	16-24 week, three times weekly, supervised treadmill programme using a weight belt and backpack. Training commenced with 10-20 minutes walking at a self-selected intensity with a 1lb weight loading and progressed to 45 minutes at 65-75% HRmax with a 5lb weight loading.	%BF	Mean adherence 88.2 (6.8)%	No changes in % BF (DEXA) ($p=0.14$), lean body mass ($p=0.08$) or body weight ($p=0.59$).
Payne et al., (2008)	RCT	n=20,mean age 64.7(6.3) years EG: n=10 CG: n=10 Time post rx: NR	14 week, four times weekly walking intervention, 20 minutes in duration. Intensity described as "moderate". CG received usual care.	IL-6	NR	No significant differences between groups for changes in IL-6.
Ligibel et al., (2008) Ligibel et al., (2009a)	RCT	Overall: n=101, EG: n=51, mean age 52(9), CG: n=50, mean age 53(9). Time post diagnosis: EG : 8-223 months; CG: 5.4-342 months)	16-week resistance and aerobic programme. Supervised resistance training, twice weekly for 50 minutes. Intensity: 80% 1RM, 2-4 sets of 10 repetitions, progressing by 10% as able. Unsupervised aerobic exercise, target of 90 minutes.week^{-1} at 55-80% HRmax (HR monitor, pedometer and exercise logs). CG received routine care.	BMI %BF WC Insulin Glucose HOMA-IR Adiponectin Leptin	73% attendance classes and 114 min/week of aerobic exercise completed	No significant changes in BMI ($p=0.42$), %BF (DEXA) ($p=0.26$), WC ($p=0.06$), insulin ($p=0.07$), glucose ($p=0.47$), HOMA-IR ($p=0.09$), leptin ($p=0.76$), adiponectin ($p=0.59$) or HMWA ($p=0.22$).

Authors	Design	Participants	Description of Intervention	Outcomes	Adherence	Results
YES Study Irwin et al., (2009a) Irwin et al., (2009b) Jones et al., (2013)	RCT	Overall: n=75 EG: n=37, mean age 56.5(9.5) years; CG: n=38, mean age 55.1(7.7) years. Time post diagnosis: EG: 3.6(2.2); CG: 3.3(2.6) years.	6-month aerobic intervention; supervised three times weekly and home-based twice per week. Exercise duration commenced at 15 minutes and progressed to 30-minutes from week 5 to study completion. Exercise intensity commenced at 50% HRmax and progressed to 60-80% HRmax. Adherence to the HEP was monitored using activity logs. CG received usual care	BMI %BF WC Insulin IGF-I IGFBP-3 CRP IL-6 TNF-α	73% adherence to exercise protocol.	Significant decrease in in %BF (DEXA) (p=0.002), IGF-I (p=0.03) and IGFBP-3 (p=0.006). There were no changes in BMI (p=0.42), WC (p=0.57), insulin (p=0.09), CRP (p=0.73), IL-6 (p=0.91) or TNF-α (p=0.54)
Rahnama (2010) Nuri et al., (2012)	RCT	Overall: n=29 EG: n=14 CG: n=15 Mean age: NR Time post diagnosis: NR	15 week resistance and aerobic intervention. Supervised resistance training twice weekly for 60 minutes; three sets of 10 repetitions of 1RM weeks 1-5 progressing to 14 repetition weeks 11-15. Supervised walking programme twice weekly at an intensity of 45% HRmax for 25 minutes week one and progressing to 65% HRmax for 45 minutes by week 11. CG received usual care.	BMI WC (WHR) Glucose Insulin HOMA	91% adherence to exercise protocol	Significant decrease in BMI (p=0.022), WHR (p=0.001), fasting glucose (p<0.05) and fasting insulin (p<0.05) in the EG versus the CG. No change in HOMA-IR (p-value NR)

Data are presented as mean (standard deviation) for continuous variables and n (%) for categorical variables.

Abb: RCT = randomized controlled trial; EG = exercise group; CG = control group; rx = treatment; VO_{2max} = maximal oxygen consumption; BMI = body mass index; %BF = percentage body fat; HOMA-IR = homeostatic model assessment index – insulin resistance; IGFs = insulin-like growth factors; IGFBPs = insulin-like growth factor binding proteins; CRP = C – Reactive Protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor- α; NR = not reported; lb = pound; WC = waist circumference; DEXA = dual-energy X-ray absorptiometry; HEP = home exercise programme; RM = repetition maximum; HRmax = maximum heart rate. HMWA = high molecular weight adiponectin.

Effects of Exercise on Anthropometrics

Seven of the eight interventions reviewed measured the effect of exercise on anthropometric outcomes. A number of studies reported changes in %BF. Schmitz et al., (2005) reported a significant decrease in %BF following six months resistance training (EG mean change -1.15(0.45)%, CG mean change 0.23(0.44)%, p=0.03). Irwin and colleagues (2009a) also reported a reduction in body fat following six months moderate intensity aerobic training (EG mean change -1.9%, CG mean change 1.1%, p=0.002). Body fat was measured using dual energy x-ray absorptiometry (DEXA) in both trials. Herrero et al., (2006) reported an overall decrease in mean body fat of -2.0% (95% CI, -0.3% to -3.8%, $p<0.05$) while Cheema and Gaul (2006) reported a decrease of 11.7(17.0)% ($p<0.01$) in %BF among their EG following combined aerobic and resistance training. The two latter trials used the sum of skinfolds technique. No change in body fat was reported by any other trial using a range of measurement techniques including sum of skinfolds (Courneya et al., 2003), DEXA (Knobf et al., 2008) and bioimpedance analysis (Ligibel et al., 2008).

Three trials of combined resistance and aerobic exercise, of various durations (8-16 weeks), reported changes in body weight and waist/hip girth. The trial by Rahnama et al., (2010) was the only one to report a change in body weight (p=0.03) or BMI (p=0.02). This group also reported a significant decrease in waist-to-hip ratio (WHR) (EG changed from 0.98(0.07)m to 0.94(0.07)m, CG changed from 0.96(0.03)m to 0.96(0.04)m, p=0.001). Ligibel and colleagues (2008) reported a significant reduction in hip circumference (EG mean change -2.3(3.3)cm, CG mean change -0.5(3.3)cm, p=0.02) but no significant change in waist circumference (EG mean change -1.5(4.6)cm, CG mean change 0.3(3.8)cm, p=0.06). Cheema and Gaul (2006) reported a decrease in waist circumference in their exercising group (mean change -3.2(3.6)% $p<0.01$).

Effect of Exercise on Inflammation and Adipokines

Four interventions examined the effect of exercise on adipokines and inflammatory markers. No changes in any variables were reported. Fairey et al., (2005b) reported a no change in CRP following 15 weeks moderate-to-vigorous intensity aerobic training (EG mean change -1.39mg.L^{-1}, CG mean change 0.10mg.L^{-1}, p=0.07). The same trial reported no changes in either IL-6 or TNF-α (Fairey et al., 2005a). Similarly, Payne et al., (2008) reported no change in IL-6 following 14 weeks of a moderate intensity walking programme. Most recently, Jones et al.,

(2013) reported no change in IL-6 (EG mean change 0.04(1.32) $pg.mL^{-1}$, CG mean change 0.00(1.20) $pg.mL^{-1}$, p=0.91), CRP (EG mean change -0.08(0.74)) $mg.L^{-1}$, CG mean change -0.20(1.80) $mg.L^{-1}$, p=0.73) or TNF-α (EG mean change 0.02(0.22) $pg.mL^{-1}$, CG mean change 0.08(0.47) $pg.mL^{-1}$, p=0.54) following six months aerobic training. Ligibel and colleagues (2009b) reported no changes in either adiponectin (EG mean change -1.2(3.2)$\mu g.mL^{-1}$, CG mean change -1.3(6.1)$\mu g.mL^{-1}$, p=0.59), high-molecular weight adiponectin (EG mean change -1.6(3.2)$\mu g.mL^{-1}$, CG mean change -0.6(2.1)$\mu g.mL^{-1}$, p=0.22) or leptin (EG mean change 0.0(4.0)$ng.mL^{-1}$, CG mean change 0.5(2.9)$ng.mL^{-1}$, p=0.76) following 16 weeks of resistance and aerobic training.

Effect of Exercise on Markers of Insulin Resistance

Five RCTs examined the effect of exercise on markers of insulin resistance. Only one study reported a significant decrease in fasting glucose (9.1% decrease; $p<0.05$) and fasting insulin (14.1% decrease; $p<0.05$) but no change in HOMA-IR following 15 week supervised aerobic and resistance training (Nuri et al., 2012). No changes were observed across any other trials for fasting glucose (Fairey et al., 2003, Schmitz et al., 2005, Ligibel et al., 2008), fasting insulin (Ligibel et al., 2008, Schmitz et al., 2005, Fairey et al., 2003, Irwin et al., 2009b) or insulin resistance as estimated by HOMA-IR (Fairey et al., 2003, Ligibel et al., 2008, Schmitz et al., 2005). Two moderate-to-vigorous intensity aerobic interventions reported significant decreases in IGF-I (Fairey et al., (2003) EG mean change -4.9(10.7)$ng.mL^{-1}$, CG mean change 2.5(14.8)$ng.mL^{-1}$, p=0.05; and Irwin et al., (2009b) EG mean change -7.36(6.02)$ng.mL^{-1}$, CG mean change 12.7(6.39) $ng.mL^{-1}$, p=0.03). Conflicting results were reported by these studies for IGFBP-3 with Fairey and colleagues (2003) reporting a significant increase (EG mean change 103.4(224.7)$ng.mL^{-1}$, CG mean change -77.1(313.5)$ng.mL^{-1}$, p=0.02) while Irwin and colleagues (2009b) reported a significant decrease (EG mean change -0.19(0.08)$ng.mL^{-1}$, CG mean change 0.15(0.1)$ng.mL^{-1}$, p=0.01). Schmitz and colleagues (2005) reported a significant decrease in IGF-II (EG mean change -26.23(16.73)$ng.mL^{-1}$, CG mean change 28.28(16.31)$ng.mL^{-1}$, p=0.02) following six months resistance training.

1.5.1.3 Discussion

This review summarises the evidence from exercise trials examining the effect of exercise interventions on anthropometric variables and related biomarkers of cancer risk in breast cancer survivors. The review highlights the extensive gaps that exist in the literature with regards to this topic. While improvements in body composition parameters, including decreased %BF and circumferential measures and changes in IGF-I, IGF-II and IGFBP-3 have been described by some studies, the majority failed to demonstrate significant changes. The conclusions of this review are similar to two others also published in 2012 (Ballard-Barbash et al., 2012, Lof et al., 2012).

Physical activity is hypothesised to protect against breast cancer through alterations in several obesity-related pathways (Neilson et al., 2009, Ballard-Barbash et al., 2012) and therefore there is a need to investigate the effects of structured exercise interventions on these outcomes to understand the potential of physical activity as an adjuvant to breast cancer therapy. This review identified six RCTs and two non-randomized trials evaluating the effect of exercise on various anthropometric variables including body weight, BMI, %BF and waist circumference. Significant decreases in %BF were reported by three RCTs following aerobic (Irwin et al., 2009a), resistance (Schmitz et al., 2005) and combined aerobic / resistance (Herrero et al., 2006) training. Cheema and Gaul (2006) also reported a decrease in %BF however their results should be interpreted with caution due to the non-randomized design and use of sum of skinfolds technique, as opposed to DEXA, to estimate body fat. In general, BMI and body weight remained stable throughout the interventions with only Rahnama et al., (2010) reporting changes. Despite decreases in %BF, minimal changes were reported in central fat stores as measured by either waist circumference or WHR. Abdominal fat may be a more important anthropometric target than total body fat due to the metabolic properties of visceral fat tissue (section 1.3.1). In non-breast cancer survivor populations significant reductions in abdominal fat stores have been reported with moderate intensity aerobic exercise (Irwin et al., 2003b, Slentz et al., 2005, Ross et al., 2004).

Six trials have measured the effect of exercise on metabolic biomarkers in this cohort. Outcomes included inflammatory markers (Fairey et al., 2005b, Payne et al., 2008, Jones et al., 2013), adipokines (Ligibel et al., 2009b) and measures of glucose metabolism (Ligibel et al., 2008, Fairey et al., 2003, Irwin et al., 2009, Schmitz et al., 2005, Nuri et al., 2012)). Only one trial reported significant reduction in fasting glucose and fasting insulin (Nuri et al., 2012). Surprisingly, this trial did not report any change in HOMA-IR. HOMA-IR is calculated as a product of glucose and insulin and therefore changes in the former could be expected to result in an overall reduction in HOMA-IR.[5] All other trials reported null results.

The potential explanations for an overall lack of change in metabolic parameters remains to be established however insufficient reductions in adiposity and inadequate trials length are two possibilities. As adipokines are derived almost exclusively from the adipose tissue a reduction in body fat, particularly in central fat, may be required to stimulate change. Studies in non-breast cancer populations have reported significant decreases in leptin (Frank et al., 2005, Friedenreich et al., 2011), IL-6 (Campbell et al., 2009) and CRP (Campbell et al., 2009) and a significant increase in the leptin/adiponectin ratio (Friedenreich et al., 2011) following 12 months high intensity aerobic exercise in overweight postmenopausal women. These groups also experienced a significant decrease in BMI, %BF and central adiposity. Similarly, improvements in insulin (Frank et al., 2005, Friedenreich et al., 2011), insulin resistance (Frank et al., 2005, Friedenreich et al., 2011) and insulin sensitivity (Slentz et al., 2005) have been reported in healthy cohorts with associated improvements in anthropometric outcomes. Among the trials reviewed examining metabolic outcomes, only one reported a reduction in adiposity (Jones et al., 2013). While moderate-to-vigorous intensity exercise alone may improve insulin sensitivity in non-cancer populations, exercise combined with fat-loss is most effective in this regard (Lamarche et al., 1992, Ross et al., 2004) and should be the target for future trials in breast cancer survivors. The interventions described in the trials reviewed spanned from eight weeks to six months in duration. As discussed in section 1.5, total volume of exercise may be an important determinant of the effectiveness of an intervention on metabolic variables. In general, aerobic interventions of at least 12 month duration are required for changes to occur (Frank et al., 2005, Friedenreich et al., 2011, Campbell et al., 2009).

[5] HOMA-IR provides an estimate of insulin resistance that is discussed in the Methods chapter, section 2.5.6.

The IGF-axis is another potential target for exercise to improve breast cancer outcomes. Significant decreases in IGF-I were reported by two aerobic interventions (Fairey et al., 2003, Irwin et al., 2009b). Similarly, decreases in IGF-II have been reported following resistance training (Schmitz et al., 2005). There was conflicting evidence regarding changes in IGFBP-3 (Fairey et al., 2003, Irwin et al., 2009b). It could be expected that increasing levels of IGFBP-3 would be beneficial as this would act to control bioavailability of IGF-I, however association between IGFBP-3 and breast cancer have been inconsistent (Rinaldi et al., 2006). The optimal exercise prescription required to alter these proteins has not been fully established (Friedenreich et al., 2011, Arikawa et al., 2010). The clinical significance of the findings from this review regarding the effect of exercise on the IGF-axis is unclear. As research in this area continues, the IGF-axis may become an important target for intervention.

Few studies examined change in habitual physical activity levels following intervention. Inactivity at baseline was a requirement for three programmes (Ligibel et al., 2008, Herrero et al., 2006, Irwin et al., 2009a, Ligibel et al., 2009b, Irwin et al., 2009b) and all other trials stating that participants spent the majority of time inactive prior to study entry (exception: Cheema and Gaul, (2006)). Ligibel and colleagues (Ligibel et al., 2008, Ligibel et al., 2009b) and Irwin and colleagues (Irwin et al., 2009a, Irwin et al., 2009b) reported increases of 11 minutes.week^{-1} and 129 minutes.week^{-1} respectively versus baseline activity levels, however these values were self-reported and therefore do not account for inactivity or sedentariness. As discussed in section 1.4.5 above sedentary behaviour is a prominent characteristic in breast cancer survivors. Sedentary time is associated with an increase in abdominal fat (Slentz et al., 2005) and is associated with numerous metabolic and anthropometric breast cancer risk factors (Lynch et al., 2011a, Lynch et al., 2010). Future trials should endeavour to include an accurate measure of change in physical activity following intervention, such as accelerometry, which could objectively measure sedentary time in addition to moderate-to-vigorous intensity activity.

Overall, trials reviews were high quality RCTs (section 1.5.1.2). Small sample sizes (16-101 participants) may have however resulted in insufficient power to detect changes. Only three trials calculated sample size using power analysis (the REHAB trial (Courneya et al., 2003, Fairey et al., 2003, Fairey et al., 2005a, Fairey et al., 2005b), the YES study (Irwin et al., 2009a,

Irwin et al., 2009b, Jones et al., 2013) and Ligibel and colleagues (Ligibel et al., 2008, Ligibel et al., 2009b)). Similar trials in non-breast cancer cohorts have included between 170-310 women (Frank et al., 2005, Irwin et al., 2003b, Slentz et al., 2005, Friedenreich et al., 2011). Multiple variables were examined in all studies however statistical correction for multiple comparisons was not considered, thus increasing the risk of type I error. Furthermore, no trial included long-term follow-up of participants. The importance of the reviewed interventions lies in their potential for improving long-term breast cancer prognosis and therefore an evaluation of how the benefits of exercise interventions are maintained following programme completion is crucial.

While most studies included participants within five years of diagnosis, this extended to almost thirty years in some trials (Cheema and Gaul, 2006, Ligibel et al., 2008, Ligibel et al., 2009b). It may be more clinically relevant to involve a group who are at a similar survivorship-point to control for factors such as hormone therapy use or cancer-related fatigue which may resolve as survivorship progresses. The timing of an intervention in relation to diagnosis may also be important in terms of the build-up to the moderate-to-vigorous intensity activity necessary to result in meaningful improvements in the biomarkers studied. Survivors in the acute stage post treatment may require a more gradual introduction to high intensity exercise, while long-term survivors may be able to cope with higher intensity activity from an earlier stage. There is a need for trials in the early phase after breast cancer treatment. Early intervention may prevent weight gain, improve biomarker profiles and have a greater impact on survival than an intervention completed later into survivorship.

1.5.1.4 Conclusion

While there is evidence that exercise interventions can exert a positive influence on %BF, IGFs and IGFBPs in breast cancer survivors, gaps remain to fully elucidate the optimum exercise dose in terms of programme length or frequency for changes in anthropometric and related cancer biomarkers. The correct timing of an intervention in relation to breast cancer diagnosis remains to be established. Interventions occurring early in survivorship have the benefit of reducing the risk of developing long-term sedentary habits and weight gain however such interventions may be confounded by treatment-related side-effects limiting the ability of survivors to exercise at the higher intensity aerobic levels needed to bring about significant changes in biomarkers of breast cancer risk.

Biological Mechanisms linking Physical Activity to Breast Cancer - Summary

A number of biological pathways, including anthropometrics, inflammation, insulin resistance, sex hormones and IGFs, have been proposed which are hypothesised to explain the link between physical activity and breast cancer.

Observational studies have demonstrated significant relationships between moderate-to-vigorous intensity physical activity and sedentary time with selected biomarkers of breast cancer risk in healthy postmenopausal women and breast cancer survivors.

Exercise interventions in healthy populations have demonstrated the positive effects of exercise on anthropometric variables and insulin sensitivity, however the volume of exercise performed appears critical.

A systematic review examining the effect of exercise interventions of known biomarkers of breast cancer risk in breast cancer survivors highlighted the paucity of data that is available in this regard.

1.6 Thesis Aims and Objectives

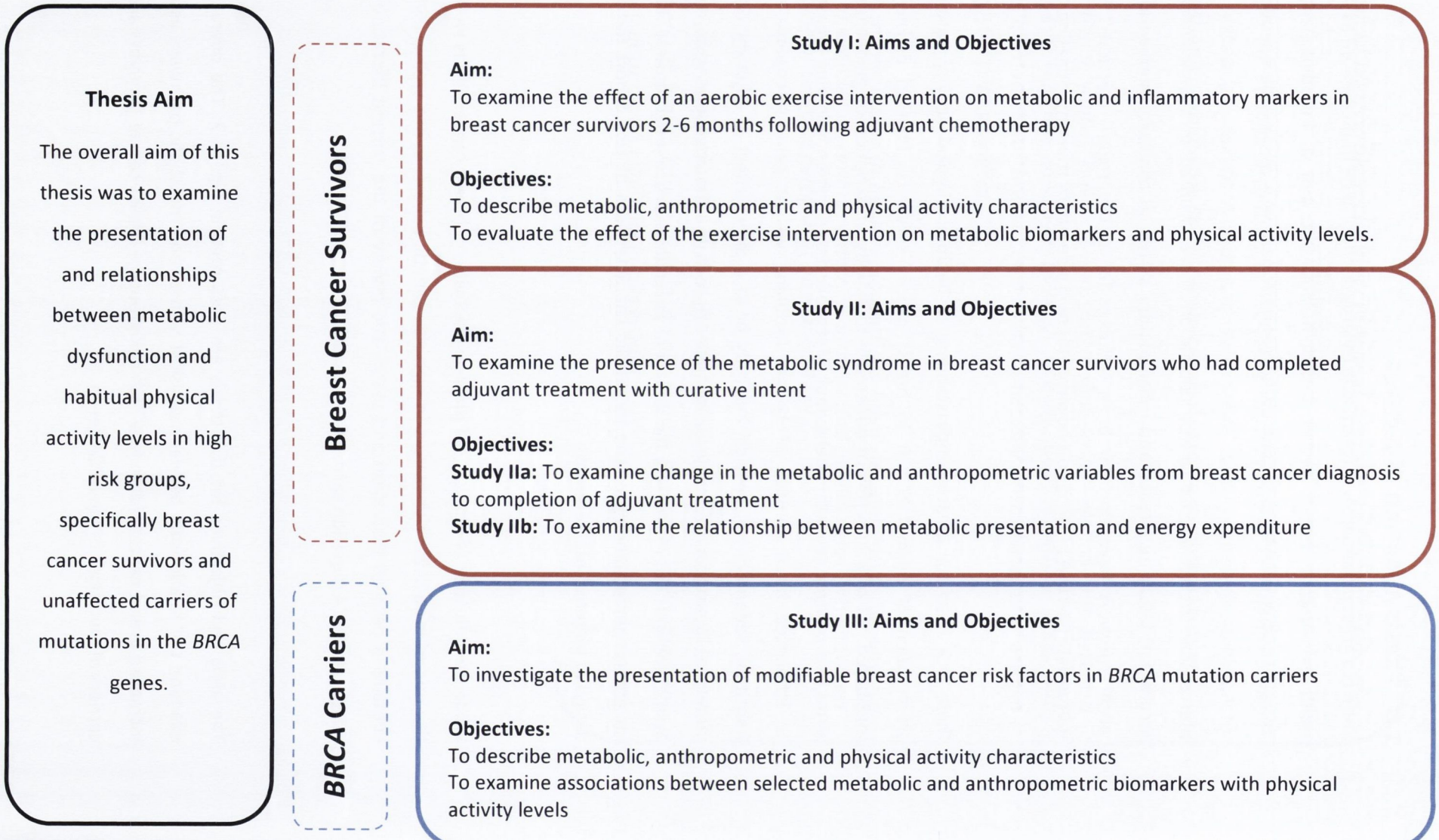
There is a great potential for physical activity programmes to be implemented as an adjunct to traditional adjuvant breast cancer treatment with the aim of improving morbidity and mortality outcomes. Metabolic and anthropometric pathways are key therapeutic targets and potentially surrogate markers for breast cancer prognosis. As discussed in section 1.5, exercise interventions in non-breast cancer populations have resulted in significant reductions in visceral fat, insulin resistance and inflammatory status. In contrast, interventions in breast cancer survivors have thus far been unsuccessful in this regard (section 1.5.1), despite appropriate exercise prescription however there is a dearth of trials investigating this issue.

There is a need for greater understanding of habitual physical activity patterns and the presentation of dysmetabolism in breast cancer survivors. Physical activity should be considered not only in terms of adherence to activity prescription or guidelines but also in terms of prolonged sedentary behaviour. Metabolic deterioration following breast cancer may be influenced by a number of factors including weight gain, sarcopenia, menopausal transition, sedentariness, physical inactivity or as a direct effect of adjuvant treatment and therefore breast cancer survivors do not represent a homogenous group in terms of dysmetabolism. This may affect the impact of potential exercise programmes. There is a need for greater understanding of the metabolic characteristics of this cohort for the potential design of targeted interventions.

While the influence of obesity and physical inactivity on breast cancer risk is well established, the role of modifiable risk factors in high risk genetic cohorts is not well known. Chapter 6 contains a detailed discussion and systematic review of the current literature available in relation to *BRCA* mutation carriers.

The aims and objectives for this thesis are presented in Figure 7. The overall aim was to examine the relationship between physical activity and metabolic pathways associated with increased breast cancer risk in two high risk groups – breast cancer survivors and unaffected carriers of mutations in the *BRCA* genes.

Figure 7 Thesis Aims and Objectives



Chapter 2 Methodology

2.1 Introduction

This chapter will describe the study designs, sampling methods, data analysis and background to assessments used in this thesis. A number of assessments are common to all studies and subsequent chapters will refer back to the relevant sections in this chapter when describing individual study methodologies.

2.2 Background Research Methods

2.2.1 Study Designs

Study designs that are commonly employed in clinical research include RCTs and observational studies. RCTs are considered the gold standard of clinical research allowing evaluation of a cause-effect relationship between treatment and outcome. Observational studies encompass a range of study designs including cohort studies, cross-sectional studies and case-control studies (Noordzij et al., 2009, Stel et al., 2007).

The RCT is considered the most reliable experimental design available for evaluation of therapy or intervention effects (Noordzij et al., 2009, Stel et al., 2007). Participants are randomly allocated to either experimental or control groups thereby preventing selection bias, and reducing the likelihood of systematic differences between groups in factors that may be known or unknown to the researcher (Fox et al., 2007). Various methods of randomisation are available including computer generated random lists or coin-tossing. Ideally, both the participant and the researcher should be "blind" to group allocation until study completion. Studies may be "single blind", where the assessor is unaware of the participant group allocation, or "double-blind", where neither the assessor nor the participants are aware of group assignment. Double-blinding may not be possible in some RCTs such as exercise trials. Blinding prevents systematic bias from the outcome assessor who may be inclined to assess participants differently if they are aware of group allocation.

There are a number of challenges associated with running RCTs. Practically RCTs are expensive to conduct due to the tight selection criteria, making recruitment a lengthy and taxing process. Pre-conceived participant preferences regarding group allocation, may affect adherence and drop-out rates, particularly with control groups. Ethically, it may not be appropriate to deny a control group treatment which could potentially be life-saving, despite the effectiveness of the treatment being unknown.

Cohort studies follow a selected study cohort over time to examine factors that may be associated with the development of a particular outcome (Stel et al., 2007, Mann, 2003). In this way, cohort studies define the natural history of the disease and identify potential causes or risk factors. They can be either prospective or retrospective in design. Prospective cohort studies examine potential causal factors for the development of disease and follow up the cohort over a period of time to examine those who develop the condition of interest and those who do not. Due to their long term nature these studies may take years to complete, risking loss of participants to follow up. Retrospective cohort studies do not have this issue. In a retrospective study data is collected for another reason prior to the study commencing and is re-examined in a post hoc fashion. While the study period may span a number of years, the time needed to collect and analyse the data is much shorter. This design also has the advantage of reducing bias or behaviour change in the study cohort as the outcome of interest has already occurred ("Hawthorn effect"), however as the study was not originally designed for this purpose, information may not have been collected in a stringent manner and there is increased change of statistical bias.

Cross-sectional studies provide information on variables of interest or features of disease at a single-point in time (Stel et al., 2007, Mann, 2003). While cross-sectional studies are most commonly employed to determine prevalence of a disease or risk factors in a population, they can also be used to examine associations between variables. In this way, cross-sectional studies can be hypothesis forming for RCTs which can then go on to rigorously test cause-effect interactions. They require minimal resources and compared to RCT designs they are quick and inexpensive, requiring no long-term follow up.

The foremost disadvantage of both cohort and cross-sectional studies is the potential influence of unknown confounding variables; a factor that affects both the outcome and the variable being tested. While statistical analysis can correct for known confounding variables, there are potentially an unlimited number of unknown confounding variables which could affect results. Selection bias is also an issue as sample being tested may not be representative of the overall population.

2.2.2 Sampling

In quantitative research it is important that sampling methods and sample size are adequate to ensure that findings are generalisable to the population and that statistical results can be detected. For a study to possess "external validity" the sample must be representative of the population, assuming that the study is designed to be generalised to the population and not specific of one sample (Fox et al., 2007). Testing all patients with a particular disease or clinical trait is usually impossible and expensive, unless the trait in question is particularly rare. Probability sampling is used to select a sample that is representative of the population under study without biasing results (Bland, 2000). A random sample is selected from a target population (e.g. unaffected *BRCA* mutation carriers) referred to as the sampling frame. Random sampling implies that every person within the sampling frame has an equal probability of being selected for participation in the study (Fox et al., 2007).

Probability sampling techniques include simple random sampling, systematic sampling and stratified random sampling. Simple random sampling involves randomly selecting the calculated sample of participants from the total population (Bland, 2000). Systematic sampling selects, assigns a number to everyone in the sampling frame and then systematically selects every participant at a fixed interval within the frame (e.g. every 10^{th} person). Stratified random sampling ensures that particular cohorts are represented within the sample selected by subdividing the population into strata prior to sampling and then random sampling within each strata is performed (Fox et al., 2007).

When probability sampling is not possible, non-probability sampling techniques can be used. Non-probability sampling methods are inherently biased as participants are not selected in a

random manner and therefore the degree to which they differ from the wider population is unknown (Bland, 2000). The most common type of non-probability sampling is convenience sampling, whereby recruitment for a study is completed based on participant availability until the target sample is reached. Another non-probability method that may be used is quota sampling, whereby the researcher decides in advance on certain characteristics that will be used to stratify the sample. In contrast to stratified random sampling, participants are not selected randomly within the strata and therefore findings cannot be generalised to the population (Fox et al., 2007, Bland, 2000). Purposive sampling involves the recruitment of a specific sample or specific individuals (Schreuder and Gregoire, 2001). While non-probability samples may not be representative of wider populations they can be useful for informing pilot or exploratory studies and may be required due to issues including expense or time constraints (Schreuder and Gregoire, 2001).

A key consideration with any investigation is the number of observations required to adequately test the hypothesis under investigation. Too many observations may lead to a waste of resources while too few will reduce the power of the study, making it impossible to detect true significant results (Suresh and Chandrashekara, 2012). There are two sources of error attributed to the inherent random variation associated with testing. Type I error occurs if the null hypothesis is rejected when in fact it is true. Conversely, type II error occurs when the null hypothesis is accepted when in reality it is false. When determining sample size the objective is to find a balance between the risk of either type I or type II error occurring .

A number of parameters must be considered when calculating sample size. Descriptive studies need large sample sizes to generate acceptable confidence intervals while experimental studies require less participants (Suresh and Chandrashekara, 2012). Studies examining outcomes based on categorical variables require larger sample sizes compared to those based on continuous outcomes. When calculating sample size a number of parameters need to be defined. The level of significance (α), defines the probability of type I error occurring (normally 0.05 or 0.01). A low significance level (e.g. 0.01) requires more study participants than a higher level. The variance or standard deviation is defined based on results from previous research. The effect size (δ) defines the minimal difference / change / relationship between two variables considered important to de detect. Both the significance level and the effect size are

estimated based on previous literature if available. The probability of type II error occurring (β) defines the power of the study, i.e. in other words β is the chance that the study will detect statistical change or results. Statistical power is usually defined at 80%. Other factors such as participant withdrawal from studies, loss to follow-up and missing data should also be considered (Suresh and Chandrashekara, 2012). Sample size calculations are based on the study hypothesis, the outcomes being measured and the proposed statistical analysis.

2.2.3 Reliability and Validity

2.2.3.1 Reliability

Reliability refers to the degree to which an outcome is free from random error (Carter et al., 2011, Stokes, 2011a). Random error can occur at any point throughout the measurement process due to the inaccuracy of either the measurement device or the assessor. Systematic error should be considered and limited at the study design stage (e.g. by calibrating measuring equipment).

Reliability can be defined as either relative or absolute reliability. Relative reliability, reported as either inter- or intra-rater reliability examines the relationship between two or more sets of repeated measures error (Carter et al., 2011, Stokes, 2011a). Inter-rater reliability examines the consistency with which different raters assign scores to the same measure. Intra-rater reliability examines the consistency with which the same rater assigns scores to the same measure on separate occasions. Absolute reliability, expressed as the standard error of the mean, is the extent to which a score varies on repeated measurement (Carter, 2011, Stratford, 2004). The standard error of the mean is used to measure minimal detectable change; the minimum change required to consider real change and not change attributed to measurement error (Stokes, 2011a). It is essential to understand the acceptable levels of relative and absolute reliability of a measure in order to make a meaningful statement about real change.

The reliability of a measure can be analysed in a number of ways (Stokes, 2011a, Finch et al., 2002). The level of agreement between continuous level data can be assessed using intra-class correlation coefficients (ICC) or Pearson Product Moment Correlation Coefficients (PPMCC).

ICC measure percentage agreement between and within raters and is usually presented with kappa co-efficients (K) or weighted kappa co-efficients (K*w*). The K accounts for agreement that could exist between raters by chance, while the Kw allows for partial agreement between raters. The PPMCC examines the linear association between two sets of continuous data, not necessarily the level of agreement between variables. PPMCC is often cited inappropriately as a statement of reliability. Internal consistency considers how items within the same test relate to each other and to the overall score (Stokes, 2011a). Internal consistency can be reported by either examining the association between different items in the same test (PPMCC) or by using Cronbach's alpha, which is calculated from pairwise correlations between items, to compare individual items to the overall score.

2.2.3.2 Validity

Validity refers to the extent that an instrument or tool measures what it intends to measure (Finch et al., 2002). There are a number of domains of validity which require evaluation, including face, content, criterion and construct validity (Stokes, 2011b). Face validity examines if, "on the face of it", an outcome measures what it intends to measure (Stokes, 2011b). It is generally defined by consensus based on expert opinion. A tool with good face validity is more likely to be used and accepted in practice. Content validity can also be defined by expert consensus. It considers the individual items that are included and omitted from the instrument, ensuring that it completely assesses the domain of interest (Finch et al., 2002).

Criterion validity examines the accuracy of the measure against the gold standard method of measurement (Finch et al., 2002, Stokes, 2011b). In many cases the gold standard is a more expensive, time consuming method that requires experienced staff and sophisticated equipment. Criterion validity can either be concurrent or predictive. Concurrent validity compares the current measure to the gold standard at a single point in time while predictive validity refers to the relationship with a future assessment or event (Stokes, 2011b) Concurrent validity can be assessed using PPMCC or spearman's rank order correlations. Predictive validity is quantified using sensitivity, specificity, positive and negative predictive values and likelihood ratios (Stokes, 2011b). Sensitivity refers to the ability of a measure to correctly identify the presence of a disease while specificity refers to the ability to correctly identify that a disease is not present. Likelihood ratios combine both sensitivity and specificity

values to estimate how much the measure will change the odds of having a disease. Similarly, positive predictive values quantify the number of individuals, with a positive result, who have the outcome of interest, while negative predictive values quantify the numbers with a negative result who do not have the outcome of interest.

Finally, construct validity examines the constructs or ideas from which the hypothesis for the measure is formed. Construct validity encompasses all other forms of validity (face, content and criterion) and is therefore evaluated in terms of each individual component (Finch et al., 2002, Stokes, 2011b). Construct validity should be considered in terms of both longitudinal and cross-sectional design. An instrument may be validated to assess a particular characteristic at one point in time, however it may not be developed to measure change over time (Finch et al., 2002).

2.2.4 Principles of Data Analysis

Preliminary data analysis involves descriptive statistics and assessing data distributions for normality. Descriptive statistics for categorical variables such as nominal or ordinal level variables, state the frequency of the observation within the data set and the relative percentage of that frequency within the dataset (Carter et al., 2011). Graphically, categorical variables can be depicted using pie-charts and bar charts. Continuous variables (scale data) are described by a measure of central tendency (mean (μ), median or mode) and a measure of variation about the mean (standard deviation (σ) or inter-quartile range). Continuous variables are represented graphically by a histogram, which allows for visual interpretation of whether the dataset follows a normal distribution or not. Normality is an assumption underlying a number of statistical tests and is illustrated by a normal curve that is symmetrical about the mean. The Kolmogorov-Smirnov (K-S) test tests for normality of a distribution and provides a statistical value to demonstrate normality ($p<0.05$) or a non-normal distribution ($p>0.05$). When distributions are non-normally distributed log-transformations can be applied to attempt to achieve log-normality. If normality cannot be achieved then non-parametric tests must be used for further analysis on that dataset. Normally distributed data is described as mean (standard deviation) and non-normally distributed data is described as median (inter-quartile range).

The choice of statistical test depends primarily on the study hypothesis although there are other considerations such as the level of measurement involved (categorical versus continuous) and whether the data adheres to the assumptions underlying the test (Mullins, 2003, Carter, 2011). To assess differences in continuous variables between groups (e.g. cancer cohort vs. healthy controls) methods available include independent-samples t-test, paired samples t-test, and analysis of variance (ANOVA) (Bland, 2000).The non-parametric equivalents of these tests include the Wilcoxon rank sum test, the Kruskal-Wallis test and Friedmans test. T-tests are used when only two groups are involved. Independent t-test compare two separate groups which have undergone the same measurements while paired t-tests compare two separate measurements taken on the same group at different time-points. ANOVA is used to compare measures taken from more than two groups or more than two time-points. Repeated measures ANOVA allows for the assessment of between-group changes over repeated measures (i.e. to examine if the change experienced in an exercise group was significantly different from that in the control group over a number of measurements). Differences in categorical variables can be assessed using Pearson's chi-squared test for variables with >5 observations per category or by Fishers exact test for distributions that violate this assumption (<5 observations per category). Non-parametric tests are inherently less robust than parametric data analysis (Whitley and Ball, 2002).

Confidence intervals provide a range of probabilities within which the true probability would lie 95% of the time (95% CI) (Guyatt et al., 1995) and are calculated as 1.96 (mean ± standard error) (standard deviation of the sampling distribution calculated as the sample $\sigma/\sqrt{n}$ (n=sample population)) (Gardner and Altman, 1986). Confidence intervals can be used to describe the interval for a mean of a specific range of values in a particular cohort. This can be useful for describing the interval within which the mean change in a variable following intervention would lie and for determining significance (e.g. following implementation of an exercise programme). If the confidence interval contains zero then the treatment difference is equal to the null hypothesis and it can be concluded that there is no difference in the variable being tested (Young and Lewis, 1997). If a confidence interval does not include zero then results can be interpreted as significantly different from the null hypothesis. Moreover confidence intervals provide information about the size of the treatment effect and its clinical relevance (Young and Lewis, 1997, Gardner and Altman, 1986). In contrast, hypothesis testing provide a p-value of either >0.05 or <0.05, which merely indicated whether the observed

result is significantly different from zero. Confidence intervals may also be useful to inform trials with larger sample sizes by identifying variables within a pilot study which are most likely to respond to an intervention.

Relationships between variables can be explored using correlations and regression ananlysis. Correlation analysis is used to describe the strength and direction of the linear relationship between two variables while regression can be used to determine if a set of variables can predict a particular outcome. PPMCC are used to examine associations between normally distributed variables and Spearman's Rho for non-normally distributed variables. Regression examines how change in one variable, the independent variable, influences another related variable, the dependent variable (Bland, 2000).

In addition to data normality, statistics tests have associated underlying assumptions which data must comply with for valid application of the test. Most tests assume independent observations, whereby each observation or measurement is not influenced by another measurement. In situations where observations are collected in a group setting this assumption has the potential to be violated. Homogeneity of variance assumes that samples are obtained from populations of equal variance and that the variability of each set of scores are similar. When completing an independent t-test Levene's test is generated to assess equality of variance in different samples. Repeated measures ANOVA assumes sphericity. Sphericity requires that the variances of the repeated measures are equal and the correlations between the repeated measures are equal. Mauchly's test for Sphericity is used to test this assumption. If the assumption is violated ($p<0.05$) then adjustments are made in the analysis and the Greenhouse Geisser test is used.

Finally, while all efforts were made during outcome assessment to ensure all data was collected, there were some cases of missing data. In Study I, missing data in follow-up assessments, including missing data from participants who had dropped out, was imputed using the last-observation-carried-forward procedure. In Study IIa, missing data from either of the two assessments was treated as missing and participants were excluded from that analysis. In Study III missing data from the prospective study will be imputed with using the last-observation-carried-forward procedure.

2.3 Lifestyle Behaviours and Measures

Lifestyle behaviours and measures (physical activity and body composition) and metabolic screening were assessed in all studies presented in this thesis. Other measures including aerobic fitness, RMR and assessment of dietary intake were measured as secondary outcomes in selected studies. The following section will discuss the measurement of physical activity and body composition. Subsequent sections will discuss and describe metabolic screening and the measurement of secondary outcomes.

2.3.1 Physical Activity

Measurement of physical activity is multidimensional, encompassing frequency, duration, intensity and time spent in activity. Measurement is further complicated by the often unregulated nature of activity. Activities such as sports are planned and structured and are therefore easier to quantify. Unplanned activity can be more difficult to quantify and incorporates a range of activity domains including occupation, household and transport (Plasqui and Westerterp, 2007). Doubly labelled water (DLW) is considered the gold standard method of measuring energy expenditure. DLW is an isotope based technique of measuring total energy expenditure and basal metabolic rate to calculate activity related energy expenditure, which is only used with small study samples (Westerterp, 2009, Katch et al., 2011c). In addition, while information on total daily energy expenditure can be gathered, activity frequency, intensity and duration cannot be measured using DLW (Plasqui and Westerterp, 2007). Energy expenditure as a result of physical activity can also be estimated to a high degree of accuracy using indirect calorimetry, which provides a measure of respiratory gas exchange (oxygen consumption) during exercise (Rowlands et al., 2004, Hussey et al., 2009).

The energy cost of physical activities can be expressed in terms of metabolic equivalent (MET) values. One MET is defined as the ratio of metabolic rate to RMR and is roughly equivalent to energy expended during quiet sitting (3.5 $mlO_2.kg^{-1}.min^{-1}$) (Norton et al., 2010). The Compendium of Physical Activities contains a list of MET intensity codes relating to the energy costs of physical activities (Ainsworth et al., 2011). The MET levels of each activity within the compendium are determined by dividing the energy cost of each activity (VO_2 $ml.kg.^{-1}min^{-1}$) by $3.5ml.kg.^{-1}min^{-1}$. Resultant MET intensities can be classified to express exercise intensity

categories where sedentariness is defined as 1-1.5 METs, light intensity as 1.5-3.0 METs, moderate intensity as 3.0-6.0 METs and vigorous intensity activity as 6.0-9.0 METs (Norton et al., 2010). MET intensities can be combined with duration of activity to express physical activity in terms of MET-h.week^{-1} or MET-minutes(min).week^{-1}. MET-h.week^{-1} are calculated by multiplying the number of hours in the week that the activity was completed by the MET intensity value for that activity. For example, physical activity guidelines recommend 30 minutes.day^{-1} (2.5 hours.week^{-1}) of moderate intensity activity (3.0 METS) which is equivalent to 7.5 MET-h.week^{-1}.

The measurement of habitual physical activity may be performed by either subjective or objective techniques. Subjective methods include behavioural observation and activity questionnaires, while objective methods include physiological outcomes and use of motion sensors. Behaviour observation is the oldest method of measuring physical activity where an observer records participant activity habits over a defined period (Westerterp, 2009). The foremost advantage of this method is that information on the context within which the activity is being performed can be documented. Disadvantages include the need for a trained observer to be present to record activity which results in low participant numbers and tedious work practices. Concern that the presence of an observer may indirectly alter participant activity patterns also limits the usefulness of behaviour observation. Behaviour observation is best suited to paediatric populations who may be less aware of observer and more inclined to complete usual activity patterns or when activity is completed within a confined space (Hussey, 2005).

Physical activity diaries and recall questionnaires are the most common assessment tools used in large scale projects, as they are cheap, easy to deliver and have a low patient burden (Ainsworth et al., 1998, Westerterp, 2009). Questionnaires can be self-administered or interview based and can be sub-divided into three categories: global, recall and quantitative history. Global questionnaires are short (1-4 items) tools which give a general impression of an individual's activity status and are accurate at determining whether a participant undertakes any vigorous intensity activity (Ainsworth et al., 1998). Recall questionnaires examine physical activity patters over the past week or fortnight. Scores are expressed as kilocalories.day^{-1} or as MET values to reflect time spent in different intensities of activity. Recall questionnaires can

accurately collect time spent in moderate and vigorous intensity activity, but are less accurate at quantifying light or sedentary activity (Jacobs et al., 1993). Finally, quantitative history questionnaires examine intensity, frequency, and duration of a range of activities over the preceding months or years. Activity is expressed as either kilocalories.day^{-1} or MET-h.day^{-1} (Ainsworth et al., 1998).

All questionnaires have the disadvantage of relying on recall and subjective interpretation of activity intensity, frequency, etcetera., which often results in inaccurate and exaggerated reporting of actual physical activity levels, particularly in groups who are overweight (Noonan and Dean, 2000). When choosing a physical activity questionnaire the population being examined and the activities they are likely to engage in must be considered. Women are more likely to engage in activities that are unstructured in nature due to home, family care, work and community responsibilities. Therefore, a physical activity survey should endeavour to encompass the maximum number of activity domains, including occupational, recreational and household, to adequately reflect habitual activity habits.

Physical activity can be measured in real time using objective methods such as the physiological response of heart rate to exercise. Heart rate can be monitored over a period of days and predictive equations, based on the assumption of a linear relationship between heart rate and oxygen uptake, can be used to estimate energy expenditure from heart rate data collected (Westerterp, 2009). While heart rate can be used to estimate activity intensity there are a number of confounding issues. Firstly, other stimuli, such as caffeine or nicotine, can stimulate the heart to beat faster, leading to an overestimation of activity intensity. Secondly, individuals who are physically fit may achieve a higher intensity of activity at a lower heart rate than sedentary individuals. While heart rate is a useful tool, it is advisable to use in combination with other physical activity assessment procedures.

The objective measurement of physical activity by motion sensors, such as pedometers and accelerometers, has gained increased interest in the past number of years. Pedometers are small devices, worn on the hip or ankle, which count the number of steps taken per day (Bassett et al., 2008). They are suitable for use in large epidemiology studies to objectively measure total activity. New models of pedometers record steps in minute intervals, thus

providing an estimation of activity intensity and duration. Accelerometers are the most advanced measurement of physical activity in the free-living setting (Trost et al., 2005, Westerterp, 2009). Accelerometers measure acceleration and deceleration of movement using internal time-sampling mechanism which allows information on activity intensity, frequency and duration to be captured. Accelerometers have advantages in that they are non-invasive, small in size, do not interfere with activity and can be given to subjects for use over a prolonged period of time (Trost et al., 2005). They are designed to capture movement in either the vertical plane only (uniaxial) or in up to three planes (vertical, horizontal and sagittal) simultaneously (triaxial). Limitations include underestimation of energy cost related to upper limb movements and during static work, including standing, due to the positioning of devices on the hip or waist (Powell and Rowlands, 2004). Equally, they are known to under-estimate the energy cost of traversing a slope and cannot be worn during water-based activity (Powell and Rowlands, 2004, Rowlands et al., 2004). Devices such as the SenseWear Pro Armband® attempt to overcome this by combining accelerometer data with body temperature to gain a more accurate estimation of physical activity. Others incorporate GPS or heart rate data for increased accuracy.

There are a number of accelerometers available commercially including the SenseWear Pro armband® (BodyMedia, Pittsburgh, PA), the Intelligent Device for Energy Expenditure and Activity®(MiniSun, Frensno, CA, USA), the ActiGraph range of accelerometers (Pensacola, FL) and the RT3 activity monitor (Stayhealthy Inc. Montrovia, California, USA). No conclusive evidence exists to recommend one activity monitor type over another (Trost et al., 2005, Ward et al., 2005). Decisions on the most suitable accelerometer should be based not only on the reliability and validity of the monitor, but also practical considerations such as monitor size, information gathered, technical support from the company and comparability with other studies. The RT3 is a small, non-intrusive, triaxial accelerometer that has been used previously in both our research group (Hussey et al., 2009, Feeney et al., 2011) and by others in oncologic populations (Sloane et al., 2009). The validity and reliability of the monitor has been established (section 2.3.1.1) and it was chosen to objectively measure physical activity in this thesis.

2.3.1.1 Objective Assessment of Physical Activity in this Thesis

The triaxial RT3 activity monitor (originally the Tritrac-R3D) is a small (71 x 56 x 28 mm, 65.2g) lightweight, battery operated (1 x 1.5 volt AAA alkaline battery) device (Figure 8). A sensor, located within the monitor, records accelerations along three orthogonal planes: vertical (x), horizontal (y) and sagittal (z). Accelerations are converted to a digital signal and then processed to generate activity counts with greater accelerations resulting in a higher number of counts. Vector magnitudes (VM) are calculated by totalling activity counts from all three planes $(x^2 + y^2 + z^2)^{0.5}$. The RT3 accelerometer is designed to have a dynamic range of 0.05-2.00g, is sensitive to frequencies in the range of 2-10 Hz and is calibrated at 5.3 Hz (www.stayhealthy.com).

Figure 8 RT3 Activity Monitor



Data can be collected in four modes. Modes 1 and 2 sample and store activity counts on an individual axis (mode 1) or VM activity (mode 2) over one second intervals while modes 3 and 4 carry out the same respective procedures over one minute epochs. Modes 1 and 2 facilitate more detailed data collection but are less economical on memory with a maximum collection time of 9 hours. Data collected on a minute-to-minute basis (modes 3 and 4), can be collected and stored for up to 21 days (Rowlands et al., 2007). When data collection is complete, information can be downloaded from the RT3 device via a docking station to a computer where it is converted to Microsoft Excel files.

The inter-instrument and intra-instrument reliability of the RT3 have both been investigated. Good intra-monitor reliability has been reported by studies investigating under both mechanical set-up (CV <1.81% for speeds of 150 and 275 RPM, tested in two directions (anthro-posterior and medio-lateral) for three blocks of 24-hours) (Krasnoff et al., 2008) and in free-living conditions (six activities: sitting, treadmill walking (4km.h^{-1}, and 6km.h^{-1}) treadmill running (8km.h^{-1} and 10km.h^{-1}) and repeated sit-to-stand activity, measured two days apart) (Powell and Rowlands, 2004).

Substantial inter-monitor variability has been reported. Three studies have reported wide inter-monitor variation using mechanical set-up procedures involving shaker/vibration plates (Powell et al., 2003, Esliger and Tremblay, 2006, Krasnoff et al., 2008). Powell and colleagues (2003) reported greatest inter-monitor variation at lower frequencies (2.1 Hz) (coefficient of variation (CV) 21.9-26.7%) but decreased as frequency increased (5.1 Hz: CV 6.3-9.0%; 10.2 Hz CV 4.2-7.2%). Eliger and Tremblay (2006) reported intermonitor CV of 42.9% and Krasnoff and colleagues reported a CV ranging from 9.5% to 34.7%.

During standardised activities, studies have reported moderate to high inter-monitor reliability at low to moderate intensity activities, but that variation increases by up to 82% with increasing intensity of activity (Powell and Rowlands, 2004, Rowlands et al., 2007). Reneman and Helmus (2010), reported moderate reliability (ICC=0.75 (95% CI 0.46 to 0.095) during three activities (treadmill walking at 3.0 and 5.0 km.h^{-1} and quiet sitting), however variation or agreement is not reported. Compared to inter-monitor variability of other commercially available activity monitors the RT3 demonstrates lower variability than the uniaxial monitors the Actigraph and the Actical, in both mechanical set-up (Esliger and Tremblay, 2006) and free-living experiments (Rowlands et al., 2007). It is recommended that when using a number of monitors within a trial that intermonitor variability is assessed prior to testing and that during repeated measures participants use the same monitor. The collection of RT3 activity monitors used in this study were calibrated as part of a routine departmental audit.

The validity of the RT3 activity monitor has been investigated in a range of populations including children (Hussey et al., 2009), functionally impaired older adults (Sumukadas et al., 2008), manual wheel-chair users (Hiremath and Ding, 2009), overweight and obese women (Jacobi et al., 2007) and adults with chronic disease including COPD (Van Remoortel et al., 2012) and neurological dysfunction (Hale et al., 2008). The validity of the device has also been established in healthy adults (Rowlands et al., 2004, Hendrick et al., 2010, Maddison et al., 2009, Wetten et al., 2013, Rothney et al., 2008, Rowlands et al., 2007).

In healthy cohorts, RT3 VM output has been compared to whole room calorimetry (Wetten et al., 2013, Rothney et al., 2008), indirect calorimetry (Rowlands et al., 2004), DLW (Maddison et al., 2009) and step frequency (Rowlands et al., 2007). The RT3 was found to underestimate the energy cost of lower intensity and of sedentary activities ($p<0.001$ for both) (Wetten et al., 2013, Rowlands et al., 2004, Rothney et al., 2008). Agreement between RT3 output and energy expenditure has been found to increase with increasing activity intensity (Maddison et al., 2009, Rowlands et al., 2007). The RT3 correlated significantly and strongly with oxygen consumption across a range of regulated and unregulated moderate and vigorous intensity activities ($r=0.85$; $p<0.01$) (Rowlands et al., 2004). While the RT3 showed good agreement with DLW over 15 days of measurement in free-living conditions, RT3 measured total energy expenditure was underestimated by 4% and activity-related energy expenditure by 14% (Maddison et al., 2009). Hendrick and colleagues (2010) reported no difference in RT3 VM counts during overground versus treadmill walking at self-selected and brisk speeds ($p>0.05$), however wide limits of agreement were recorded.

The RT3 has been shown to be a suitable measure of activity in overweight and obese adults (Jerome et al., 2009, Jacobi et al., 2007). In overweight and obese women, RT3 VM output recorded over two week was comparable to that measured by DLW ($r=0.55$; $p<0.05$) (Jacobi et al., 2007). In a study of 1070 overweight and obese adults, Jerome and colleagues (2009) found that the RT3 was a reliable method of measuring moderate and vigorous intensity activity and that longer wearing times did not result in more accurate estimates of these activity domains.

VM thresholds corresponding to moderate intensity activity (VM=984 counts) and vigorous intensity activity (VM=2341 counts) have been established (Rowlands et al., 2004). There is no known cut-point for sedentary behaviour. In a group of functionally impaired older adults, Sumukadas and colleagues (2008) reported that activities such as resting, sitting and standing were associated with VM counts below 250, however sedentary behaviours (1.0-1.5 METS) were not distinguished from light intensity (1.5-3.0 METS) activity.

2.3.1.2 RT3 Measurement Protocol

The RT3 was used to objectively measure physical activity levels in the studies presented in Chapters 3, 5 and 6. The following procedures were followed.

Measurement Procedure

In the work presented in this thesis, RT3 activity monitors were programmed to record data in mode 4. This allowed the monitor to record data for up to 21 days. During this 21 day period participants were asked to wear the monitor for 7 days during waking hours and to post it back to the centre in a stamped addressed envelope provided. Participants were provided with the monitor upon completion of their assessment along with both written (Appendix V) and verbal instructions on its use. Participants were also provided with an activity diary to record the length of time they were wearing and not wearing the monitor. Upon return of the monitor to the research centre, data was downloaded via the RT3 docking station to a computer and converted in an Excel file.

Data Analysis

All data analysis was completed in Microsoft Excel. Activity intensity was defined from previously validated cut-points for healthy adults: light intensity activity: 984 VM, moderate intensity activity: 2341 VM, vigorous intensity activity >2341 VM (Rowlands et al., 2004). As no validated cut-point exists for RT3 measured sedentary activity, sedentary behaviour was defined as ≤100VM (Healy et al., 2011).

Data analysis was completed in two ways. Firstly, percentage time spent in each domain of physical activity was estimated. The activity diary was analysed in conjunction with the RT3 output and non-wearing time (bed, bath and shower time) was deleted. Missed days were identified and deleted. In a small number of cases, where the activity monitor was returned without the accompanying activity diary a 10 hour night / monitor non-wearing time per day was assumed. This was based on average monitor off-time from previous populations studied in the laboratory using the RT3. An average value of time per day in each intensity of activity was calculated (total minutes spent in activity intensity in the week ÷ number of days the monitor was worn).

Secondly, data was analysed for adherence to physical activity guidelines. Adherence to physical activity guidelines was defined in two ways; i) 30 minutes moderate-to-vigorous intensity activity at least 5 days per week (WCRF/AICR, 2007, Garber et al., 2011) and ii)150 minutes moderate-to-vigorous intensity activity per week (Garber et al., 2011). The guidelines stipulate that activity should be accumulated in bouts of at least 10 minutes duration (Garber et al., 2011). Analysis was completed in accordance to the guidelines used in NHANES (Tucker et al., 2011). Both moderate and vigorous intensity minutes were treated equally within each 10 minute bout. Analysis was performed using the conditional formatting function in Microsoft Excel and the file was examined manually for bouts of moderate-to-vigorous intensity activity lasting ≥10 minute.

2.3.1.3 Subjective Assessment of Physical Activity

Physical activity was measured subjectively using questionnaires in all studies. While there are a number of limitations with using physical activity questionnaires, as discussed above, they are the most extensively used method of recording physical activity and therefore were included as an adjunct to objectively measured activity. Questionnaires were chosen based on the specific aims of the study, the time-period being examined, the domain of physical activity being measured and previous use in oncologic populations.

2.3.1.4 Global Questionnaire - The Godin Leisure-Time Exercise Questionnaire

The Godin Leisure-Time Exercise Questionnaire (Godin questionnaire) is a simple, self-administered, four-item questionnaire that is designed to measure an individual's leisure-time activity during a typical week (Appendix VI). The questionnaire has been used widely in various oncologic populations including breast (Courneya et al., 2003), ovarian (Stevinson et al., 2007) and colorectal cancers (Courneya and Friedenreich, 1997). In the first question, participants are asked to consider the number of occasions they spend per week, of at least 15 minutes duration, in strenuous[6], moderate and mild exercise. A total leisure score (TLS) is calculated as the sum of weekly frequencies of strenuous, moderate and vigorous intensity activity by their corresponding MET values: *[TLS = (9 METs x strenuous activity time) + (5 METs x moderate activity time) + (3 METs x light activity time)].* The second question asks participants to consider how often they engage in activity long enough to work up a sweat with respondents choosing from the options: *"often", "sometimes"* or *"never/rarely".*

Participants involved in the RCT (Chapter 3) were asked to complete the Godin Questionnaire (Appendix VI) at each assessment time point to monitor change in subjectively reported physical activity levels throughout the intervention. The prospective cohort study described in Chapter 6 includes the Godin Questionnaire as part of the annual questionnaire. Participants were asked to complete the questionnaire independently and the study assessor was available if questions occurred.

The validity of the Godin questionnaire has been established in healthy cohorts. Godin and Shephard, (1985) reported significant correlations between TLS and both maximal oxygen uptake ($r=0.24$; $p<0.001$) and %BF ($r=0.13$; $p<0.01$) in 306 healthy men and women. Self-rated sweating score was significant correlated with both maximal oxygen uptake ($r=0.26$; $p<0.001$) and %BF ($r=0.21$; $p<0.001$). Similarly, Jacobs et al., (1993), reported that both the TLS and the self-rated sweating score were significantly correlated with maximal oxygen uptake ($r=0.56$; $p<0.05$, $r=0.57$; $p<0.05$ respectively) and with %BF ($r=-0.43$; $p<0.05$, $r=-0.40$; $p<0.05$ respectively), in their sample of 78 men and women. Both Jacobs et al., (1993) and Miller et al., (1994) reported significant correlations between TLS and accelerometer output from the Caltrac accelerometer ($r=0.32$; $p<0.05$, $r=0.45$; $p<0.01$ respectively). Jacobs and colleagues

[6] The Godin questionnaire uses the term "strenuous" to describe vigorous intensity activity.

(1993), reported a significant relationship between Caltrac output and the self-reported sweating score ($r=0.29$; $p<0.05$).

Reliability studies have examined short-term reliability (two-week and one-month) for each activity domain, TLS and sweat score among adults (Godin and Shephard, 1985, Jacobs et al., 1993). Significant correlations were reported by both studies ($0.24 < r < 0.94$; $p<0.05$) across all categories. Correlations were highest for strenuous intensity activities and lowest for light intensity activities.

2.3.1.5 Quantitative History Questionnaires

Quantitative history questionnaires are used in epidemiological research to measure frequency, duration and intensity of physical activity in the preceding months or year. They can account for seasonal or lifestyle changes in physical activity and demonstrate moderate correlations with direct measures of activity (correlation coefficient range 0.23-0.40) (Ainsworth et al., 1998). Due to the detail required, these types of questionnaires can be time consuming to complete (up to 30 minutes) and adhere to structured interview guidelines. There are a number of quantitative history questionnaires available that are suitable for use in breast cancer research including the Modifiable Activity Questionnaire, the Past Year Total Physical Activity Questionnaire and the Cardia Physical Activity Questionnaires. All questionnaires have been validated and used in oncologic populations (http://appliedresearch.cancer.gov/tools/paq/validation.html (accessed 31.01.2013)). The Tecumseh Questionnaire was chosen for use in this thesis for a number of reasons. Firstly, the questionnaire has two components, a leisure-time physical activity section and an occupational physical activity section, which can be used in combination or separately. Secondly, the questionnaire is accompanied by stringent interview guidelines and has a clear layout ensuring upmost consistency between interviews. Finally, it is relatively short to complete (10-20 minutes) ensuring participants do not become irritated when asked to provide such a detailed activity record.

The original Tecumseh Questionnaire was developed with the purpose of assessing habitual physical activity during the preceding year as part of the Tecumseh Community Health Study (Montoye, 1975). The original Tecumseh questionnaire was impractical for use in studies due to its length and detailed interview technique. The questionnaire was revised and divided into two parts; *"The Minnesota Leisure-Time Physical Activity Questionnaire"* which focuses of leisure-time and recreational physical activity, and the *"Tecumseh Occupational Physical Activity Questionnaire"* which measures occupation-related activity (Montoye, 1996). Both questionnaires measure frequency of activity during the preceding year in terms of months and time per occasion, and combine this information with intensity scores to measure physical activity in terms of energy expenditure or METs (Taylor et al., 1978, Steele and Mummery, 2003). The questionnaires can be used separately or results can be combined.

The Minnesota Leisure-Time Physical Activity Questionnaire

The Minnesota Leisure Time Physical Activity Questionnaire (Minnesota questionnaire) (Appendix VII) was developed with the purpose of investigating the relationship between habitual leisure-time physical activity and CVD risk factors (Taylor et al., 1978). The 63 item questionnaire, examining sports, recreational, yard and household activities, has been used by numerous large epidemiological studies such as the Multiple Risk Factor Prevention Trial (Leon et al., 1987, Leon et al., 1997), the Minnesota Heart Survey and the U.S. Railroad Study (Slattery et al., 1989). Both original and modified versions of the questionnaire have been used to measure activity in oncologic populations (Chen et al., 1997, Courneya et al., 2008b).

The questionnaire is delivered according to structured interview guidelines (Taylor et al., 1978) taking 10-20 minutes to complete. The interviewer reads the listed activities and the participant confirms if they completed the activity in the previous 12 months by answering "yes" or "no". Activities to which the participant answers "yes" require further questioning to establish the months during which the activity was performed, the number of times per month the activity was performed and the average number of time spent in the activity during each occasion.

The validity of the Minnesota questionnaire has been rigorously tested against a range of outcomes including DLW, body composition, oxygen uptake, the Caltrac accelerometer and detailed physical activity records. Earlier validation studies, performed almost exclusively in men, reported significant associations between the Minnesota questionnaire TLS and exercise test treadmill duration (Taylor et al., 1978, Leon et al., 1981) and sub-maximally estimated physical fitness (De Backer et al., 1981). Albanes et al., (1990) reported weak correlations between the questionnaire and measured caloric intake (rho=0.13) and resting energy expenditure (rho=0.17). Kapik et al., (1993), reported significant correlations between treadmill VO_{2peak} and both total (r=0.19) and heavy[7] (r=0.43) activity and similarly between %BF and total (r=-0.24) and heavy (r=-0.24) activity. Wilbur et al., (1993) reported significant correlations between the TLS and fitness as measured using the Monarch cycle ergometer ($r=0.21$; $p<0.001$) and self-reported global physical activity records ($r=0.23$; $p<0.0001$) in 375 middle-aged women. Richardson et al., (1994) found that total, heavy and light activity as measured by the Minnesota questionnaire were all significantly correlated with VO_{2peak} ($r=0.47$; $p<0.01$, $r=0.43$; $p<0.01$, $r=0.27$; $p<0.05$ respectively). Richardson et al., (1994) also reported a moderate correlation with 48-hour physical activity recall records for total and heavy activities ($r=0.47$; $p\leq0.01$, $r=0.55$; $p\leq0.01$ respectively).

More recently studies have validated the questionnaire against direct measures of physical activity including the Caltrac accelerometer and DLW. Jacobs et al., (1993) reported no associations between any questionnaire measures and accelerometer readings in 78 men and women. In contrast, Starling et al., (1999) reported significant associations between total energy expenditure from the Minnesota questionnaire and accelerometer output and DLW. Bonnefoy et al., (2001) reported a significant relationship between DLW and questionnaire measured moderate ($r=0.50$; $p<0.05$) and heavy ($r=0.28$; $p<0.05$) intensity activity in 19 older men. Both Starling et al., (1999) and Bonnefoy et al., (2001) reported that the questionnaire underestimated total energy expenditure by 56% and 62% respectively compared to DLW. High short-term (one month) test-retest reliability of the Minnesota questionnaire has been reported by two authors (Folsom et al., 1986, Richardson et al., 1994), with a slight bias towards less reporting of activity during the second assessment. Richardson and colleagues (1994) reported high reliability on-year test-retest coefficients across all activity categories ($p<0.01$).

[7] The Minnesota questionnaire uses the term "heavy" to describe vigorous intensity activity.

The Tecumseh Occupational Physical Activity Questionnaire

The Tecumseh Occupational Physical Activity Questionnaire (Tecumseh questionnaire) (Appendix VIII) includes 29-items related to the type of activity undertaken during working hours over the past year, in addition to activity related to transport to/from work and stair climbing (Steele and Mummery, 2003). The questionnaire is self-administered and can measure activity related to a maximum of three occupation-related activities in the previous 12 months. Occupation related activities are reported in hours per week and includes a list of 16 activities ranging from "sitting-light work" to "using heavy power tools". The transport section records the type of transport used (car, bicycle, walk, tram), the frequency and distance travelled to work each day. Participants are also asked to recall the number of flights of stairs climbed at work per day (1 flight = 10 steps). The total score is adjusted for weeks spend on holiday or not working (Appendix VIII).

The Tecumseh questionnaire was used as part of the prospective cohort study described in Chapter 6 of this thesis. Due to the overlap with the Minnesota questionnaire for certain activities related to transport to work, care should be taken to only record this information once if using both questionnaires (Montoye, 1996). In the study described in Chapter 6, transportation to/from work and flights of stairs was recorded using the Minnesota questionnaire only. Previous studies (Steele and Mummery, 2003) omitted these sections from the Tecumseh questionnaire and focused information attained from that questionnaire solely of physical activity related to occupation.

The validity of the Tecumseh questionnaire has been established against a number of direct measures of physical activity, including occupational physical activity records, accelerometer output, DLW and indirect measures including maximal oxygen uptake and body composition. The first evaluation of the questionnaire was completed by Ainsworth et al., (1993) on 75 men and women, aged 23-59 years. The questionnaire was found to be the most comprehensive survey of occupational physical activity when compared to other occupational surveys due to moderately high partial correlation coefficients ($p<0.05$) between average Tecumseh scores and 48-hour occupational physical activity recall (Ainsworth et al., 1993).

Ainsworth and colleagues, (1999) further investigated the validity of the questionnaire, on 46 women aged 20-60 years. Moderate correlations were observed between total occupational physical activity (Tecumseh questionnaire) and seven-day occupational activity records ($r=0.46$; $p<0.001$), between moderate intensity standing and the Caltrac accelerometer ($r=0.34$; $p<0.10$) and between light-to-moderate intensity standing and maximal oxygen uptake ($r=0.32$; $p<0.05$). No relation was found with body composition (Ainsworth et al., 1999). Wilbur et al., (1993) found no relationship between Tecumseh score and cardiorespiratory fitness or body composition in 375 women, however they did report a significant positive correlation with a self-reported global physical activity score ($r=0.10$; $p<0.05$) and an negative correlation with systolic blood pressure ($r=-0.14$; $p<0.05$). The reliability of the Tecumseh questionnaire has been tested in 77 adults, with reported test-retest coefficients of 0.92 for measures taken one week apart and 0.69 for measures taken three months apart (Jacobs et al., 1993).

2.4 Body Composition

The measurement of body composition is an essential component of evaluating the impact of excess body fat on health. In the clinical setting anthropometric methods used to measure body composition include BMI, circumferential measurements and sum of skinfolds technique. Bioimpedance analysis (BIA) is also used widely clinically and has advantages over BMI in that estimates of fat free mass (FFM) and %BF are provided. Laboratory methods to measures components of body composition such as computerised topography (CT), MRI and DEXA produce very accurate images of body compartments however these more sophisticated methods are expensive to administer and require technical expertise (Wagner and Heyward, 1999). In this thesis, body composition was measured using anthropometry and BIA.

2.4.1 Anthropometry

Anthropometry refers to the measurement of the size and proportion of the body using measures of body weight, height, circumferences and length. These methods are cheap and feasible to perform and are the most widely used measure of body composition (van der Kooy and Seidell, 1993).

BMI is the simplest method of indirectly assessing fatness. It provides an estimate of ideal weight in relation to a person's height and is used to classify persons who are underweight (<18.5kg.m^{-2}), normal weight (18.5-24.9 kg.m^{-2}), overweight (25-29.9 kg.m^{-2}) or obese (Class I: 30-34.5kg.m^{-2}; Class II: 35-39.9kg.m^{-2}; Class III: ≥40kg.m^{-2}) using the formula (weight (kg)/height (m)^2) (WHO, 2000). BMI is used widely in the clinical and research setting due to its straightforward approach and its correlation with body fatness however, since it cannot distinguish between fat mass and muscle mass the method may misclassify those with a high muscle mass as either overweight or obese (Neovius et al., 2007). Circumferential measures such as waist circumference (see section 2.5.2) are recommended for use in combination with BMI measures to identify those at increased risk for chronic disease (WHO, 2011).

2.4.1.1 Anthropometry Measurement Protocols

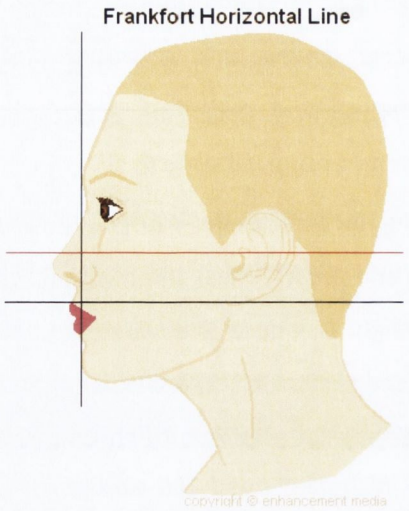
Body Weight

Body weight was measured, to the nearest 0.1 kg, on the digital scales of the Tanita MC 180 Multi-Frequency Body Composition Analyzer (described in section 2.4.2 below). Participants were measured in one layer of light clothes, following a 12-hour fast. The machine deducts a predetermined weight, equivalent to one layer of light clothing, from the participants recorded weight.

Standing Height

Standing height was measured using a portable SECA stadiometer. Participants were asked to stand, without shoes, on the footplate, with their back against the stadiometer, legs together, arms down by their sides and mid-axillary line in parallel to the stadiometer. The head was positioned in the Frankfort horizontal plane (Figure 9), the standard plane used for the correct orientation of the head, established by a line passing through the tragion (front of the ear) and the lowest point of the eye socket. The headboard was lowered until it touched the crown of the head, compressing the hair. Measurements were taken to the nearest 0.1cm.

Figure 9 Position of the Head in the Frankfort Horizontal Plane



2.4.2 Bioimpedance Analysis

BIA was used in addition to anthropometry to estimate components of body composition including FFM and %BF. BIA is a viable alternative for measuring components of body composition, that is cheap, non-invasive and quick to perform (Jaffrin, 2009). BIA is based on the principle of impedance, i.e. the opposition that a circuit presents to the passage of a current when a voltage is applied. Electrolytes within the body are naturally conductive. Lean tissue, which contains a large amount of water and electrolytes, is a good electrical conductor, and fat, which contains less water, is a poor conductor (Wagner and Heyward, 1999). Therefore when a low level electric current (800μA) is introduced into the body at a set frequency (50 kHz), the resistance met to various tissues in the body can be used to estimate relative percentage of body fat and FFM. The main advantages of BIA are related to its feasibility and practically in the clinical setting (Ward, 2012).

The BIA system used in this thesis was the Tanita MC 180 MA Multi-Frequency Body Composition Anaylzer (Tanita Corp, Tokyo, Japan) (Figure 10). This particular model has advantages over earlier versions as it uses 8-electrodes instead of four which allows segmental measurement (trunk, arms and legs), use of multi-frequency electrical levels to estimate both intra- and extra-cellular water and the incorporation of a body scales to measure body weight (Volgyi et al., 2008, Tanita, 2005).

Figure 10 Tanita MC 180 MA Multi-Frequency Body Composition Anaylzer



The validity of the 8-electrode model of Tanita BIA has been established. Pietrobelli et al., (2004) compared BIA to DEXA in normal healthy males and females, reporting no significant difference between any of the body segments measured by BIA versus DEXA ($r \geq 0.95$; $p < 0.001$). The 8-electrode model showed improved correlations with %BF when compared to previous 4-electrode models. Similarly, Volgyi et al., (2008) reported moderate correlations in men ($r = 0.54$; $p < 0.05$) and moderate to high correlations in women ($r = 0.37$-0.91; $p < 0.05$) between the BIA and DEXA measurements, but that BIA values were consistently 2-6% lower than DEXA. It should be acknowledged however that BIA provides an estimation of body composition and therefore limitations apply. BIA has been shown to report consistently lower values of percentage fat mass when compared to DEXA among a group of centrally obese women (Neovius et al., 2006, Volgyi et al., 2008) and as BMI increases, the discrepancy between BIA and DEXA also increases (Neovius et al., 2006).

2.4.2.1 Bioimpedance Analysis Measurement Protocol

Preparation

The level gauge on the Tanita MC 180 Multi-Frequency Body Composition Analyzer was checked to ensure the machine was level with the floor. The feet of the machine were adjusted accordingly (Multi-Frequency Body Composition Analyzer MC-180MA Instruction Manual). All participants were fasting for ≥12 hours for blood sampling (≥3 hours recommended for BIA measurement). Participants were asked to void before the measurement if they hadn't done so in the previous 30 minutes. The palms of hands and soles of feet were checked and cleaned for any dirt or dust particles prior to measurement.

Measurement Procedure

Participants stood on the machine in bare feet, ensuring correct placement on the electrodes. Body composition mode was selected. The following information was inputted: gender, standard body type[8], age and height. To complete the measure (<20 second duration), participants held the hand-held electrodes and stood upright, ensuring that thighs were not touching and that arms were straight down by their sides. The following details were recorded: body weight, BMI, %BF, FFM, muscle mass and total body water.

[8] Two body type options are available: "standard" and "athletic". "Athletic" should only be selected for people fulfilling the following criteria: ≥12 training.week^{-1}; member of a gym or sports organisation aiming to compete competitively, bodybuilders or sports professionals. "Standard" body type was selected for all participants studied as "athletic" was deemed inappropriate.

2.5 Metabolic Screening

Metabolic screening was conducted primarily by measuring for the presence of the MetSyn. Glucose dysregulation was also measured using HOMA-IR to estimate insulin resistance and by HbA_{1c}, the gold standard for measuring glucose dysfunction. Low grade chronic inflammation was measured by CRP.

2.5.1 The Metabolic Syndrome

As described in Chapter 1 (section 1.3.2) the definition of the MetSyn has evolved greatly over the past number of years. In this thesis MetSyn was defined according to the latest criteria from the consensus statement by Alberti and colleagues (2009) (Table 5). Clinical diagnosis of the syndrome was made in the presence of any three of the five criteria. The following sections will discuss the theoretical background to the measurement of each component of the syndrome.

Table 5 Clinical Criteria for Diagnosis of the Metabolic Syndrome

Measure	Categorical Cut-Off Points
Elevated waist circumference	≥94cm in males; ≥80cm in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated TG (drug treatment for elevated TG is an alternative indicator)	≥150 $mg.dL^{-1}$ (1.7 $mmol.L^{-1}$)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator)	< 40 $mg.dL^{-1}$ (1.0 $mmol.L^{-1}$) in males; <50 $mg.dL^{-1}$ (1.3 $mmol.L^{-1}$) in females
Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator)	≥100 $mg.dL^{-1}$

Abb: TG = triglycerides; HDL-C = high density lipoprotein cholesterol

2.5.2 Elevated Waist Circumference

Waist circumference provides an estimate of the amount of abdominal fat (Despres et al., 2001) and has been validated as a surrogate measure of visceral fat compared to CT measurements in healthy adults ($r=0.85$; $p<0.0001$) (Gradmark et al., 2010) and overweight women ($r=0.76$; $p<0.001$) (Zamboni et al., 1998). WHR (waist circumference ÷ hip circumference), describes the relative distribution of abdominal to gluteal fat (Despres et al., 2001) can also be measured, however is a less accurate measure of visceral fat compared to waist circumference (Zamboni et al., 1998). Waist circumference is considered a better measure of change in abdominal fat in women due to the potential for simultaneous increase in both waist and hip measurements with age, leading to a relatively stable WHR (Lemieux et al., 1996). Therefore only waist circumference was assessed in the studies described.

As discussed in Chapter 1, section 1.3.2, disagreement exists regarding the most appropriate cut-off points for waist circumference. In this thesis, central obesity was defined as per the International Diabetes Federation Task Force on Epidemiology and Prevention cut-off values (80cm in females) as this is consistent with research carried out in the Department of Surgery, Trinity Centre for Health Science, St. James's Hospital, Dublin examining the relationship between abdominal obesity and cancer (Healy et al., 2010a, Ryan et al., 2008). In all studies described, waist circumference was however described as both >80cm and >88cm to examine the relative percentage in each category.

2.5.2.1 Waist Circumference Measurement Protocol

Waist circumference was measured using a non-stretch flexible tape placed directly on the skin at the mid-point between the superior border of the iliac crest and the lowest rib, following normal expiration (WHO, 2011). Participants were asked to identify the two anatomical points on their own body and estimate the mid-point. Participants held the tip of the tape in place while they turned on the spot, allowing the tape to wrap around them. The tape was checked to ensure it was positioned perpendicular to the long axis of the body and parallel to the floor. Measurements were taken in duplicate, to the nearest millimetre, and averaged for data entry. All measurements were completed by the same rater with the exception of Study IIa (Chapter 4) where initial measurements were completed by Dr. Laura Healy and Dr. Paul Carroll as part of separate projects.

2.5.3 Blood Pressure

Blood pressure represents the force or pressure exerted by the blood against the walls of the arteries during a cardiac cycle (Katch et al., 2011b). The gold standard method of measuring blood pressure is by measuring intra-arterial pressure using a catheter; a method which is inappropriate for asymptomatic individuals (Ehrman et al., 2010). The auscultatory method is recommended for accurate blood pressure measurement in the clinical or research environment (Chobanian et al., 2003). Measurements can be taken using either a mercury or aneroid sphygmomanometer which has been calibrated prior to use. An inflatable cuff is placed around the upper arm and the pressure is increased to occult the brachial artery. As the pressure is released from the cuff, the examiner listens through a stethoscope at the cubital fossa for Korotkoff sounds. The auscultatory method was used to measure blood pressure during all assessments in this thesis. Oscillometric methods, using electronic sphygmomanometers, can also be used to measure blood pressure, however this technique should only be used when auscultatory techniques are not possible due to inaccuracies (Amoore, 2012). Oscillometric methods were used to monitor blood pressure during the exercise class (Chapter 3).

2.5.3.1 Blood Pressure Measurement Protocol

During all assessments blood pressure was measured using the auscultatory method according to the guidelines of Chobanian and colleagues (2003) using a Welch Allyn Maxi-Stabil 3 Aneroid Sphygmomanometer and a 3M™ Littmann® stethoscope.

In preparation, participants sat quietly in a chair for at least 5 minutes with back supported, feet on the ground, arm supported at heart level. The cuff was wrapped firmly around upper arm at heart level aligned with brachial artery ensuring that the cuff encircled at least 80% of the upper arm. The stethoscope bell was placed below the antecubital space over the brachial artery. The cuff pressure was inflated quickly to ≥20 mmHg above the first Korotkoff sound and then released slowly at rate equal to 2 to 5 mmHg per second. Systolic blood pressure was defined at the point at which the first of two or more Korotkoff sounds was heard (phase 1) and diastolic blood pressure at the point before the disappearance of Korotkoff sounds (phase 5) (Table 6).

Measurements were taken in duplicate and averaged for data entry. In breast cancer survivor cohorts' measurement were completed on the non-surgical side and in the *BRCA* cohort on the right arm for consistency.

Table 6 Phases of the Korotkoff Cycle

Phase of Korotkoff Cycle	Description
Phase 1 (SBP)	First, initial sound of faint, repetitive, and clears tapping sounds. Approximates the SBP
Phase 2	A soft tapping or murmur sound that has a swishing quality. It begins 10-15 mmHg after the onset of phase 1 sounds.
Phase 3	Return of loud tapping sounds which are crisper and louder than phase 1 or 2 sounds.
Phase 4 (true DBP)	Sounds become muffled and are less distinct and less audible, may be described as soft or blowing.
Phase 5 (clinical DBP)	Complete disappearance of sound that usually occurs 8-10 mm Hg from phase 4.

Abb: SBP = systolic blood pressure, DBP = diastolic blood pressure

2.5.4 Blood Biochemistry

The following sections describe the blood biomarkers that were measured for metabolic screening. This includes not only the parameters included in the definition of the MetSyn (high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and fasting glucose) but also a complete lipid profile, HbA_{1c}, insulin resistance and a measure of inflammation. The section concludes with the venous sampling protocol used in this thesis.

2.5.5 Lipid Profiles

Hyperlipidaemia is a crucial component of atherosclerotic plaque formation and increases mortality from CVD (Katch et al., 2011d). Lipids, such as cholesterol and TG, are non-soluble in water and therefore must combine with a carrier protein to form a lipoprotein when circulating in the blood. Total serum cholesterol reflects a combination of the different lipoproteins in circulation. Individual lipoproteins serve different functions. Low-density lipoprotein (LDL-C) and very low density lipoprotein transport cholesterol and TG to organs and artery walls and therefore contribute to the formation of fatty plaques in the arteries. HDL-C transports lipids to the liver, where they are synthesised and excreted. Blood lipids can

be altered by diet and hormonal treatment such as oral contraceptive or hormonal therapy for breast cancer (Redig and Munshi, 2010), and treated most effectively using statins.

A lipid profile is the term given to the measurement of total cholesterol (TC), HDL-C, LDL-C and TG. The TC:HDL-C ratio (TC divided by HDL-C) estimates CVD risk; >4.5 indicates a high risk of CVD and a ratio of 3.5 or lower is considered healthy. LDL-C is not measured directly in the lipid profile but rather it is estimated using other components of the lipid profile inputted into Friedewald's equation. Friedewald's equation is invalid if TG levels are >4.5 $mmol.L^{-1.}$ Measurements should be taken following at least a 9- 12 hour fast (National Cholesterol Education Program Expert Panel, 2002)

2.5.6 Measures of Glucose Metabolism

Elevated fasting plasma glucose is the original measure of glucose dysmetabolism used to diagnose T2DM (Malkani and Mordes, 2011, ADA, 2012). Samples should be collected following at least 8 hours of no caloric intake, but can be affected by a number of extrinsic factors such as intense exercise, prolonged fasting, acute illness or alcohol (Malkani and Mordes, 2011) and should be supplemented with additional measures for a definitive diagnosis of T2DM.

HbA_{1c} provides a measure of average blood glucose levels over the preceding 2-3 months and is considered the gold standard for measuring glycaemic control (Hanas and John, 2010). Plasma HbA_{1c} correlates well with mean plasma glucose levels, but unlike glucose testing, fasting samples are not required and measurements are not affected by acute changes in diet or activity. A value ≥6.5% is considered diagnostic for T2DM (ADA, 2012, Malkani and Mordes, 2011).

Insulin resistance is not included in the current definition of the MetSyn, however is considered a core component of the syndrome and is therefore essential to measure for comprehensive metabolic screening (Alberti et al., 2009, ADA, 2012). The gold standard method of measuring insulin resistance is the hyperinsulinaemic-euglycaemia clamp test,

however for the majority of trials, this method is inappropriate due to the labour and equipment related costs. Other methods include the oral glucose tolerance test or mathematical equations using fasting insulin or glucose values (Borai et al., 2011).

HOMA-IR is widely used tool for calculating insulin resistance which has been validated against the gold standard (Matthews et al., 1985). The model is based on the assumption of a feedback loop between the liver and the β-cells in the pancreas and describes the interactions between glucose and insulin dynamics using the following formula: ((fasting insulin ($mU.L^{-1}$) x fasting glucose ($mmol.L^{-1}$)) / 22.5) (Matthews et al., 1985, Muniyappa et al., 2008). It is suitable for use in people with glucose intolerance, mild to moderate diabetes and other insulin resistant conditions. High HOMA-IR values indicates low insulin sensitivity (insulin resistance) while low values indicates high insulin sensitivity.

2.5.7 Inflammatory Marker

CRP is a protein, found in blood, increases during the inflammatory response to injury or infection (Katch et al., 2011d). CRP increases rapidly in response to acute inflammation. Chronic low-grade inflammation is considered a core element of CVD and the MetSyn. CRP is the most widely used marker of inflammation as it is an almost perfect marker of inflammation and is economical to measure (Biasucci, 2004). Inflammatory levels can be reduced by pharmacological agents such as statins and ACE inhibitors.

2.5.7.1 Venous Sampling Measurement Protocol

Venous blood samples were collected in the morning following a 12-hour fast by a trained phlebotomist (Emer Guinan or Phlebotomy staff at the out-patients department St. James's Hospital). Participants were asked to refrain from moderate-to-vigorous intensity exercise for 24 hours prior to collection. Participants were allowed to drink water during the fasting period and medications for cardiovascular stability were permitted (i.e. antihypertensive medications).

Samples were taken by venepuncture after minimal compression with a tourniquet. Blood samples were taken in tubes containing fluoruide oxalate to measure glucose, in lithium coated tubes to measure the lipid profile (TC, HDL-C, LDL-C, and TG) and HbA_{1c} and in red serum tubes to measure insulin and CRP. Two serum and one EDTA tube were also collected for storage. Following collection, tubes were inverted 8-10 times to ensure that the coagulant was mixed throughout. Samples were analysed for lipid profile, glucose, insulin and CRP within a few hours by the Central Pathology Laboratory at St. James's hospital according to standard procedures. Extra tubes were processed and aliqouted for storage in -80°C freezer according to the procedure outlined in Appendix IX.

2.6 Secondary measures

The following sections will detail measurements which did not feature in all studies presented in this thesis, but which were completed as part of individual protocols. These include measurement of dietary intake, aerobic fitness and RMR.

2.6.1 Assessment of Dietary Intake

Many of the components of the MetSyn, in addition to body fatness, can be influenced by both diet and exercise (Leao et al., 2011). When implementing an exercise intervention with the aim of modifying metabolic and anthropometric variables (Chapter 3) it is necessary to account for change in diet in order to fully attribute potential results to exercise alone.

Accurate dietary assessment is difficult to attain, however there are a number of techniques available including food frequency questionnaires (FFQ), 24-hour diet recall, and estimated dietary records (http://dapa-toolkit.mrc.ac.uk/dietary-assessment/index.html accessed 17.10.2012). All methods are relatively inexpensive to administer however all are subject to bias and inaccuracies related to misreporting by participants (Kipnis et al., 2002). FFQ's provide a global estimate of an individual's habitual dietary intake over a defined period (week, month, year), however are completed in retrospect and therefore increase the risk of underreporting or over-reporting dietary intake (Kipnis et al., 2002). Similarly, a 24-hour diet recall is an interview-based technique that gathers information regarding food and beverage consumption in the last 24-hours.

Estimated food diaries are a prospective method of measuring detailed dietary intake. Limitations associated with completion of a food record include participant burden, risk that the participant may complete the diary in retrospect and the act of completing a food diary may alter dietary intake and thus provide inaccurate results (http://dapa-toolkit.mrc.ac.uk/dietary-assessment/index.html accessed 17.10.2012). In order to improve accuracy and compliance, detailed written instructions should be provided in addition to face-to-face explanations.

2.6.1.1 Assessment of Dietary Intake Measurement Protocol

Dietary intake was assessed using an estimated 3 day diet diary (Medical Research Council, Human Nutrition Research Food Diary, Cambridge, UK). Participants were asked to record all food and beverages consumed over 3 consecutive days comprising 2 weekdays and 1 weekend day and received verbal and written instructions (Appendix X) on how to complete the diary.

For each food or beverage item, participants provided details of brand names, cooking methods, nutritional additives used during cooking, portion size consumed and details on any leftovers. Portion sizes were recorded as household measures, such as cups and tablespoons, weights given by manufacturers on packaging or as measures of small, medium or large portion sizes with the assistance of a food atlas provided within the food diary. A food atlas provided a pictorial representation of these portion sizes for 15 commonly consumed foods. Participants were also instructed to answer a supplemental dietary questionnaire contained within the food diary consisting of 12 questions to acquire information on types and brands of milk, butters, spreads, oils and breads used, whether the fat and skin of meat is usually consumed and food preparation techniques used. Details of recipes used were also sought, including a list of ingredients. Participants were encouraged to keep the food diary as they went about their day and to refrain from recording retrospectively by memory. Participants were instructed to maintain usual eating habits throughout the assessment period. Data on the use of nutritional supplements were also collected and if consuming nutritional supplements, participants were asked to provide the brand name, the name of the nutritional supplement in full and the dosage of supplement taken.

Nutrient and food group analyses were conducted using WISP (Weighed Intake Software Package) version 3.0 (Tinuviel Software) nutrient analysis software programme incorporating the use of McCance and Widdowson Food Composition Tables 5th and 6th editions with supplements.

2.6.2 Aerobic Fitness

Aerobic fitness describes the functional capacity of the cardiorespiratory system. The gold standard criterion for assessing aerobic fitness is by measuring maximal oxygen uptake (VO_2max). VO_2max defines the maximal amount of oxygen a person can consume to produce energy aerobically every minute (Katch et al., 2011e). Maximal exercise testing is the gold standard method of measuring aerobic fitness. The most accurate method for measuring VO_2max is using gas exchange, involving the measurement of expired gases and respiratory volume during a maximal exercise test (Lear et al., 1999). VO_2max can also be estimated from other physiological parameters such as heart rate. VO_2max can be expressed in either absolute terms ($l.min^{-1}$) or relative to body mass ($ml.kg^{-1}.min^{-1}$). Maximal test protocols usually involve an incremental test which terminates when the participant either reaches exhaustion or another subjective reason for stopping. Protocols can be completed either in the laboratory setting using treadmill or cycle ergometer based protocols or in the field setting using bleep tests. Test protocols should be complete within 8-12 minutes (Vanhees et al., 2005).

Maximal exercise testing or open circuit spirometry to measure expired gases is not always safe or indicated. VO_2max testing is associated with a number of risks due to the maximal nature of testing and therefore for safety, and particularly in clinical populations, medical supervision is required (Jones et al., 2008). Researchers are encouraged to consider the setting and purpose of their exercise testing. In Study I in this thesis, aerobic capacity testing was measured in the physiotherapy department at St. James's Hospital with access to cardiac specialist nursing staff and the hospital "crash team" in case of emergency. The cohort studied however were only 2-6 months post chemotherapy and a large percentage of participants (62%) had received anthracycline based chemotherapy and/or trastuzumab, both of which are associated with cardiotoxicity (Criscitiello et al., 2012, Floyd et al., 2005). In Study IIb, testing was completed at the Trinity Centre for Health Sciences, St. James's Hospital. While an automated external defibrillator is available at this site and the tester had training in

Advanced Cardiac Life Support, on-site medical supervision was not available. In both studies aerobic capacity was measured for fitness classification purposes, in Study I to assign participants to a baseline aerobic fitness category for subsequent exercise prescription and in Study IIb for descriptive purposes with future interventions in mind. Therefore it was deemed neither necessary nor appropriate to conduct maximal exercise testing in these cohorts.

When a maximal exercise test is not indicated, a submaximal exercise test, without gas-exchange measurement, may be performed (Jones et al., 2008, May et al., 2010). Submaximal tests predict fitness on the basis of workload achieved at a predetermined submaximal heart rate (Noonan and Dean, 2000), usually 80-90% HRmax (HRmax = 220-age ((Thompson, 2010b))). Submaximal exercise tests are appropriate for individuals who are deconditioned, including oncologic populations, or when testing outside of the clinical setting (Lear et al., 1999, Noonan and Dean, 2000, Jones et al., 2008).

Inherently a number of limitations exist with submaximal exercise testing largely related to the underlying assumptions regarding the relationships between heart rate and V_{O_2max}, that may be particularly altered in cancer survivors (McNeely et al., 2006). Several adjuvant treatments are associated with cardiotoxicity increasing risk of cardiomyopathy (Shapiro and Recht, 2001, Theodoulou and Seidman, 2003), which would affect heart rate and its potential to be used as a predictive outcome during an exercise test. In this thesis, participants with a LVEF <40%, as measured by a routine multi gated acquisition (MUGA) scan, were excluded to optimize heart rate accuracy during submaximal exercise testing.

The Modified Bruce Protocol is an adaptation of the original Bruce protocol used to measure cardiorespiratory fitness (Noonan and Dean, 2000). The original Bruce Protocol starts at a speed of 1.7 mph and a grade of 10%. In contrast, the Modified version of the protocol starts at the same speed but with the treadmill horizontal (grade = 0%). The speed at which the treadmill moves remains the same for the first three stages of the protocol, during which the slope increases. The Modified Bruce Protocol is found to elicit similar physiological responses, particularly in heart rate, compared to equivalent workloads on the Bruce protocol in both healthy individuals (Trabulo et al., 1994) and in those with coronary artery disease (McInnis and Balady, 1994, McInnis et al., 1992). The protocol was chosen for use in this thesis as it is a

walking test, which reflects the activity that both breast cancer survivors and the larger population most frequently engage in (Irwin et al., 2004, Hallal et al., 2012), and therefore is likely the most familiar form of activity to use for an exercise test, for its ease of delivery and its previous use in other oncologic populations (Spence et al., 2007).

2.6.2.1 The Modified Bruce Measurement Protocol

Safety Considerations

Participants in Study I (2-6 months post chemotherapy) received written medical clearance to complete the exercise test from their treating oncologist. Participants in Study IIb (2-5 years post diagnosis) completed the physical activity readiness questionnaire (PARQ) (Appendix XI) which was developed by the Canadian Society for Exercise Physiology to identify adults who may be at risk by commencing or increasing exercise (Adams, 1999). The PARQ collects information regarding the presence of a heart condition, chest pain, dizziness, bone or joint pain, use of antihypertensive medication or diuretics and any other known contraindication to exercise. Further details were required if participants responded "yes" to any questions. For example, participants taking beta-blockers to control blood pressure were excluded due to the lowering effects of these medications on heart rate (primary test outcome) however other anti-hypertensive medications were permitted provided resting blood pressure measurement on the morning of testing were within normal ranges. Many participants taking adjuvant hormonal therapy experienced regular bone or joint pain. In this circumstance participants were advised to be aware of any increase in symptoms during the test. Testing was not completed if participants responded "Yes" to $\geq$2 questions.

Resting heart rate was measuring following at least a 5 minute rest period prior to testing. Upon test completion, participants were monitored for signs of distress (pallor, chest pain, dyspnoea) and continued to wear the Polar heart rate monitor until heart rate had returned to within 10bpm of resting levels.

Testing Procedure

Participants wore a heart rate monitor (Polar FT4F Heart Rate Monitor) to monitor heart rate response during the test. Testing commenced with a 5 minute warm-up / familiarisation period during which participants walked on the treadmill at 2.7 $km.hr^{-1}$ (starting speed for first three levels of the Modified Bruce Protocol). Participants were permitted to use 1-2 fingers for handrail support but not as a means of maintaining balance.

Following the warm-up, the treadmill was stopped, and heart rate was monitored until it returned to within 10bpm of resting levels. Participants were shown some gentle stretches for the major lower limb muscle groups (quadriceps, hamstrings and gastrocnemius). The testing protocol and target heart rate was explained to participants prior to commencing the test. The protocol progressed by increasing the speed and/or treadmill gradient every three minutes as per Table 7. Participants were asked to rate themselves on the Borg Rate of Perceived Exertion Scale (Appendix XII) at the end of each stage (with 30 seconds remaining). Otherwise participants were advised not to talk during the test unless to communicate difficulties with the protocol. Heart rate was recorded at the end of each stage. The test was terminated when participants reached 85% HRmax (calculated as 85% (220-age)) or if they requested to stop due to physical problems such as pain, fatigue, dizziness or difficulty breathing. The ACSM guidelines for stopping an exercise test were adhered to (Thompson, 2010a) The test ended with a cool-down which consisted of asking participants to walk at a comfortable slow pace to allow the heart rate to slowly return to resting levels.

Table 7 Modified Bruce Treadmill Protocol

Stage	Speed ($km.hr^{-1}$)	Grade (%)	Duration (min)
0	2.72	0	3
0.5	2.72	5	3
1	2.72	10	3
2	4.0	12	3
3	5.44	14	3
4	6.72	16	3
5	8.0	18	3
6	8.8	20	3
7	9.6	22	3

Predictive Equations

While regression equations are available for the Modified Bruce protocol these tend to overestimate exercise capacity and as the steady-state heart rate requirement is rarely met in clinical populations, it is recommended to report exercise capacity using metabolic equivalents (METS) (Lear et al., 1999). Energy expenditure can be estimated by multiplying MET values by 3.5 (Ainsworth et al., 2000). To achieve the steady-state requirements to accurately estimate energy expenditure, MET values were only taken from the stage from which at least two minutes were completed.

The ACSM propose a set of metabolic calculations for predicting energy expenditure using MET values (Glass, 2007). The ACSM walking equation (VO_2max = (3.5) + (speed ($m.min^{-1}$) x 0.1) + (grade (decimal) x speed ($m.min^{-1}$) x 1.8)) was chosen for use in this work as it is one of the most widely used equation and is most accurate for speeds of 1.9 – 3.7 mph (Glass, 2007). This speed range is similar to the speed range from stage 0 to stage III of the Modified Bruce Exercise protocol (1.7 – 3.4 mph). Participants were not expected to reach stages beyond this during their exercise test. The ACSM equations have been shown to accurately predict the energy expenditure associated with walking when compared to other widely used equations (Hall et al., 2004). Finally, results were compared to age and gender-matched normative data for VO_2max to classify fitness as poor, fair, average, good or excellent (Appendix XIII)(Katch et al., 2011e).

2.6.3 Resting Metabolic Rate

Direct calorimetry is the most accurate method of measuring RMR, however this technique is considered impractical as it is expensive, cumbersome and testing is generally unpleasant for the subject (Groff and Gropper, 1999). A number of predictive mathematical equations also exist including the Mifflin-St Jeor equation, the Harris-Benedict equation and the Schofield equation, using gender, age, weight and height to estimate RMR. Such equations are used extensively in the clinical setting due to their ease of use and in-expense, however they are associated with a number of limitations and errors, limiting their accuracy for use in research (Frankenfield et al., 2005).

RMR is most commonly measured by indirect calorimetry which measures the respiratory quotient (RQ). RQ represents the heat produced by oxidative processes, by calculating the ratio of expired carbon dioxide to oxygen consumed (VCO_2/VO_2) (Matarese, 1997, Groff and Gropper, 1999). In this thesis RMR was measured by indirect calorimetry using the QUARK metabolic cart (Cosmed, Rome, Italy). The QUARK metabolic cart is an open-circuit calorimeter that has been validated to measure RMR in both spontaneously breathing (Blond et al., 2011) and mechanically ventilated patients (Sundstrom et al., 2013). Gas collection can be completed by either "breath by breath collection" or the canopy dilution method. The canopy method, which involves covering the head of the participant with a transparent plastic hood, connected to a blower to produce a constant flow of air into the hood, was used in this thesis. In spontaneously breathing healthy weight, overweight and obese adults, the QUARK metabolic cart canopy technique has been highly correlated with the gold standard indirect calorimeter DELTATRAC II™ for RMR ($r=0.95$), RQ ($r=0.30$), VO_2 ($r=0.93$) and VCO_2 ($r=0.95$) ($p<0.05$ for all) and displayed narrow limits of agreement for all measures (Blond et al., 2011).

2.6.3.1 Resting Metabolic Rate Measurement Protocol

RMR was assessed in accordance with the guidelines of Compher and colleagues (2006). A ten minute canopy protocol has been shown to be a reliable method of measuring RMR in free-living postmenopausal women (Horner et al., 2001).

Equipment and Participant Preparation

Prior to every test, both the flow device, measured with a bidirectional digital turbine, and gas analyser device (sampling line) were calibrated. The turbine was calibrated using a 3 litre calibration syringe. The system allows automatic calibration of gas analysers to zero, gain and delay of O_2 and CO_2 gas sensors (Quark User manual, COSMED, Italy).

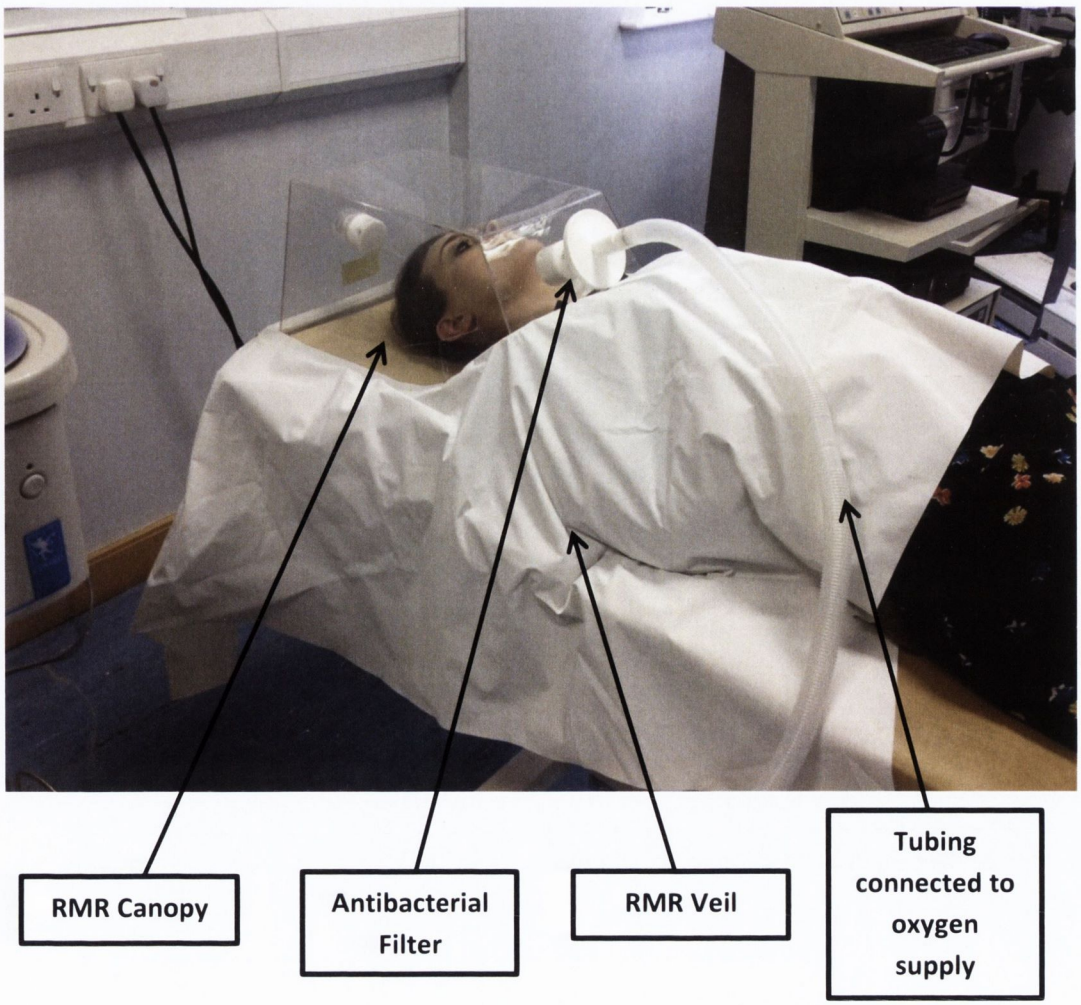
Participants were fasting for 12 hours (at least 6 hours recommended by Compher et al., 2006) and were required to abstain from caffeine overnight, nicotine for at least 2 hours and alcohol for at least 2 hours prior to measurement. Participants were asked not to complete any moderate intensity physical activity for at least 2 hours or vigorous intensity activity for at least 14 hours prior to testing. Participants were informed of these requirements in an

information leaflet which was delivered by post prior to the assessment. Prior to testing participants rested comfortably in the supine position for 7-20 minutes.

Testing Procedure

During testing the following criteria were adhered to, to ensure a suitable environmental setting: room temperature of 20°C-25°C (if the participant was cold a blanket was provided), quiet room and room lights turned off (light entered via the window). Participants were asked to refrain from moving during the test. To commence testing the tube and antibacterial filter were connected to the canopy and a continuous flow of oxygen was applied from the canopy blower. The canopy was placed over the participants head and shoulders and the veil was checked for air leaks (Figure 11).

Figure 11 RMR Testing Set-Up



Ventilatory rate was regulated directly by the QUARK RMR to achieve a FeCO2 between 0.7% and 1.3%. The test commenced when steady-state FeCO2 was achieved. Testing was completed over 20 minutes, with the initial 5 minutes discarded. During testing FeCo2 was managed by adjusted ventilatory rate to maintain a value between 0.7% and 1.3%. RQ was maintained between 0.7 and 1.0. Results were taken from a 5-minute stable period within the subsequent 15 minutes of testing defined by the following criteria:

- RQ: >0.7, <1.0 (≤5% variation)
- ≤10% variation in VO_2
- ≤10% variation in VCO_2

The system software used the abbreviated Weir equation to calculate RMR: [RMR = (3.9 (VO_2) + 1.1 (VCO_2))*1.44], where 3.9 represents the number of calories generated when 1L of oxygen is consumed and 1.1 represents calories produced when 1L of carbon dioxide is consumed (Matarese, 1997). RMR was expressed in absolute values ($kJ.day^{-1}$) and as RMR adjusted for FFM ($kJ.day^{-1}.kg^{-1}$) using the methods recommended by Ravussin and Bogardus (1989) (Chapter 5, section 5.3.3.1)

2.7 Ethical Approval

Ethical approval for all studies contained in this thesis was granted by the Joint Research Ethics Committee of the Adelaide and Meath, incorporating the National Children's Hospital / St. James's Hospital. All participants provided written informed consent. Letters of ethical approval for all studies can be found in Appendix I.

Chapter 3 Study I: The PEACH Trial

The Effect of Aerobic Exercise on Metabolic and Inflammatory Markers in Breast Cancer Survivors – A Pilot Study

Statement of Author's Contribution

The study concept and design were developed by the student Emer Guinan (EG), lead investigator on the PEACH trial Dr Julie Broderick (JB) and project supervisor Dr Juliette Hussey (JH). The assessment protocol and procedures were investigated and developed by EG. The intervention protocol was developed by JB. Participant recruitment and attainment of informed consent was completed by both EG and JB. All outcome assessments were completed by EG. Exercise classes and progression were managed by JB. Data analysis and interpretation was completed by EG and JB with contributions from statistician Dr. Kathleen Bennett (KB). Medical advice was received from co-supervisor Ms Elizabeth Connolly, Dr. Dearbhaile O'Donnell (medical oncologist) and Professor M John Kennedy (medical oncologist). EG was responsible for drafting Chapter 3 in this thesis and the subsequent manuscript. All authors approved the final version of the published manuscript.

3.1 Introduction

This chapter contains the methods, results and discussion of the first study undertaken as part of this thesis. Study I describes a pilot exercise intervention designed to examine the effect of an 8-week aerobic exercise programme on metabolic and inflammatory markers indicative of breast cancer risk in breast cancer survivors 2-6 months post chemotherapy. While previous interventions have examined the effect of exercise on various biomarkers individually (Chapter 1, section 1.5.1), the study described in this chapter is the first to examine the effect of exercise on all components of the MetSyn in breast cancer survivors. In addition, trials that have been conducted to date have included breast cancer survivors at various times into survivorship, spanning 1 to almost 30 years post diagnosis. Courneya and Friedenreich describe the period from 3-6 months post cessation of adjuvant treatment as the "rehabilitation period", a time when the side-effects of treatment reduce and normal life resumes (Courneya and Friedenreich, 2001). Unlike previous studies, Study I described within this chapter, included only participants within this defined rehabilitation period.

This study has been published in Supportive Care in Cancer (Appendix II)

Guinan E., Hussey J., Broderick J.M., Lithander F.E., O'Donnell D., Kennedy M.J., Connolly E.M. (2013) The Effect of Aerobic Exercise on Metabolic and Inflammatory Markers in Breast Cancer Survivors – A Pilot Study. Support Care Cancer DOI 10.1007/s00520-013-1743-5

3.2 Objectives and Research Design

The overall aim of Study I was to examine the effect of an aerobic exercise intervention on metabolic and inflammatory markers in breast cancer survivors 2-6 months following adjuvant chemotherapy.

The specific objectives of Study I were:

- To describe the metabolic risk profile of breast cancer survivors 2-6 months post cessation of chemotherapy.
- To evaluate the effect of an 8-week aerobic exercise intervention on a clustering of anthropometric and blood biomarkers for breast cancer risk, including the MetSyn, insulin resistance and CRP in breast cancer survivors 2-6 months post completion of adjuvant chemotherapy.
- To investigate the effect of an 8-week exercise intervention on objective and self-reported physical activity and adherence to physical activity guidelines.
- To monitor changes in dietary intake during an exercise intervention.

Study I was designed as an ancillary study to a larger RCT entitled the Prescribed Exercise after Chemotherapy (PEACH) trial. The PEACH trial took place in St. James's hospital during 2009 and 2010. The PEACH trial was a single-blind RCT which examined the effect of an 8-week aerobic exercise intervention on physical activity, aerobic fitness and quality of life in a heterogeneous group of cancer survivors 2-6 months post chemotherapy. The published PEACH protocol can be found in Appendix II (Walsh et al., 2010). The ancillary study (Study I) described in this thesis included the same exercise intervention and assessment time-points as the PEACH trial, however primary outcomes were different as explained in the methods section below (section 3.3.2). The design characteristics of an RCT are discussed in Chapter 2, section 2.2.1.

3.3 Methods

3.3.1 Sampling and Recruitment

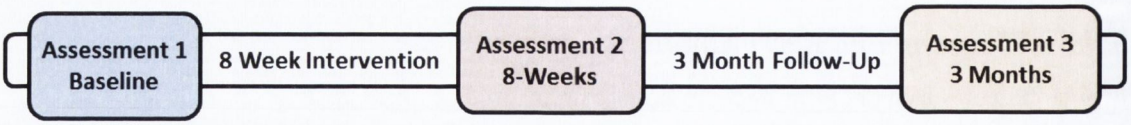
Breast cancer survivors who had previously consented to participate in the PEACH trial were recruited for the ancillary study. Participants were excluded for the following reasons i) evidence of active cancer, ii) chronic medical and orthopaedic conditions that would preclude exercise, iii) on beta-blocker medications, iv) BMI >35kg.m^{-2}, v) prior history of cancer in the previous 5 years (exception: non-melanoma skin cancer and non-invasive cancer of the cervix, vi) confirmed pregnancy, vii) dementia or psychiatric illness that would preclude ability to participate, viii) incomplete haematological recovery after chemotherapy (WCC <3, Hb <10 or platelets <100), ix) LVEF post chemotherapy < 50% or >20% deterioration of baseline pre-systemic treatment.

Recruitment was completed by the author (Emer Guinan) and the lead investigator of the PEACH trial Dr. Julie Broderick. Participants were recruited from the oncology day ward at St. James's hospital during outpatient adjuvant chemotherapy appointments and at St. Luke's' Hospital Dublin during outpatients radiotherapy appointments. At both centres participants were informed of the study by the medical staff and were directed to speak with study personnel if they were interested in receiving further information. In addition, potentially suitable participants identified through the hospital database who were receiving adjuvant treatment elsewhere were mailed study information leaflets (Appendix III) and expression of interest forms inviting them to contact study investigators if interested in participating.

3.3.2 Measures and Testing Protocol

All measurements and the exercise intervention were completed in the Department of Physiotherapy Outpatient Department, St. James's Hospital. This setting was chosen to ensure maximum safety and to facilitate rapid access to hospital emergency services, including the "crash team", in case of adverse events. Participants attended three assessment appointments, following a 12 hour fast, during which all measures were completed. Testing was completed at baseline (pre-randomisation), immediately post-intervention (8-week visit) and three months post-intervention (3-month visit) (Figure 12).

Figure 12 PEACH Trial Assessment Time-Points



Participants were randomised to either an exercise group (EG) or control group (CG) following the baseline visit as per the PEACH trial using a computer-generated random number list (GraphPad Software, San Diego, CA). Assessments were completed by the same researcher at every visit (Emer Guinan) who was blinded to the participants' group assignment. Randomisation and exercise class supervision was completed by Dr. Julie Broderick. The background, validity and reliability of all measures performed have been described in Chapter 2. All measurements were completed following a 12-hour fast.

The following measurements were completed in the listed order:

- **Standing height** was measured according to the procedures outlined in section 2.4.1.1.
- **Body composition**, including body weight, was measured using BIA according to the procedures outlined in section 2.4.1.1 and section 2.4.2.1.
- **Fasting blood samples** were drawn to measure insulin, glucose, HbA_{1c}, lipid profile and CRP as per the procedure outlined in section 2.5.7.1. Insulin resistance was estimated using HOMA-IR (section 2.5.6).
- Participants resting in a seated position and completed the: **Godin questionnaire** (section 2.3.1.4)
- **Resting blood pressure** was measured according to the procedures outlined in section 2.5.3.1.
- **Waist circumference** was measured according to the procedures outlined in section 2.5.2.1.
- **Aerobic fitness** was estimated using the Modified Bruce Treadmill protocol as per the protocol outlined in section 2.6.2.1
- Participants were provided with an **RT3 activity monitor** to wear for one week when leaving the centre (measurement procedure outlined in section 2.3.1.2).
- Participants were provided with a **3-day food diary** to be completed within one week of fasting blood samples (measurement procedure described in section 2.6.1.1).

3.3.3 Exercise Intervention

Following randomisation to the EG, participants completed an eight-week aerobic exercise intervention. This intervention included a twice weekly supervised exercise class and a home exercise programme. The home exercise programme was initially prescribed for at least one day per week and progressed to at least three days per week (alternate days to the supervised class). The CG did not engage in a structured exercise programme during the study period but were offered an exercise advice session following the final assessment. The class was supervised by a physiotherapist (Dr. Julie Broderick) and an assistant physiotherapist. Class size was restricted to 10 participants to allow at 1:5 patient:instructor ratio. The class was preceded by a 7-10 minutes warm-up (longer duration during initial classes) consisting of progressive aerobic exercises including marching on the spot and side-stepping and concluded with a 5 minute cool-down and stretching period.

Following the baseline aerobic fitness test, participants were classed as having "poor", "fair" or "average" fitness levels as per age and gender appropriate criteria (Appendix XIII) (Katch et al., 2011e) and these categories informed individualised exercise prescription during the class. Exercise class intensity and duration was progressed as shown in Table 8. Heart rate zones were calculated as a percentage of heart rate reserve (HRR) using the Karvonen formula: *[Target heart rate = ((maximum heart rate - resting heart rate) x % exercise intensity) + resting heart rate].* The Karvonen formula is a widely used mathematical equation that calculates exercise intensity based on heart rate (Goodman et al., 1988, Omiya et al., 2000). As there were no suitable guidelines for exercise prescription in cancer populations, exercise intensity and class duration were prescribed based on ACSM recommendations (Ehrman et al., 2010). As per the ACSM recommendations deconditioned individuals with lower fitness levels commenced at an aerobic intensity of 40% HRR while more conditioned individuals (average fitness levels) commenced at an intensity of 50% HRR. It should be noted however, that the use of HRR in oncology populations has limitations due to potential increases in heart rate variability following adjuvant chemotherapy and anti-HER2 directed treatments (Theodoulou and Seidman, 2003). To improve accuracy and safety during the exercise class, participants subjectively rated their perceived exertion using the Borg Rating of Perceived Exertion scale (Appendix XII). Participants were advised to train at a moderate intensity level (ratings 12-14).

Heart rate was monitored during the exercise classes using Polar heart rate monitors (Polar FT4F Heart Rate Monitor (Figure 13). Participants rotated between three aerobic exercise stations during the class that included the stationary bike, treadmill, rowing ergometer, stepper or other aerobic activities such as marching on the spot which were deemed suitable by the class instructor and required the participant to exercise in the prescribed heart rate zone. Participants completed 7 minutes on each of the three stations in the initial class which increased progressively throughout the programme to a maximum of 14 minutes per aerobic station at week 8.

Figure 13 Polar FT4F Heart Rate Monitor Watch and Sensor Belt



Participants were educated on how to use the Polar heart rate monitor during the exercise class and provided with one to bring home to monitor exercise intensity during the home exercise programme. The intensity of the home exercise programme progressed in the same manner as the supervised class (Table 8). Participants were free to complete any activity they preferred. The home exercise programme commenced by asking participants to exercise for 20 minutes at least one day per week in week 1 and increased to 150 minutes in week 8. This was chosen to ensure participants were exercising independently to recommended physical activity guidelines at programme completion (Garber et al., 2011, Schmitz et al., 2010, AICR, 2007). Data from the Polar heart rate monitor was downloaded at the start of each class to monitor adherence to the home exercise programme. In addition, participants completed exercise diaries and rated exercise intensity on the Borg Rating of Perceived Exertion Scale (see Appendix XIV for full home exercise instructions).

Table 8 Progression of the Intensity and Duration of the PEACH Programme

	Intensity (HR Zones)			Duration (min)	
	Poor	Fair	Average	Exercise Class*	HEP**
Week 1	35-55% HRR	40-60% HRR	45-65% HRR	21	20
Week 2	35-55% HRR	40-60% HRR	45-65% HRR	24	40
Week 3	40-60% HRR	45-65% HRR	50-70% HRR	24	60
Week 4	40-60% HRR	45-65% HRR	50-70% HRR	30	90
Week 5	45-60% HRR	50-65% HRR	55-70% HRR	30	105
Week 6	45-60% HRR	50-65% HRR	55-70% HRR	36	135
Week 7	50-60% HRR	55-70% HRR	65-75% HRR	36	135
Week 8	50-60% HRR	55-70% HRR	65-75% HRR	42	150

** Prescribed duration of exercise class; ** Target total duration of home exercise.*

Abb: HR = heart rate; HRR = heart rate reserve; HEP = home exercise programme

3.3.4 Data Analysis

Data was analysed using SPSS version 18.0 software (SPSS, Inc., Evanston, IL). Distributions were checked for normality using the K-S normality test. Data was analysed using an intention-to-treat analysis and the last-observation-carried forward procedure was used for missing variables. Secondary analysis examined if outcomes were influenced by adherence to the programme. Participants were grouped into two categories; adherence to >90% of the exercise class or attended all three CG assessments (per-protocol analysis) or those who either dropped out or adhered to <90% of the exercise class.

Baseline characteristics were compared using independent sample t-tests for normally distributed continuous variables, Wilcoxen Rank Sign test for non-normally distributed continuous variables and Pearson chi-squared and Fishers exact tests for categorical variables. Changes in endpoints were examined using repeated measures ANOVA. Where the assumption of sphericity was violated the Greenhouse Geisser test was used. Non-normally distributed data was examined using the Wilcoxon test (fasting glucose and CRP).[9] Unlike the repeated measures ANOVA this method did not allow for examination of between-group changes over repeated measures. Therefore between-group differences in variables at baseline, 8-weeks and 3-months were examined separately. Mean changes in variables from

[9] The non-parametric equivalent of the repeated measures ANOVA, the Friedman's test, was not used as the test could not distinguish between groups at any time-point.

baseline to 8-weeks, and from baseline to 3-months, are described with 95% CI. Statistical significance was set at $p<0.05$.

The lowest detectable value for CRP was 1 $mg.L^{-1}$. Therefore CRP was analysed in two ways: i) results <1$mg.L^{-1}$ were assigned a value of 1$mg.L^{-1}$ and the dataset was treated as a non-parametric scale variable and analysed using Wilcoxon Rank Sign test as described above, and ii) CRP results were divided into two groups (<3 $mg.L^{-1}$ and >3$mg.L^{-1}$) based on the cut-points for chronic low-grade inflammation (Grundy et al., 2005) and analysed as ordinal level data using Friedman's test. One participant with a baseline CRP value over ten-fold higher than subsequent results was excluded from CRP analysis as this result most likely represented an acute inflammatory event. Another participant was prescribed Metformin following baseline assessment and was excluded from analysis of metabolic variables.

3.4 Results

3.4.1 Participant Characteristics

Recruitment for the PEACH trial was completed between March 2010 and December 2010. A total of 200 participants were screened, 130 of whom did not meet study inclusion criteria. Reasons for ineligibility included evidence of active disease (n=6), living too far from study site (n=27), presence of confounding comorbidities (n=20), BMI >35$kg.m^{-2}$(n=12), history of cancer in the last five years (n=6), use of beta-blockers (n=5), participation in other studies that would confound results (n=18) and other (including lack of medical consent and poor adherence to chemotherapy treatment) (n=36).

Forty-three participants were enrolled onto the PEACH trial (accrual target of 64)[10], 32 of whom had breast cancer and 26 consented to the additional assessments associated with the study described in this chapter. Sixteen participants were randomly assigned to the EG and 10 to the CG. The groups had unequal numbers as participants were randomised as per the larger PEACH trial which included a heterogeneous population of cancer survivors. Baseline

[10] Refers to power analysis completed for the PEACH trial (Walsh et al., 2010)

demographics and treatment details, including group baseline comparisons are described in Table 9.

Table 9 Study I Participant Characteristics and Treatment Details

Variable	Total (n=26)	Exercise Group (n=16)	Control Group (n=10)	p-value*
Age (years)	48.1 (8.8)	50.1 (8.3)	45.1 (9.1)	0.16
Menopausal status†				
Premenopausal	18 (69.2)	9 (56.3)	9 (90)	0.09
Postmenopausal	8 (30.8)	7 (43.8)	1 (10)	
Marital status				
Married	14 (53.8)	9 (56.3)	5 (50)	0.76
Single	12 (46.2)	7 (43.7)	5 (50)	
Ethnicity				
Caucasian	25 (96.2)	15 (93.8)	10 (100)	1.00
Asian	1 (3.8)	1 (6.3)	0	
Current smoker	7 (26.9)	3 (18.8)	4 (40)	0.37
Months since diagnosis	8.6 (1.1)	8.5 (1.2)	8.8 (1.1)	0.52
Months since chemotherapy	3.7 (1.06)	3.8 (1.0)	3.6 (1.2)	0.69
Cancer Stage				
I	7 (26.9)	3 (18.8)	4 (40)	0.74
II	13 (50)	10 (62.6)	3 (30)	
III	6 (23.1)	3 (18.8)	3 (30)	
Surgery				
WLE	13 (50)	9 (56.3)	4 (40)	0.69
Mastectomy	13 (50)	7 (43.8)	6 (60)	
Axillary Clearance	15 (57.7)	9 (56.3)	6 (60)	
Radiotherapy	24 (92.4)	15 (93.8)	9 (90)	1.00
Hormonal Therapy	20 (76.9)	11 (68.8)	9 (90)	0.35
Tamoxifen	15 (57.6)	7 (43.8)	8 (80)	0.32
AI	5 (19.2)	4 (25)	1 (10)	
Additional Therapies				
Trastuzumab	5 (19.2)	3 (18.8)	2 (20)	1.00
Lapatinib	1 (3.8)	0	1 (10)	

Data are presented as the mean (standard deviation) for continuous variables and as frequency (percentage) for categorical variables. † Refers to menopausal status at diagnosis.

**p values comparing the exercise and control groups at baseline.*

Abb: WLE = Wide Local Excision; AI = Aromatase Inhibitors

All participants received anthracycline and/or taxane containing adjuvant chemotherapy (AC and taxol n=13; TC n=10; other n=3). Six participants, three per group, continued to receive anti-HER2 directed therapy during the intervention period. There were no differences between those included in the intention-to-treat analysis versus those included in the per-protocol analysis in terms of cancer stage (p=0.74), time since completion of chemotherapy (p=0.69), baseline BMI (p=0.98) or baseline physical activity (p>0.05 for all activity domains).

3.4.2 Data Normality

All variables were normally distributed at all three assessment time-points with the exception of fasting glucose (baseline and 3-months), TG (3-months) and CRP (baseline, 8-weeks, 3-months). Physical activity was measured by both the RT3 activity monitor and the Godin questionnaire. The following physical activity variables were not normally distributed: moderate intensity activity (RT3) (3-months), vigorous intensity activity (RT3) (baseline and 3-months), light activity (Godin) (baseline, 8-weeks, 3 months) and strenuous activity (Godin) (baseline, 8-weeks, 3-months). In an attempt to achieve log-normality, log transformations were applied to all variables. Log-transformed T2 TG had a K-S significance level of p=0.04 (Chapter 2, section 2.2.4). This variable was accepted as normally distributed. Log transformed vigorous activity (RT3) was also normally distributed. Non-parametric tests were used for fasting glucose, CRP, moderate intensity activity (RT3), light activity (Godin) and strenuous activity (Godin).

Distributions included in the per-protocol analysis were all normally distributed with the exception of fasting glucose (3-months), CRP (baseline, 8-weeks and 3 months), vigorous intensity activity (RT3) (baseline and 3-months), light activity (Godin) (baseline, 8-weeks, 3 months) and strenuous activity (Godin)(baseline, 8-weeks, 3-months). Log transformed vigorous intensity activity (RT3) was normally distributed, however normality was not achieved for the other variables and therefore non-parametric tests were used in the analysis.

3.4.3 Baseline Metabolic Profile

Baseline metabolic profile for all participants and baseline group comparisons are shown in Table 10. Overall, 50% of participants were overweight (n=13) and 23% (n=6) obese at study entry, with 19 participants (73%) centrally obese. At baseline the MetSyn was present in 34% (n=9) of participants.

Table 10 Study I Baseline Metabolic Profile

Characteristic	Total (n=26)	Exercise Group (n=16)	Control Group (n=10)	p-value*
Anthropometry				
Body weight (kg)	67.9 (11.3)	67.2 (11.6)	69.1 (11.4)	0.69
BMI ($kg.m^{-2}$)	26.4 (4.1)	26.4 (4.5)	26.3 (3.6)	0.98
BMI Categories				
Underweight	0	0	0	1.00**
Healthy weight	7 (27)	4 (25)	3 (30)	
Overweight	13 (50)	9 (56)	4 (40)	
Obese	6 (23)	3 (19)	3 (30)	
Waist circumference (cm)	86.5 (10.7)	87.4 (11.9)	85.1 (8.9)	0.60
Central obesity (WC >80cm)	19 (73)	12 (75)	7 (70)	1.00
Percentage body fat (%)	35.0 (4.8)	34.9 (4.9)	35.2 (4.9)	0.88
Fat free mass (kg)	43.8 (5.9)	43.38 (6.2)	44.39 (5.6)	0.68
Blood Pressure				
SBP (mmHg)	121.5 (11.8)	124.6 (11.5)	116.7 (10.9)	0.96
DBP (mmHg)	77.1 (9.3)	78.4 (10.7)	75.0 (6.4)	0.38
Hypertensive (BP >130/85mmHg)	4 (15)	3 (19)	1 (10)	1.00
Anti-hypertensive medication†	6 (23)	3 (19)	3 (30)	0.05
Lipid Profile				
TC ($mmol.L^{-1}$)	5.4 (1.0)	5.8 (1.0)	4.8 (0.5)	0.003
Dyslipidemia (TC > 5.2$mmol.L^{-1}$)	12 (46)	11 (69)	2 (20)	0.04
HDL-C ($mmol.L^{-1}$)	1.6 (0.5)	1.6 (0.6)	1.5 (0.5)	0.78
LDL-C ($mmol.L^{-1}$)	3.1 (0.9)	3.5 (0.9)	1.5 (0.8)	0.002
TG ($mmol.L^{-1}$)	1.5 (0.7)	1.4 (0.7)	1.5 (0.8)	0.86
Cholesterol medications†	2 (7)	2 (13)	0	0.51

Characteristic	Total (n=26)	Exercise Group (n=16)	Control Group (n=10)	p-value*
Glucose Metabolism				
Fasting glucose ($mg.dL^{-1}$)	87.3 (15)	86.4 (11)	86.4 (16)	0.85
Fasting Insulin ($mU.L^{-1}$)	9.1 (4.5)	10.5 (4.9)	6.9 (2.8)	0.06
Hyperinsulinemia (>$12mU.L^{-1}$)	6 (23)	5 (31)	0	0.12
Insulin resistance (HOMA-IR)	2.0 (1.0)	2.3 (1.1)	1.5 (0.6)	0.05
HbA_{1c} ($mmol.mol^{-1}$)	35.8 (2.5)	35.9 (2.3)	35.6 (2.9)	0.73
Glucose medications†	0	0	0	-
Inflammatory Marker				
CRP ($mg.L^{-1}$)	2.0 (3.6)	2.4 (7.5)	1.0 (0.8)	0.05
Metabolic Syndrome	9 (35)	6 (38)	3 (30)	1.00

Data are presented as the mean (standard deviation) for normally distributed continuous variables, as median (interquartile range) for non-parametric continuous variables and as frequency (percentage) for categorical variables.

**p values comparing the exercise and control groups at baseline.*

*** Fisher Exact test for groups "Healthy weight" versus" Overweight / Obese"*

† Refers to the number of participants taking prescribed medication

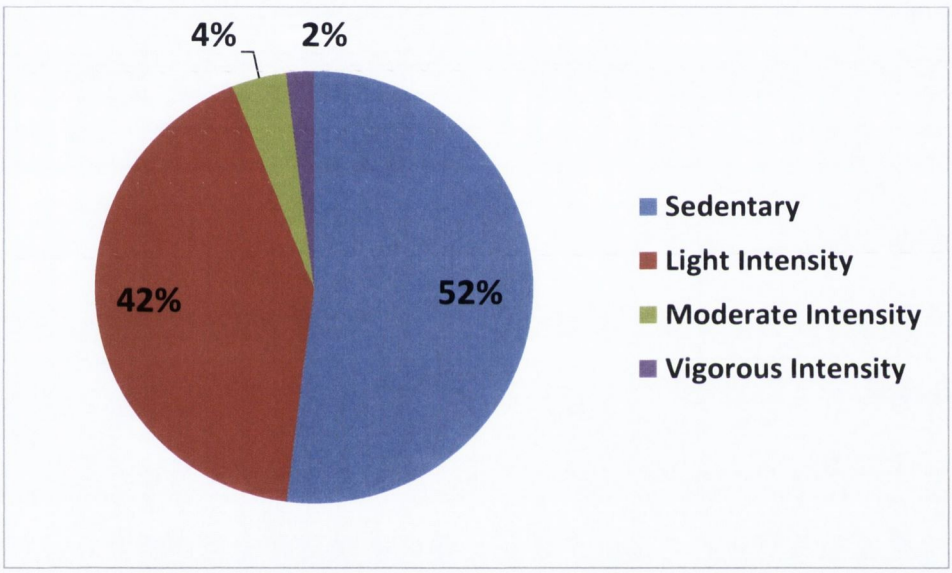
Abb: BMI = body mass index; WC = waist circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; HbA_{1c} = glycated haemoglobin A_{1c}; HOMA-IR = homeostatic model assessment index; CRP = C - Reactive Protein.

As shown in Table 10, groups were similar at baseline for all body composition measures and for all blood pressure-associated parameters ($p>0.05$), with the exception of use of anti-hypertensive medication which was significantly higher in the CG ($p=0.05$). Lipid profiles were significantly worse in the EG for TC ($p=0.002$), dyslipidaemia ($p=0.04$) and LDL-C ($p=0.001$). Similarly, HOMA-IR scores and inflammatory status were significantly higher in the EG ($p=0.05$ for both).

3.4.4 Baseline Physical Activity Levels and Aerobic Fitness

Baseline mean percentage time spent in each domain of physical activity, adherence to physical activity guidelines and baseline aerobic fitness categories for the total group and baseline comparisons are shown in Table 11. The majority of waking hours (52%) were spent sedentary (Figure 14). At baseline only 5 participants (20%) exercised to recommended physical activity guidelines. The majority of participants displayed "poor" or "fair" fitness levels.[11] Groups did not differ for activity or baseline fitness classifications.

Figure 14 Percentage Time Spent in Each Domain of Physical Activity



Percentage of time spent in each domain of activity in the overall group at entry to the study (baseline assessment).

[11]Participants were excluded from the study if baseline fitness levels were classed as "good" or "excellent". In the current study, no participant was excluded from the study based on this criterion.

Table 11 Study I Baseline Physical Activity Levels and Aerobic Fitness

Activity Domain	Total (n=26)	Exercise Group (n=16)	Control Group (n=10)	p-value*
Physical Activity				
RT3 Activity Monitor**				
Sedentary (min.day^{-1})	419.7 (143.2)	446.0 (127.0)	385.8 (107.9)	0.72
Light (min.day^{-1})	335.2 (92.3)	318.1 (72.1)	346.7 (101.0)	0.86
Moderate (min.day^{-1})	31.8 (32.6)	26.4 (26.7)	33.8 (43.4)	0.37
Vigorous (min.day^{-1})	19.2 (43.5)	15.7 (15.7)	11.2 (13.5)	0.41
Godin Questionnaire				
Light (MET-min.week^{-1})	0.0 (7.5)	1.5 (10.5)	0.0 (13.5)	0.88
Moderate (MET-min.week^{-1})	17.2 (15.8)	14.7 (18.5)	21.3 (9.8)	0.31
Strenuous (MET-min.week^{-1})	0.0 (0.0)	0.0 (0.0)	0.0 (9)	0.15
Total Weekly (MET-min.week^{-1})	25.1 (17.0)	23.1 (19.8)	28.2 (11.2)	0.47
Physical Activity Guidelines				
30 minutes 5 days.week^{-1}	3 (12)	2 (13)	1 (10)	1.00
150 minutes.week^{-1}	7 (27)	4 (15)	3 (30)	0.50
Aerobic Fitness Category†				
Poor	11 (42)	6 (38)	5 (50)	0.14
Fair	10 (38)	5 (31)	5 (50)	
Average	5 (20)	5 (31)	0 (0)	

Data are expressed as mean (standard deviation) for normally distributed continuous data, as median (interquartile range) for non-normally distributed continuous data and as frequency (percentage) for categorical data.

**p-value for independent samples t-test for normally distributed data and Wilcoxon Rank Sum Test for non-parametric data for difference between groups at baseline.*

*** One baseline RT3 data missing in the control group.*

† Refers to the percentage of participants within each fitness category. See Appendix XIII for age and gender specific population data.

3.4.5 Adherence to the Exercise Protocol

Adherence to the exercise protocol by the EG was monitored through i) attendance at supervised exercise class and ii) time spent in prescribed heart rate zone, as monitored using the Polar heart rate monitor both at home and in the supervised class. The mean percentage attendance at the supervised exercise class for those included in the intention-to-treat analysis was 71.9(34.4)% and 98.44 (2.9))% for those included in the per-protocol analysis. Two participants dropped out of the EG due to time constraints. A further six adhered to <90% of the exercise class but completed follow-up assessments. Reasons for <90% adherence included caring for a family member (n=2), return to work (n=1), concurrent adjuvant anti-Her2 directed treatment appointments (n=1) and family commitments (n=2).

Information from the Polar heart rate monitor was downloaded and examined for time spent exercising in the prescribed heart rate zones. During the supervised class, participants in the intention-to-treat analysis were in the prescribed heart rate zone for 102.65% of prescribed time and participants in the per-protocol analysis were in the zone for 107.04% of the prescribed time (i.e. participants spent slightly longer than prescribed in their individual heart rate zones). Similarly, participants spent a greater percentage of time engaging in exercise during the home exercise programme than that prescribed by the intervention (intention to treat analysis group completed 153% of prescribed minutes exercising and those in the per-protocol analysis completed 215% of prescribed exercise minutes). Individuals included in the intention to treat analysis spent an average of 36% of exercise time in the prescribed heart rate zones while those in the per protocol analysis spent 53% of exercise time in the prescribed heart rate zone.

Two members of the CG did not complete the final assessment due to illness unrelated to their breast cancer (recurrent upper respiratory tract infection (n=1), transient ischaemic attack requiring hospitalisation (n=1)) and were therefore excluded from the per-protocol analysis. The final per-protocol analysis included eight participants in the EG and eight in the CG.

3.4.6 Change in Metabolic and Inflammatory Variables

The results of the intention-to-treat analysis, with accompanying confidence intervals, for anthropometric, metabolic and inflammatory variables are presented in Table 12. There were no significant changes over the course of the intervention in any variables using this analysis. In contrast, the results of the per-protocol analysis (Table 13) show a significant (p=0.05) decrease in waist circumference in the EG versus CG over the study period.

The confidence intervals[12] in the intention-to-treat analysis (Table 12) suggest a number of within-group changes including a decrease in both waist circumference and HbA_{1c} in the EG (0-8weeks), and an increase in fasting insulin and in HOMA-IR scores in the CG (0-8week). There were also some suggestions of changes in TC, HDL-C and LDL-C in both groups over the study period. In the per-protocol analysis, body weight, BMI and %BF all appeared to decrease within the EG at both 0-8-weeks and 0-3 months (Table 13). Fasting insulin, HOMA-IR score and HbA_{1c} all decreased in the EG (0-8-weeks). Both groups experienced within-group changes in systolic and diastolic blood pressure and in variables within the lipid profile.

The Wilcoxon Rank Sum test was used to examine changes in the non-parametric variables of fasting glucose and CRP. Mean change and confidence intervals for both variables are presented in Table 12. There were no statistically significant differences between groups for either variable from 0-8-weeks (fasting glucose p=0.68; CRP p=0.07) or from 0-3months (fasting glucose p=0.84; CRP p=0.69). Similarly, in the per-protocol analysis (Table 13), groups were not different from each other at either time-point (0-8weeks: fasting glucose p=0.83; CRP p=0.42; 0-3months: fasting glucose p=0.45; CRP p=0.32). Similarly, when CRP was analysed in groups (<3 $mg.dL^{-1}$ vs. >3 $mg.dL^{-1}$) using Friedman's test, no changes were found using either intention to treat or per-protocol analysis (Table 14).

[12] Confidence intervals which contain zero suggest no change. A confidence interval that does not contain zero suggests a significant within group change (Chapter 2, section 2.2.4)

Table 12 Change in Metabolic and Inflammatory Biomarkers – Intention to Treat Analysis

Variable		Baseline	8 Weeks	3 months	Δ0-8 weeks	Δ0-3 months	p-value*
	n	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (95% CI)	Mean (95% CI)	
Body Composition							
Weight (kg)							
Exercise Group	16	67.2 (11.6)	66.7 (11.5)	66.9 (11.3)	-0.4 (-0.8 to -0.0)	-0.2 (-0.8 to 0.3)	0.53
Control Group	10	69.0 (11.3)	69.3 (10.7)	69.5 (11.5)	0.3 (-0.3 to 1.0)	0.5 (-0.4 to 1.5)	
BMI ($kg.m^{-2}$)							
Exercise Group	16	26.3 (4.4)	26.2 (4.4)	26.2 (4.3)	-0.1 (-0.3 to 0.0)	-0.0 (-0.3 to 0.2)	0.43
Control Group	10	26.3 (3.6)	26.4 (3.3)	26.5 (3.6)	0.1 (-0.1 to 0.3)	0.2 (-0.1 to 0.6)	
Percentage Body Fat (%)							
Exercise Group	16	34.8 (4.8)	34.4 (5.0)	34.2 (4.3)	-0.4 (-0.8 to -0.0)	-0.6 (-1.0 to -0.2)	0.25
Control Group	10	35.1 (4.9)	35.2 (4.7)	35.5 (4.7)	0.0 (-0.2 to 0.4)	0.3 (-0.1 to 0.7)	
Fat Free Mass (kg)							
Exercise Group	16	43.3 (6.1)	43.4 (6.1)	43.7 (6.0)	0.0 (-0.0 to 0.2)	0.3 (0.1 to 0.5)	0.41
Control Group	10	44.3 (5.6)	44.5 (4.9)	44.4 (5.1)	0.1 (-0.3 to 0.6)	0.0 (-0.4 to 0.5)	
Waist Circumference (cm)							
Exercise Group	16	87.4 (11.9)	85.6 (12.5)	86.2 (12.2)	-1.8 (-2.7 to -0.8)	-1.2 (-2.4 to 0.1)	0.45
Control Group	10	85.1 (8.9)	84.8 (10.8)	84.8 (12.3)	-0.2 (-1.3 to 0.9)	-0.3 (-1.8 to 1.3)	
Blood Pressure							
SBP (mmHg)							
Exercise Group	16	124.6 (11.5)	118.5 (16.5)	117.0 (14.2)	-6.1 (-8.4 to -3.7)	-7.6 (-9.7 to -5.5)	0.53
Control Group	10	116.7 (10.9)	114.4 (9.5)	111.8 (12.8)	-2.3 (-4.9 to 0.4)	-4.9 (-7.9 to -1.7)	
DBP (mmHg)							
Exercise Group	16	78.4 (10.7)	78.8 (9.7)	76.1 (7.8)	0.4 (-0.9 to 1.7)	-2.3 (-3.9 to -0.8)	0.71
Control Group	10	75.0 (6.4)	74.6 (4.4)	74.0 (7.2)	-0.4 (-2.5 to 1.7)	-1.0 (-3.4 to 1.4)	

Variable		Baseline	8 Weeks	3 months	Δ0-8 weeks	Δ0-3 months	p-value*
	n	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (95% CI)	Mean (95% CI)	
Lipid Profile							
TC ($mmol.L^{-1}$)							
Exercise Group	15	5.8 (1.0)	5.6 (1.1)	5.6 (0.9)	-0.2 (-0.4 to -0.0)	-0.2 (-0.4 to -0.1)	0.69
Control Group	10	4.8 (0.5)	4.4 (0.7)	4.3 (0.6)	-0.4 (-0.6 to -0.2)	-0.5 (-0.6 to -0.3)	
HDL-C ($mmol.L^{-1}$)							
Exercise Group	15	1.6 (0.6)	1.5 (0.4)	1.5 (0.3)	-0.0 (-0.1 to 0.1)	-0.1 (-0.2 to 0.1)	0.96
Control Group	10	1.5 (0.5)	1.5 (0.5)	1.4 (0.4)	-0.1 (-0.1 to 0.01)	-0.1 (-0.1 to -0.0)	
LDL-C ($mmol.L^{-1}$)							
Exercise Group	14	3.5 (0.9)	3.4 (0.9)	3.3 (0.9)	-0.1 (-0.3 to 0.0)	-0.2 (-0.3 to -0.0)	0.78
Control Group	10	2.6 (0.5)	2.3 (0.5)	2.3 (0.9)	-0.3 (-0.4 to -0.1)	-0.3 (-0.4 to -0.1)	
TG ($mmol.L^{-1}$)							
Exercise Group	15	1.4 (0.7)	1.4 (0.9)	1.4 (0.6)	-0.02 (-0.2 to 0.2)	-0.02 (-0.3 to 0.1)	0.37
Control Group	10	1.5 (0.8)	1.3 (0.8)	1.2 (0.7)	-0.2 (-0.2 to -0.1)	-0.3 (-0.4 to -0.2)	
Glucose Metabolism							
Fasting Glucose ($mg.dL^{-1}$)							
Exercise Group	15	86.4 (11)	90.0 (9)	88.2 (9)	0.6 (-0.9 to 2.2)	2.0 (-0.3 to 4.3)	0.84**
Control Group	10	86.4 (16)	89.1 (11.2)	87.3 (11.7)	-0.4 (-2.2 to 1.4)	2.2 (-0.3 to 4.7)	
Fasting Insulin($mU.L^{-1}$)							
Exercise Group	14	10.5 (4.9)	10.4 (4.6)	10.2 (4.5)	-0.1 (-1.2 to 1.1)	-0.3 (-1.6 to 1.0)	0.51
Control Group	9	6.9 (2.8)	9.1 (4.5)	7.4 (2.8)	2.2 (1.1 to 3.4)	0.5 (-0.8 to 1.8)	
Insulin Resistance (HOMA)							
Exercise Group	14	2.3 (1.1)	2.3 (1.1)	2.3 (1.0)	0.1 (-0.1 to 0.3)	0.02 (-0.3 to 0.4)	0.66
Control Group	9	1.5 (0.6)	1.9 (0.9	1.7 (0.8)	0.5 (0.3 to 0.7)	0.5 (-0.8 to 1.8)	
HbA_{1c} ($mmol.mol^{-1}$)							
Exercise Group	15	35.9 (2.3)	34.1 (2.0)	35.7 (2.0)	-1.8 (-2.5 to -1.2)	-0.3 (-0.9 to 0.3)	0.07
Control Group	9	35.6 (2.9)	35.9 (3.6)	36.9 (3.9)	0.3 (-0.5 to 1.2)	1.3 (0.6 to 2.1)	

Variable		Baseline	8 Weeks	3 months	Δ0-8 weeks	Δ0-3 months	p-value*
	n	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (95% CI)	Mean (95% CI)	
Inflammatory Marker							
CRP ($mg.dL^{-1}$)							
Exercise Group	14	2.4 (7.5)	1.1 (2.1)	2.0 (3.9)	-1.5 (-2.4 to -0.7)	-0.6 (-1.6 to 0.3)	0.69**
Control Group	10	1.0 (0.8)	1.0 (2.5)	1.0 (2.0)	0.4 (0.0 to 0.7)	-0.0 (-0.4 to 0.4)	

Data expressed as mean (standard deviation) for normally distributed data and as median (interquartile range) for non-normally distributed data (fasting glucose and CRP).

**P for repeated measures ANOVA comparing changes between the exercise group and the control group from baseline to 3 months post intervention (time*group effect). ** p-value for Wilcoxon test for difference between the groups at 3 months.*

Abb: WC = waist circumference; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; HbA_{1c} = glycated haemoglobin A_{1c}; HOMA = homeostatic model assessment index; CRP = C – Reactive Protein

Table 13 Change in Metabolic and Inflammatory Variables - Per-Protocol Analysis

Variable		Baseline	8 Weeks	3 months	Δ0-8 weeks	Δ0-3 months	p-value*
	n	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (95% CI)	Mean (95% CI)	
Body Composition							
Weight (kg)							
Exercise Group	8	70.2 (10.4)	68.6 (3.8)	68.3 (10.1)	-1.5 (-2.1 to -1.0)	-1.8 (-2.7 to -1.1)	0.09
Control Group	8	68.9 (12.3)	69.5 (11.5)	69.7 (12.4)	0.5 (-0.3 to 1.4)	0.7 (-0.5 to 2.0)	
BMI ($kg.m^{-2}$)							
Exercise Group	8	27.3 (3.5)	26.7 (3.4)	26.5 (3.1)	-0.6 (-0.8 to -0.4)	-0.7 (-1.1 to -0.4)	0.08
Control Group	8	26.5 (4.1)	26.7 (3.8)	26.8 (4.1)	0.2 (-0.1 to 0.5)	0.3 (-0.2 to 0.8)	
Percentage Body Fat (%)							
Exercise Group	8	35.4 (3.8)	34.2 (3.9)	33.8 (2.9)	-1.1 (-1.7 to -0.6)	-1.6 (-2.2 to -1.0)	0.08
Control Group	8	36.1 (5.1)	35.9 (5.1)	36.2 (5.2)	-0.2 (-0.6 to 0.0)	0.0 (-0.5 to 0.6)	
Fat Free Mass (kg)							
Exercise Group	8	45.2 (6.1)	45.1 (6.5)	45.1 (6.3)	-0.0 (-0.3 to 0.1)	-0.0 (-0.3 to 0.2)	0.55
Control Group	8	43.6 (5.3)	44.1 (4.7)	43.9 (4.9)	0.5 (-0.0 to 1.1)	0.3 (-0.2 to 1.7)	
Waist Circumference (cm)							
Exercise Group	8	89.9 (10.1)	85.7 (9.7)	85.3 (9.6)	-4.2 (-5.1 to -3.4)	-4.6 (-5.6 to -3.6)	0.05
Control Group	8	85.1 (10.1)	84.8 (12.3)	84.8 (13.9)	-0.0 (-1.4 to 1.3)	-0.3 (-2.3 to 1.7)	
Blood Pressure							
SBP (mmHg)							
Exercise Group	8	125.4 (15.0)	120.7 (20.9)	120.8 (5.8)	-4.6 (-7.3 to -2.1)	-4.6 (-6.8 to -2.5)	0.71
Control Group	8	114.8 (10.9)	112.6 (9.9)	109.4 (13.3)	-2.1 (-5.1 to 0.7)	-5.4 (-9.0 to -1.8)	
DBP (mmHg)							
Exercise Group	8	81.6 (14.0)	79.2 (13.7)	79.8 (9.4)	-2.4 (-3.7 to -1.1)	-1.8 (-4.3 to 0.6)	0.49
Control Group	8	73.6 (6.4)	74.9 (4.3)	74.1 (7.8)	1.2 (-0.7 to 3.2)	0.5 (-1.9 to 2.9)	

Variable		Baseline	8 Weeks	3 months	Δ0-8 weeks	Δ0-3 months	p-value*
	n	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (95% CI)	Mean (95% CI)	
Lipid Profile							
TC ($mmol.L^{-1}$)							
Exercise Group	7	5.9 (1.3)	5.5 (1.0)	5.7 (1.1)	-0.3 (-0.6 to -0.0)	-0.1 (-0.4 to 0.0)	0.49
Control Group	8	4.8 (0.4)	4.4 (0.7)	4.3 (0.5)	-0.3 (-0.6 to -0.2)	-0.4 (-0.7 to -0.3)	
HDL-C ($mmol.L^{-1}$)							
Exercise Group	7	1.3 (0.1)	1.4 (0.1)	1.4 (0.1)	0.0 (-0.1 to 0.1)	0.0 (0.0 to 0.1)	0.29
Control Group	8	1.5 (0.4)	1.5 (0.4)	1.4 (0.42)	-0.0 (-0.1 to 0.01)	-0.0 (-0.2 to -0.0)	
LDL-C ($mmol.L^{-1}$)							
Exercise Group	7	3.7 (1.1)	3.5 (1.0)	3.5 (0.9)	-0.2 (-0.4 to -0.0)	-0.2 (-0.4 to -0.1)	0.97
Control Group	8	2.6 (0.4)	2.3 (0.5)	2.3 (0.4)	-0.2 (-0.5 to -0.1)	-0.2 (-0.4 to -0.1)	
TG ($mmol.L^{-1}$)							
Exercise Group	7	1.6 (0.2)	1.3 (0.4)	1.5 (0.6)	-0.2 (-0.5 to -0.0)	-0.1 (-0.4 to 0.1)	0.37
Control Group	8	1.4 (0.8)	1.3 (0.8)	1.1 (0.7)	-0.1 (-0.2 to -0.01)	-0.3 (-0.4 to -0.1)	
Glucose Metabolism							
Fasting Glucose ($mg.dL^{-1}$)							
Exercise Group	7	84.6 (16)	88.2 (10.8)	84.6 (5.4)	0.5 (-1.1 to 2.2)	-1.0 (-2.7 to 0.7)	0.45**
Control Group	8	84.6 (16)	89.1 (10.3)	87.3 (8.5)	-1.1 (-3.2 to 0.9)	2.0 (-1.0 to 5.1)	
Fasting Insulin($mU.L^{-1}$)							
Exercise Group	6	11.3 (6.2)	8.9 (4.6)	9.1 (5.2)	-1.9 (-2.8 to -1.2)	-1.6 (-4.0 to 0.7)	0.27
Control Group	7	6.8 (3.2)	10.4 (5.4)	8.6 (4.6)	2.7 (1.3 to 4.0)	0.4 (-1.1 to 2.1)	
Insulin Resistance (HOMA)							
Exercise Group	6	2.4 (1.4)	2.0 (1.4)	1.9 (1.0)	-2.4 (-2.6 to -2.2)	-0.4 (-0.9 to 0.1)	0.42
Control Group	7	1.4 (0.6)	2.2 (1.0)	1.9 (1.2)	0.5 (0.2 to 0.8)	0.2 (-0.2 to 0.7)	
HbA_{1c} ($mmol.mol^{-1}$)							
Exercise Group	7	35.0 (2.52)	33.71 (2.21)	35.0 (1.63)	-1.29 (-2.4 to -0.1)	0.0 (-1.27 to 1.27)	0.49
Control Group	8	35.29 (2.9)	35.5 (2.07)	36.88 (3.04)	-0.14 (-0.9 to 0.7)	1.14 (0.4 o 1.9)	

Variable		Baseline	8 Weeks	3 months	Δ0-8 weeks	Δ0-3 months	p-value*
	n	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (95% CI)	Mean (95% CI)	
Inflammatory Marker							
CRP ($mg.dL^{-1}$)							
Exercise Group	7	2.8 (10.1)	1.4 (2.1)	1.4 (2.1)	-3.2 (-5.1 to -1.4)	-2.6 (-4.2 to -1.1)	0.32**
Control Group	8	1.0 (0.8)	1.0 (2.5)	1.0 (2.0)	0.3 (-0.1 to 0.7)	-0.0 (-0.6 to 0.5)	

*Data expressed as mean (standard deviation) for normally distributed data and as median (interquartile range) for non-normally distributed data (fasting glucose and CRP).*P for repeated measures ANOVA comparing changes between the exercise group and the control group from baseline to 3 months post intervention (time*group effect). ** p-value for Wilcoxon test for difference between the groups at 3 months.*

Abb: WC = waist circumference; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; HbA_{1c} = glycated haemoglobin A_{1c}; HOMA= homeostatic model assessment; CRP = C – Reactive Protein

Table 14 Change in CRP Groups (<3 vs. >3mg.L-1)

Analysis	CRP Group ($mg.L^{-1}$)	Exercise Group			Control Group			p-value*	p-value**
		Baseline	8-Weeks	3-Months	Baseline	8-Weeks	3-Months	8-Weeks	3-Months
Intention to Treat	***<3***	8 (57)	10 (71)	8 (57)	8 (80)	7 (70)	8 (80)	1.00	0.39
	>3	6 (43)	4 (29)	6 (43)	2 (20)	3 (30)	2 (20)		
Per Protocol	***<3***	3 (42)	5 (71.5)	4 (50)	7 (87)	6 (75)	7 (86.5)	1.00	0.28
	>3	4 (58)	2 (28.5)	4 (50)	1 (12.5)	2 (25)	1 (12.5)		

*Data are presented as frequency (percentage). * p-value for difference between groups at 8-weeks, **p-value for difference between groups at 3 months.*

CRP = C-Reactive Protein

3.4.7 Change in Physical Activity

The results of the intention-to-treat analysis, with accompanying confidence intervals, for physical activity parameters are presented in Table 15. P-values for differences between groups at 8-weeks are displayed for non-parametric data. There were no significant differences between the EG and the CG measured by either the RT3 activity monitor or the Godin questionnaire over the study period.

Examination of accompanying confidence intervals suggests a number of significant within-group changes in both RT3 and the Godin in both the EG and the CG however the most notable changes were in Godin strenuous and total weekly MET-min.week^{-1}. At 8-weeks there was a significant difference (Wilcoxon Rank Sum test p=0.01) between groups for strenuous MET-min.week^{-1}. Total weekly MET-min.week^{-1} appeared to increase significantly in the EG from both 0-8-weeks and 0-3-months and the accompanying p-value for between-group differences approached significance (p=0.06)

Per-protocol analysis showed significant improvements in Godin total weekly MET-min.week^{-1} (p=0.005), however this was not accompanied by change in objectively measured data (Table 16). As before confidence intervals were examined for within-group changes. While there were some suggested changes in various activity domains in both groups, the most striking results were observed in Godin strenuous MET-min.week^{-1} where there was a significant increase 0-8 weeks in the EG versus CG (p=0.004).

Table 15 Change in Physical Activity Parameters - Intention to Treat Analysis

Activity Intensity		Baseline	8 Weeks	3 months	Δ0-8 weeks	p-value*	Δ0-3 months	p-value**
	n	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (95% CI)		Mean (95% CI)	
RT3 Activity Monitor								
Sedentary (min.day^{-1})								
Exercise Group	16	427.5 (145.4)	446.0 (127.0)	438.0 (121.6)	18.5 (-9.3 to 46.1)		10.5 (-14.4 to 35.3)	0.53
Control Group	9	405.6 (146.7)	385.8 (107.9)	359.5 (149.3)	-19.8 (-68.1 to 28.4)		-46.1 (-110.8 to 18.5)	
Light Intensity (min.day^{-1})								
Exercise Group	16	332.6 (69.7)	318.1 (72.1)	327.2 (70.5)	-14.5 (-24.2 to -4.9)		-5.5 (-22.6 to 11.7)	0.36
Control Group	9	339.7 (128.1)	346.7 (101.0)	315.7 (110.1)	6.9 (-15.0 to 28.9)		-24.1 (-58.4 to 10.3)	
Moderate Intensity (min.day^{-1})								
Exercise Group	16	26.4 (26.7)	25.9 (20.5)	32.5 (30.8)	-1.1 (-4.4 to 2.2)	0.83	6.75 (0.9 to 12.3)	0.61
Control Group	9	33.8 (43.3)	33.0 (25.5)	42.6 (48.3)	-7.9 (-12.0 to -3.7)		14.5 (-5.6 to 10.3)	
Vigorous Intensity (min.day^{-1})								
Exercise Group	16	24.7 (53.5)	15.7 (15.7)	15.8 (22.2)	-9.0 (-22.5 to 4.4)		-8.9 (-23.2 to 5.4)	0.49
Control Group	9	9.5 (11.8)	11.2 (13.5)	19.8 (29.4)	1.7 (0.1 to 3.3)		10.3 (-0.04 to 20.6)	

Activity Intensity		Baseline	8 Weeks	3 months	Δ0-8 weeks	p-value	Δ0-3 months	p-value
	n	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (95% CI)		Mean (95% CI)	
Godin Questionnaire								
Light (MET-min.week^{-1})								
Exercise Group	16	1.5 (10.5)	0.0 (6.7)	4.5 (15)	0.9 (-0.9 to 2.8)	0.58	2.6 (0.3 to 4.9)	0.29
Control Group	10	0.0 (13.5)	0.0 (15)	0.0 (12.7)	-1.8 (-5.3 to 1.7)		-2.1 (-6.7 to 2.5)	
Moderate (MET-min.week^{-1})								
Exercise Group	16	14.7 (18.5)	16.1 (19.3)	16.7 (17.1)	1.4 (-0.4 to 3.2)		2.0 (-0.2 to 4.3)	0.19
Control Group	10	21.3 (9.8)	14.8 (10.4)	15.0 (13.9)	-6.5 (-10.5 to -2.5)		-6.3 (-13.2 to 0.7)	
Strenuous (MET-min.week^{-1})								
Exercise Group	16	0.0 (0.0)	0.0 (8.2)	4.5 (30.3)	13.2 (8.2 to 18.1)	0.01	3.4 (-1.4 to 8.2)	0.83
Control Group	10	0.0 (9)	0.0 (15)	0.0 (0.0)	0.0 (0.0 to 0.0)		4.5 (0.0 to 9.0)	
Total Weekly (MET-min.week^{-1})								
Exercise Group	16	23.1 (19.8)	38.7 (26.9)	31.2 (21.1)	15.6 (9.5 to 21.6)		8.0 (3.3 to 12.8)	0.06
Control Group	10	28.2 (11.2)	19.9 (11.3)	24.3 (11.9)	-8.3 (-11.3 to -5.3)		-3.9 (-9.5 to 1.8)	

Data expressed as mean (standard deviation) for normally distributed data and as median (interquartile range) for non-normally distributed data

** p-value for Wilcoxon test for difference between the groups at 8-weeks for non-normally distributed data only*

***P for repeated measures ANOVA comparing changes between the exercise group and the control group from baseline to 3 months post intervention (time*group effect) for normally distributed data and P-value for Wilcoxon test for difference between the groups at 3 month for non-normally distributed data.*

Table 16 Change in Physical Activity Parameters - Per-protocol analysis

Activity Intensity		Baseline	8 Weeks	3 months	Δ0-8 weeks	p-value*	Δ0-3 months	p-value**
	n	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (95% CI)		Mean (95% CI)	
RT3 Activity Monitor								
Sedentary (min.day^{-1})								
Exercise Group	8	392.8 (121.5)	419.4 (99.7)	416.7 (80.8)	26.6 (-26.3 to 79.5)		23.9 (-11.3 to 59.1)	0.86
Control Group	8	404.1 (156.7)	373.3 (108.2)	343.7 (151.4)	-30.8 (-84.1 to 22.4)		-60.4 (-131.9 to 11.1)	
Light Intensity (min.day^{-1})								
Exercise Group	8	362.3 (51.5)	325.8 (59.1)	323.2 (63.7)	-36.4 (-51.2 to -21.8)		-39.1 (-65.6 to -12.6)	0.35
Control Group	8	334.1 (135.8)	352.8 (106.1)	318.0 (117.4)	18.6 (-2.4 to 39.7)		-16.1 (-54.1 to 21.7)	
Moderate Intensity (min.day^{-1})								
Exercise Group	8	26.4 (26.7)	25.9 (20.5)	32.5 (30.8)	-1.6 (-6.6 to 3.3)	0.56	11.8 (1.3 to 22.4)	0.83
Control Group	8	33.8 (43.3)	33.0 (25.5)	42.6 (48.4)	-7.4 (-12.1 to -2.7)		17.7 (-4.8 to 40.3)	
Vigorous Intensity (min.day^{-1})								
Exercise Group	8	17.4 (20.5)	23.6 (18.1)	24.3 (28.9)	6.1 (1.9 to 10.4)		6.9 (-3.3 to 17.1)	0.22
Control Group	8	10.6 (12.0)	12.6 (13.6)	22.2 (30.4)	1.9 (0.2 to 3.7)		11.6 (-0.02 to 23.2)	

Activity Intensity		Baseline	8 Weeks	3 months	Δ0-8 weeks	p-value*	Δ0-3 months	p-value**
	n	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	Mean (95% CI)		Mean (95% CI)	
Godin Questionnaire								
Light (MET-min.week^{-1})								
Exercise Group	8	1.5 (10.5)	0.0 (6.7)	4.5 (15)	0.7 (-0.2 to 1.7)	0.66	1.8 (-0.5 to 4.3)	0.35
Control Group	8	0.0 (13.5)	0.0 (15)	0.0 (12.7)	1.5 (-0.5 to 3.5)		1.13 (-3.2 to 5.4)	
Moderate (MET-min.week^{-1})								
Exercise Group	8	11.2 (10.9)	15.3 (13.3)	13.7 (12.1)	4.0 (0.9 to 7.2)		2.5 (-1.3 to 6.3)	0.22
Control Group	8	23.4 (9.7)	15.3 (9.6)	15.6 (13.0)	-8.1 (-12.2 to -4.1)		-7.8 (-16.0 to 0.4)	
Strenuous (MET-min.week^{-1})								
Exercise Group	8	0.0 (0.0)	0.0 (8.25)	4.5 (30.3)	9 (-0.2 to 18.2)	0.004	9 (-0.2 to 18.2)	0.33
Control Group	8	0.0 (9)	0.0 (15)	0.0 (0.0)	0.0 (0.0 to 0.0)		5.6 (0.0 to 11.3)	
Total Weekly (MET-min.week^{-1})								
Exercise Group	8	18.7 (9.7)	48.8 (25.7)	32.1 (21.4)	30.1 (21.2 to 39.1)		13.3 (6.4 to 20.4)	0.005
Control Group	8	26.4 (11.7)	19.8 (12.5)	25.3 (13.0)	-6.6 (-10.2 to -3.1)		-1.0 (-7.8 to 5.7)	

Data expressed as mean (standard deviation) for normally distributed data and as median (interquartile range) for non-normally distributed data

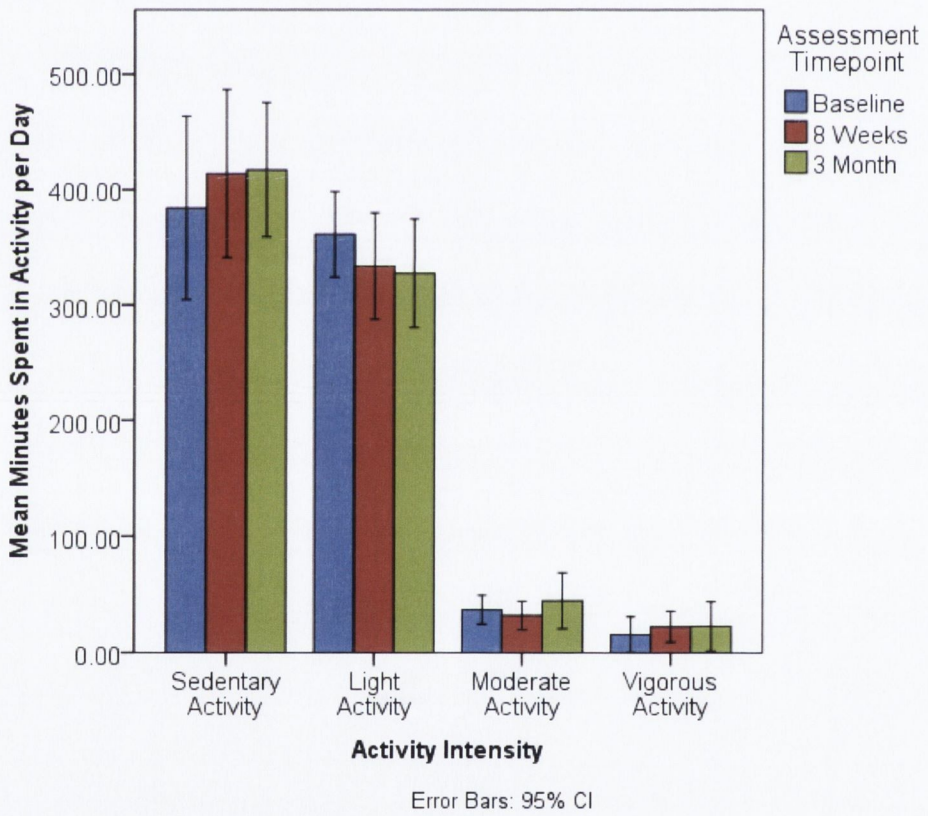
** p-value for Wilcoxon test for difference between the groups at 8-weeks for non-normally distributed data only*

***P for repeated measures ANOVA comparing changes between the exercise group and the control group from baseline to 3 months post intervention (time*group effect) for normally distributed data and P-value for Wilcoxon test for difference between the groups at 3 month for non-normally distributed data.*

3.4.7.1 Percentage Time in Activity Domains

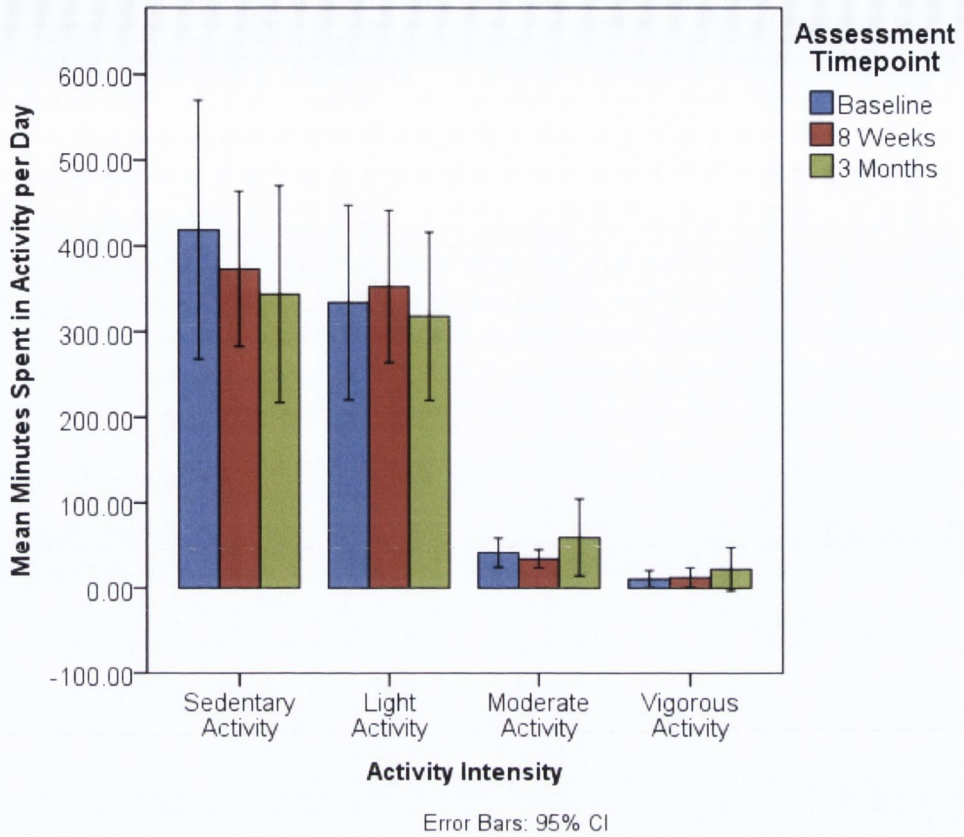
As shown in Table 15, there were no changes in objectively measured physical activity domains at the three assessments. These results were considered as percentage time per day in each activity domain. In the overall group, throughout the study over 50% of time was spent sedentary (baseline 52%, 8-weeks 51% and 3-months 50%). Light intensity activity was high (baseline 42%, 8-weeks 43% and 3-months 42%), while moderate-vigorous intensity time remained low throughout (baseline 6%, 8-weeks 6% and 3-months 8%) (Figure 15 and Figure 16).

Figure 15 Physical Activity Levels - Exercise Group



Mean minutes spent in each domain of physical activity at each assessment point throughout the intervention in the exercise group.

Figure 16 Physical Activity Levels – Control Group



Mean minutes spent in each domain of physical activity at each assessment point throughout the intervention in the control group.

3.4.7.2 Adherence to Physical Activity Guidelines

RT3 activity monitor data was analysed for adherence to recommended physical activity guidelines (Chapter 2, section 2.3.1.2). Adherence to recommended guidelines was <25% at any time point, regardless of criteria used (Table 17). There was no change in the number adhering to either 30 minutes x 5 days.week^{-1} (p=0.45) or to 150 minutes.week^{-1} (p=0.67) over the study.

Table 17 Adherence to Physical Activity Guidelines

	Number of Participants (%)					
	30 minutes x 5 days .week^{-1}			150 minutes.week^{-1}		
	Baseline	8 Weeks	3 Months	Baseline	8 Weeks	3 Months
Exercise Group	2 (13)	1 (6)	3 (19)	4 (25)	3 (19)	4 (19)
Control Group	1 (10)	0	0	3 (30)	1 (10)	2 (20)
Total	3 (12)	1 (4)	3 (12)	7 (27)	4 (15)	6 (23)

3.4.8 Change in Dietary Intake

Energy intake at baseline was 7.62 (1.69) MJ. There was no change in energy intake (p=0.37) or percentage energy derived from protein (p=0.65), fat (p=0.66) or carbohydrates (p=0.15) over the study period. Results were similar from per-protocol analysis with the exception of percentage energy derived from carbohydrates which was significantly higher in the EG than CG (p=0.03).

3.5 Discussion

This pilot study demonstrated that an 8-week aerobic exercise intervention did not improve features of the MetSyn, CRP or anthropometric variables in breast cancer survivors. Sub-analysis of those with >90% adherence to the exercise class demonstrated significant improvements in waist circumference and subjectively measured "total weekly" physical activity.

This is the first study to describe the metabolic profile in breast cancer survivors in the acute stage post adjuvant chemotherapy. The majority of participants were overweight or obese (n=19) and/or centrally obese (n=19) at baseline and nine presented with the MetSyn. Despite marked levels of central obesity, insulin resistance and CRP values were low, suggesting an obese but metabolically healthy state (Brochu et al., 2001). Prior to chemotherapy, the majority of participants in this trial were premenopausal, a group at high risk of chemotherapy-related weight gain (Goodwin et al., 1999a). The level of obesity observed may

reflect recent weight gain among this group which has yet to have an adverse impact on metabolic and inflammatory pathways. In long-term breast cancer survivors, increasing concentrations of C-peptide, leptin, IGFs and CRP have been associated with increasing BMI ($p<0.05$) (Irwin et al., 2005b, Pierce et al., 2009b) and the prevalence of the MetSyn has been reported to be as high as 54.8% in a similar cohort (Thomson et al., 2009).

As outlined in Chapter 1, physical activity can improve breast cancer related outcomes (Holmes et al., 2005, Pierce et al., 2007, Irwin et al., 2011b), most likely through alterations in insulin and inflammatory pathways and improved anthropometrics (Neilson et al., 2009). While a number of interventions identified in the systematic literature review in Chapter 1, section 1.5.1 have examined the effect of exercise on individual components of the MetSyn in breast cancer survivors (Fairey et al., 2003, Fairey et al., 2005b, Ligibel et al., 2008, Irwin et al., 2009b, Schmitz et al., 2005), this was the first study to consider all the components of the syndrome. While no changes in metabolic or inflammatory markers were observed, per-protocol analysis revealed a significant decrease in waist circumference. In addition, examination of accompanying confidence intervals, in both the intention-to-treat and per-protocol analysis, suggested that the EG experienced some significant within-group improvements in anthropometrics and in measures of glucose metabolism, with some suggestion that the CG experienced deterioration in insulin and HOMA-IR score. These results are consistent with other studies which have reported improvements in measures of glucose metabolism and anthropometric variables within exercising groups (Cheema and Gaul, 2006, Ligibel et al., 2008), but require further investigation using large RCTs to fully elucidate results.

Two major strengths of the current study were the use of accelerometry to objectively measure physical activity and the assessment of dietary intake using 3-day food diaries. As discussed in Chapter 1, section 1.5.1, other studies have failed to monitor sedentary behaviour during exercise trials. A high percentage of objectively measured sedentary time was observed in both groups at all assessment stages (Figure 15 and Figure 16). Surprisingly, this did not change despite the implementation of an intervention which included a home exercise component. As objectively measured sedentary time is significantly associated with a range of biomarkers of breast cancer risk in postmenopausal women (BMI, waist circumference, CRP, insulin and insulin resistance) interventions aimed at not only increasing

activity time, but also reducing sedentary time may be required to modify these variables (Pate et al., 2008). Subjectively, participants in the per-protocol analysis study reported significant increases in "total weekly" physical activity that was not reflected by increases in objectively measured physical activity, highlighting the discrepancies between subjective and objectively reported physical activity. As the group remained predominantly sedentary throughout the study period, even light intensity activity may have been perceived at a higher intensity, leading to inaccurate and exaggerated reporting. Inactivity, characterised by poor adherence to physical activity guidelines was also prevalent throughout, regardless of criteria used. Dietary intake was measured at each assessment point to control for changes in diet that may influence outcomes being measured. As dietary intake did not change significantly over the study period, the changes that were observed in waist circumference (per-protocol analysis) and the suggested alterations in anthropometric variables and measures of glucose metabolism within the EG were most likely stimulated by exercise alone and were not attributed to a change in diet.

The PEACH trial was primarily a supervised intervention which aimed to introduce physical activity into the normal routine using a home exercise protocol. Adherence to the prescribed exercise zone was monitored using Polar heart rate monitors which were also used to monitor compliance with the home exercise programme. Data from the Polar heart rate monitor demonstrated that participants completed 153% of the prescribed exercise minutes at home (i.e. 53% more than prescribed) but only spend an average of 36% of that exercise time in their prescribed heart rate zone. This corresponds with the physical activity measures which suggest that participants subjectively felt that they were doing more exercise, as demonstrated by the significant increase in "total weekly" activity ($p=0.005$) using the Godin questionnaire in the per-protocol analysis, but objectively their physical activity levels did not change. There is concern therefore in non-supervised studies where no effect is demonstrated, that the lack of response may be due to non-compliance or displacement of habitual physical activity as opposed to ineffective exercise prescription. These results advocate the need for supervised exercise prescription in this cohort and the objective monitoring of physical activity to ensure accuracy and compliance.

Two novel aspects of the prescribed intervention were the inclusion of only those with below average fitness levels and the subsequent individualised exercise prescription bands which prescribed and progressed exercise based on baseline fitness test results. This approach was adopted to facilitate a gradual introduction to exercise for those in with lower baseline fitness levels. Individuals with "poor" baseline fitness levels commenced the programme at a light intensity (35-55% HRR) and progressed to a moderate aerobic intensity (40-60% HRR) in week three. Both the "Fair" and "Average" fitness groups started the programme at a moderate intensity (40-60% HRR and 45-65% HRR respectively) and progressed to vigorous intensity exercise at programme completion. Moderate intensity aerobic intervention have previously been shown to modify biomarkers of interest (Frank et al., 2005, Friedenreich et al., 2012, Friedenreich et al., 2011, Irwin et al., 2003b, Ross et al., 2004), however as discussed in Chapter 1, section 1.5, total volume of exercise performed may be an important determinant of the effectiveness of a programme. The short duration of the current intervention (8-weeks) may have been insufficient to reach a training stimulus with most other programmes lasting 6-12 months.

3.5.1 Study Limitations

There are a number of limitations to this study which warrant discussion. Firstly, this pilot study was an ancillary study to a larger RCT, resulting in low participant numbers, uneven group assignment and baseline differences between groups in certain outcomes. Secondly, adherence to the prescribed protocol was poor (per-protocol analysis excluded 10/26 participants), suggesting that not all breast cancer survivors appear ready for such a demanding intervention so early in their recovery. The current study included participants within the rehabilitation period recommended by Courneya and Friedenreich (2001). This was in contrast to other interventions who have included participants at a range of times into survivorship spanning from during chemotherapy (Schneider et al., 2007) to several years post diagnosis (Cheema and Gaul, 2006, Ligibel et al., 2008). However, side-effects of chemotherapy treatments such as cancer-related fatigue or reduced cardiorespiratory fitness, in addition to ongoing treatment related issues such as adjusting to hormonal therapy medication, anti-Her directed therapies during the intervention period and continuing medical appointments may have had a strong influence over the studied group.

3.6 Conclusion

The results of this pilot study did not demonstrate that an 8 week aerobic intervention was able to elicit significant changes in metabolic, inflammatory and anthropometric markers of breast cancer risk among breast cancer survivors. There is evidence however from the decrease in waist circumference in those who adhered rigorously to the exercise protocol and the improvements in measures of glucose metabolism within the EG, to support the efficacy of designing a larger RCT, with adequate sample size and longer duration. Information on the presentation of dysmetabolism and physical activity patterns of this cohort may further inform the design of targeted interventions.

Chapter 4 Study IIa: Metabolic Syndrome in Breast Cancer Survivors

The Development of the Metabolic Syndrome and Insulin Resistance following Adjuvant Treatment for Breast Cancer

Statement of Author's Contribution

The study concept and design were developed by the student Emer Guinan (EG), supervisor Dr. Juliette Hussey (JH), co-supervisor Ms. Elizabeth Connolly and medical oncologist Professor M John Kennedy (MJK). Baseline assessments were completed by Dr Laura Healy and Dr Paul Carroll. EG developed the protocol for follow-up measures. Participant recruitment was completed by EG and facilitated by MJK. EG completed all outcome assessments, data analysis and data interpretation. EG was responsible for drafting Chapter 4 in this thesis and the subsequent manuscript. All authors approved the final version of the published manuscript.

4.1 Introduction

The PEACH trial presented in Study I (Chapter 3) did not result in any significant changes in anthropometric or metabolic biomakers associated with breast cancer prognosis. As discussed in the systematic literature review presented in Chapter 1, section 1.5.1, other trials which measured similar outcomes in this cohort also failed to demonstrate change. There is a need to consider these findings in the context of the metabolic presentation of the cohort under examination. The cohort studied in Study I was predominantly overweight, obese and centrally obese, however the majority of metabolic measures including fasting insulin and CRP were within healthy ranges (Chapter 3, Table 10, page 121). Cross-sectional studies have reported significant dysmetabolism in long-term breast cancer survivors in the presence of obesity (Thomson et al., 2009, Irwin et al., 2005b). Evidently, the presentation of dysmetabolism is not homogenous across all breast cancer survivors.

Metabolic dysfunction following breast cancer, characterised by the presence of the MetSyn (Bjorge et al., 2010a), obesity (Protani et al., 2010), insulin resistance (Duggan et al., 2011), low adiponectin (Duggan et al., 2011) and high inflammatory status (Pierce et al., 2009a) is

associated with poorer outcome. Therefore optimising metabolic presentation following breast cancer is a key therapeutic target. Data from our research group (Broderick, 2012) and colleagues in the Department of Surgery (Healy et al., 2010) have examined metabolic profiles and physical activity levels at breast cancer diagnosis and up to one year post chemotherapy. Little is known about the presentation of dysmetabolism in this cohort in the first five years of survivorship. Weight gain (Demark-Wahnefried et al., 2001a), the development of sarcopenia (Demark-Wahnefried et al., 2001a, Harvie et al., 2004), reduced physical activity levels (Lynch et al., 2010, Irwin et al., 2004) and early menopause (Park et al., 2003) are all known side-effects of adjuvant breast cancer treatment which may lead to metabolic decline in the years following treatment. Thus, metabolic profiling of breast cancer survivors who have completed adjuvant treatment may serve to inform the design of targeted exercise interventions.

Study II, presented in this thesis in Chapter 4 and Chapter 5, was undertaken to investigate the presentation of dysmetabolism in breast cancer survivors. The study is divided into two parts. Study IIa (Chapter 4) examined changes in MetSyn and metabolic variables from breast cancer diagnosis to post completion of adjuvant treatment. The sample was recruited from a group of well-profiled breast cancer survivors who had previously completed metabolic and anthropometric screening on the morning of breast cancer surgery. Study IIb, which is described in Chapter 5, was a cross-sectional analysis of the characteristics of metabolic dysfunction in breast cancer survivors and the relationship with energy expenditure.

This study has been accepted for publication in Cancer Nursing (Appendix II)

Guinan, E.M., Connolly, E.M., Healy, L.A., Carroll, P.A., Kennedy, M.J, Hussey, J. "The Development of the Metabolic Syndrome and Insulin Resistance following Adjuvant Treatment for Breast Cancer" Cancer Nursing Epub ahead of print.

In addition results from this chapter were presented as a platform presentation at the American Society of Clinical Oncology (ASCO) annual meeting June 2012 as part of the Clinical Science Symposium entitled "Diabetes and Cancer". Guinan E, Hussey J, Healy LA, Carroll P, Kennedy MJ, Connolly E (2012). Changes in Glucose, Insulin and Insulin Resistance from Pre-Surgery to Post Adjuvant Treatment for Breast Cancer. J Clin Oncol 30 (15 supplement), 1511

4.2 Objectives and Research Design

The overall aim of Study II was to examine the presence of the MetSyn in breast cancer survivors who had completed adjuvant treatment with curative intent.

The specific objectives of Study IIa were:

- To examine changes in the presence of the MetSyn and its individual components, including insulin resistance and body composition, from the time of breast cancer surgery to post cessation of adjuvant treatment for breast cancer.
- To compare differences in changes in metabolic parameters according to selected baseline characteristics (menopausal status, presence or absence of the MetSyn, smoking status) and cancer details (disease stage, adjuvant treatment).

Study IIa was designed as a cohort study with retrospective-style follow-up. This type of study design has been discussed in Chapter 2 (section 2.2.1).

4.3 Methods

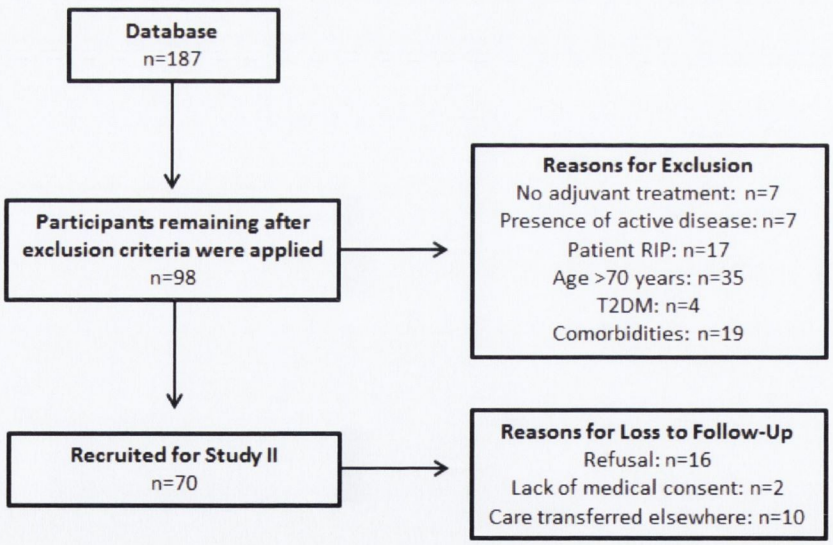
4.3.1 Sampling and Recruitment

Participants were recruited from a database of 187 patients with breast cancer who had completed metabolic and anthropometric profiling on the morning of breast cancer surgery between 2007 and 2009. Participants were eligible for Study II (IIa and IIb) if they had undergone and completed all adjuvant breast cancer treatment which may have included chemotherapy, radiotherapy and/or anti Her-2 directed biological therapy. Those continuing to take hormonal therapy were eligible to participate. Due to the retrospective design of Study IIa an attempt was made to reduce the impact of confounding factors on variables under examination. Therefore participants were excluded for the following reasons: a) age >70 years old, b) diagnosed T2DM, c) presence of medical comorbidities which may confound results. Exclusion due to medical comorbidity included: end-stage chronic obstructive pulmonary disease (n=2), congestive heart failure (n=4), use of psychotropic medication (n=2), pregnancy (n=1), ongoing issues related to breast reconstruction (n=2), multiple comorbidities /polypharmacy (n=8). Therefore, 98 patients on the database were eligible for Study II.

Recruitment for Study II was completed between May 2011 and June 2012. Potentially suitable participants were identified in advance of outpatient follow-up oncology appointments and were informed about the study by a member of the medical team. Participant information leaflets were provided (Appendix III) and eligibility screening was completed by the lead investigator. Furthermore, expression of interest forms including participant information leaflets were mailed to participants with no clinical appointment within the recruitment time-frame.

Seventy-participants were recruited for Study II, representing a 71% accrual of those available for recruitment. Reasons for loss to follow-up included care transferred to a difference centre and thus medical consent could not be obtained (n=10), refused (n=16) (including refusal following clinical appointment (n=14) and those who did not reply to expression of interest letters (n=2)) and lack of medical consent (n=2). In both cases, medical consent was refused on the grounds of social concerns. The flow of recruitment for Study II is shown in Figure 17.

Figure 17 Study II Recruitment



Flow of recruitment for Study II. Of the original 187 participants included in the breast cancer database who were profiled on the morning of surgery, 98 were suitable for Study II and 70 consented to participate. This represents an accrual of 71% of those suitable for participation. Abb: T2DM = type II diabetes mellitus

A relatively high percentage (29%) of participants who were eligible for Study II did not participate. Therefore, baseline comparison of all demographic, metabolic and anthropometric variables of those who participated in Study II (n=70) and those who did not participate (n=28) was completed (Table 18). Comparisons were made using independent sample t-tests for continuous variables and using Chi-sq and Fishers exact test for categorical variables. No differences were identified between the two groups, thus suggesting that those who participated in Study II were representative of the overall group eligible for participation. The same patient population recruited for Study II were studied in both Study IIa and Study IIb.

Table 18 Baseline Comparison of all Participants Eligible for Study II

Characteristic	Recruited (n=70)	Not Recruited (n=28)	p-value
Participant Demographics			
Age at diagnosis	49.7 (9.12)	49.8 (10.6)	0.96
Menopausal status			
Premenopausal	38 (54)	10 (35)	0.10
Postmenopausal	32 (46)	18 (65)	
Smoking History			
Current smoker	10 (14)	4 (14)	1.00
Cancer Details			
Cancer Stage			
I	20 (29)	6 (21)	0.42
II	36 (51)	13 (46)	
III	14 (20)	9 (32)	
Estrogen Receptor Positive	57 (81)	21 (75)	1.00
Surgery			
Wide local excision	32 (46)	10 (35)	0.36
Mastectomy	38 (54)	18 (65)	
Axillary Clearance	32 (46)	10 (35)	0.52
Chemotherapy	60 (86)	21 (75)	0.24
Radiotherapy	57 (81)	21 (75)	1.00
Hormone Therapy			
Tamoxifen	36 (51)	16 (57)	0.43
Aromatase Inhibitor	20 (29)	4 (14)	
Biological Therapy			
Herceptin	8 (11)	3 (11)	1.00

Characteristic	Recruited (n=70)	Not Recruited (n=28)	p-value
Anthropometrics			
Body weight (kg)	69.5 (12.4)	68.3 (11.1)	0.69
BMI ($kg.m^{-2}$)	26.9 (4.3)	25.9 (4.1)	0.35
WC (cm)	90.3 (14.6)	87.6 (14.9)	0.44
Body Fat (%)	34.4 (7.0)	35.7 (7.5)	0.51
FFM (kg)	44.3 (4.6)	43.1 (6.6)	0.39
Metabolic Profile			
Blood Pressure			
SBP (mmHg)	125.3 (12.1)	127.1 (18.6)	0.71
DBP (mmHg)	78.8 (8.8)	76.5 (12.1)	0.45
Lipid Profile			
TC ($mmol.L^{-1}$)	5.1 (0.8)	5.0 (0.9)	0.44
HDL-C ($mmol.L^{-1}$)	1.6 (0.3)	1.5 (0.4)	0.42
LDL-C ($mmol.L^{-1}$)	2.9 (0.7)	2.9 (0.8)	0.45
TG ($mmol.L^{-1}$)	1.2 (0.7)	1.3 (0.7)	0.54
Glucose Metabolism			
Glucose ($mmol.L^{-1}$)	4.9 (0.5)	5.2 (0.5)	0.54
Insulin ($mU.L^{-1}$)	6.4 (4.8)	8.5 (6.3)	0.32
HOMA-IR	1.4 (1.1)	2.1 (1.7)	0.07
HbA_{1c} ($mmol.mol^{-1}$)	35.3 (3.2)	34.6 (3.9)	0.37
Metabolic Syndrome	12 (17)	10 (35)	0.10

*Data are displayed as mean (standard deviation) for continuous variables and as frequency (percentage) for categorical variables. * = significant at $p<0.05$ Abb: BMI = body mass index; WC = waist circumference; FFM = fat free mass; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; HOMA-IR = homeostatic model assessment index – insulin resistance; HbA_{1c} = glycated haemoglobin A_{1c}.*

4.3.2 Measures and Testing Protocol

As stated above, baseline measurements were completed on the morning of breast surgery at the time of diagnosis (T0) by Dr. Laura Healy and Dr. Paul Carroll. Study IIa follow-up measurements (T1) were completed at the Exercise Laboratory in the Trinity Centre for Health Sciences, St. James's Hospital using the same methods. Participants attended for testing, following a 12 hour fast, during which all measures for Study II (Study IIa and Study IIb) were completed. The complete testing protocol for Study II can be found in Appendix IV. The background, validity and reliability of all measures have been described in Chapter 2.

The following measurements were completed for Study IIa in the listed order:

- **Standing height** was measured according to the procedures outlined in section 2.4.1.1.
- **Body composition**, including body weight, was measured using BIA according to the procedures outlined in section 2.4.1.1 and section 2.4.2.1
- **Fasting blood samples** were drawn to measure insulin, glucose, HbA_{1c} and lipid profile as per the procedure outlined in section 2.5.7.1. Insulin resistance was estimated using HOMA-IR (section 2.5.6).
- **Resting blood pressure** was measured according to the procedures outlined in section 2.5.3.1.
- **Waist circumference** was measured according to the procedures outlined in section 2.5.2.1.

4.3.3 Data Analysis

All data was analysed using SPSS version 18.0 software (SPSS, Inc., Evanston, IL). Distributions were checked for normality using the K-S normality test. Data was presented as mean ± standard error of the mean (SE). Changes in end-points were examined using paired-sample t-tests for normally distributed data and the Wilcoxen sign rank test for non-normally distributed data.

Due to inherent technical error of measurement associated with inter-rater measures of waist circumference (WHO, 2011), absolute change in waist circumference was not examined. Instead, participants were classified as "healthy waist circumference " (waist circumference <80cm) or as "centrally obese" (waist circumference ≥80cm) based on pre-defined cut-points (Alberti and Zimmet, 1998). Waist circumference was therefore analysed as a dichotomous variable and change in classification of central obesity was examined. The presence or absence of the MetSyn was also treated as a dichotomous variable and change in the proportion with the MetSyn was examined. McNemar's test for paired samples was used to assess differences in the presentation of the MetSyn and central obesity. Correlations between anthropometric measures and selected metabolic variables were carried out using PPMCC. The Kruskal-Wallis test was applied to compare differences in metabolic biomarkers across baseline clinical and lifestyle characteristics including disease stage, adjuvant treatment, menopausal status, presence of the MetSyn at diagnosis and smoking status. The study was however, underpowered to adjust to for potentially confounding factors. Significance was set at p=0.05.

4.4 Study IIa: Results

4.4.1 Participant Characteristics

Of the 70 participants recruited for Study II, nine were missing either significant T0 or T1 data and were therefore excluded from Study IIa (Study IIa total n=61). Missing data was defined as those missing all blood results (T0: n=8; T1: n=1). Participants' characteristics and treatment details for Study IIa participants are listed in Table 19 .

Table 19 Study IIa Participant Characteristics and Treatment Details

Characteristic	Mean (SD) / n (%)
Participant Demographics	
Age at diagnosis	50.96 (8.87) years
Age at follow-up assessment	54.24 (9.03) years
Time Since Diagnosis	3.28 (0.97) years
Menopausal status at diagnosis	
Premenopausal	31 (51)
Postmenopausal	30 (49)
Marital Status	
Married	43 (71)
Single	18 (30)
Smoking History	
Current smoker	9 (15)
Cancer Details	
Cancer Stage	
I	19 (31)
II	32 (53)
III	10 (16)
Estrogen Receptor Positive	51 (84)
Surgery	
Wide local excision	29 (48)
Mastectomy	32 (53)
Axillary Clearance	22 (36)
Chemotherapy	53 (87)
Radiotherapy	51 (84)
Hormone Therapy	
Tamoxifen	33 (54)
Aromatase Inhibitor	18 (30)
Biological Therapy	
Herceptin	7 (12)

Data are presented as mean (standard deviation) for continuous variables and as frequency (percentage) for categorical variables.

All participants were treated with primary surgery. The majority (87%) were treated with adjuvant chemotherapy using standard anthracycline and/or taxane based regimens including AC and taxol (n=26), TC (n=29), carboplatin and taxotere (n=2) and cyclophosphamide and doxorubicin (n=6). The majority (84%) were taking hormonal therapy at T1.

4.4.2 Data Normality

The following variables were normally distributed at T0: weight, BMI, waist circumference, %BF, diastolic blood pressure, TC, HDL-C and LDL-C. At T1 assessment the following variables were normally distributed: weight, %BF, waist circumference, TC, HDL-C and TG. Therefore, to achieve normality of distributions for each variable in each pair, natural log transformations were applied to the variables BMI, insulin, HOMA-IR, LDL-C, TG, systolic blood pressure and diastolic blood pressure, at both T0 and T1. Non-parametric tests were used for CRP, fasting glucose and HbA_{1c}.

4.4.3 Change in Metabolic and Anthropometric Variables

Changes in components of the MetSyn and anthropometric variables are shown in Table 20. Significant increases were observed in fasting insulin (mean (SE) change 2.73 (0.57) $mU.L^{-1}$, $p<0.001$), HOMA-IR (0.58 (0.14), $p<0.001$) and HbA_{1c} (4.49 (5.63) $mmol.mol^{-1}$, $p=0.001$). There was a significant increase in HDL-C (0.09 (0.04) $mmol.L^{-1}$, $p=0.04$) and a significant decrease in systolic blood pressure (-4.53 (2.23) mmHg, $p=0.03$), however the latter was offset by an increase in the numbers taking anti-hypertensive medication (T0: n=8; T1: n=13). %BF increased significantly (1.37 (0.62) %, $p=0.03$) while all other anthropometrics remained stable. At T0, 12 participants (20%) presented with the MetSyn. This increased significantly ($p=0.03$) to 18 participants (30%) at T1. The increase was attributed to an increase in the numbers taking anti-hypertensive medication and additional participants classified as hyperglycaemic (T0: n=1; T1: n=5). BMI was significantly correlated with fasting insulin and HOMA-IR scores at both T0 ($r=0.30$; $p=0.02$ for both) and T1 ($r=0.5$; $p<0.001$ for both). Waist circumference was correlated with both fasting insulin and HOMA-IR at T1 only ($r=0.56$, $p<0.0001$ for both).

Table 20 Study IIa Change in Metabolic and Anthropometric Variables

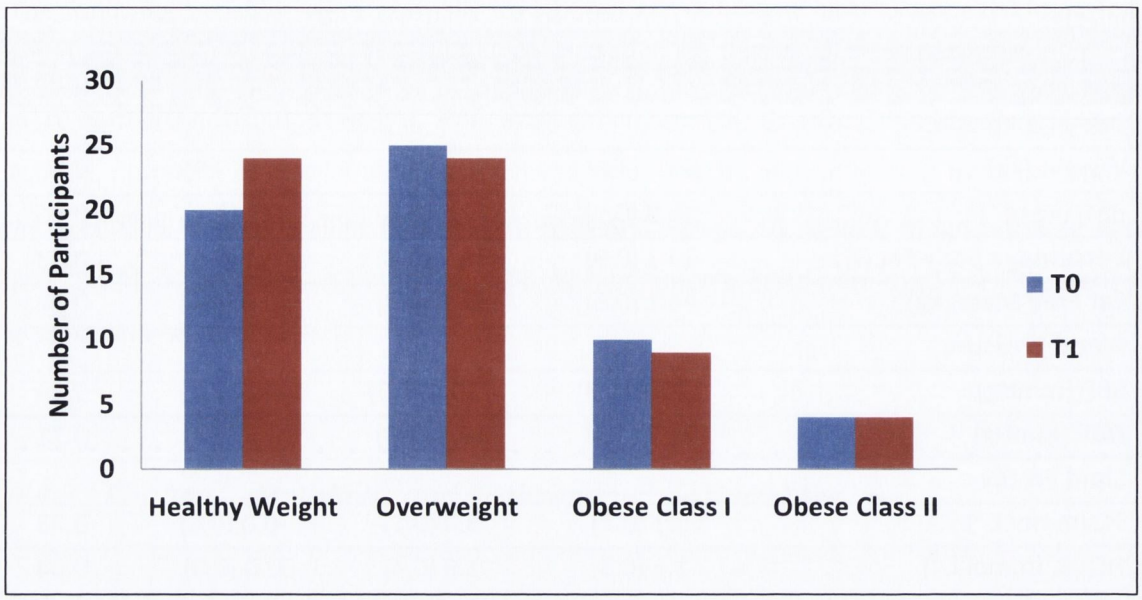
Variable	Baseline (T0) Mean (SE)	Follow-Up (T1) Mean (SE)	Mean Change (SE)	p-value
Body Composition				
Weight (kg)	69.2 (1.6)	70.1 (1.5)	0.9 (0.8)	0.30
BMI ($kg.m^{-2}$)	26.8 (0.5)	27.0 (0.5)	0.1 (3.3)	0.80
Percentage Body Fat (%)	34.3 (0.9)	35.7 (0.8)	1.3 (0.6)	0.03
Fat Free Mass (kg)	44.1 (0.6)	44.1 (0.7)	-0.0 (0.4)	0.82
Blood Pressure				
SBP (mmHg)	125.8 (1.8)	120.5 (1.5)	-4.5 (2.2)	0.03
DBP (mmHg)	78.7 (1.3)	78.3 (1.0)	0.5 (1.4)	0.71
Lipid Profile				
TC ($mmol.L^{-1}$)	5.1 (0.1)	5.0 (0.1)	-0.0 (0.1)	0.73
HDL-C ($mmol.L^{-1}$)	1.6 (0.3)	1.6 (0.4)	0.0 (0.0)	0.04
LDL-C ($mmol.L^{-1}$)	2.9 (0.0)	2.8 (0.1)	-0.0 (0.0)	0.21
TG ($mmol.L^{-1}$)	1.2 (0.0)	-0.0 (0.0)	0.0 (0.0)	0.59
Glucose Metabolism				
Fasting Glucose ($mmol.L^{-1}$)	4.9 (0.0)	4.9 (0.0)	-0.0 (0.0)	0.09
Fasting Insulin ($mU.L^{-1}$)	6.8 (0.8)	9.2 (0.5)	2.7 (0.5)	<0.001
HOMA-IR	1.5 (0.1)	2.0 (0.1)	0.5 (0.1)	<0.001
HbA_{1c} ($mmol.mol^{-1}$)	36.6 (0.4)	40 (5.5)	4.4 (5.6)	0.001

Data are displayed as mean (± standard error).

Abb: kg = kilogram; BMI = body mass index; TC = total cholesterol; $mmol.L^{-1}$ = millimoles per litre; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; HOMA-IR = homeostatic model assessment index; HbA_{1c} = glycosylated haemoglobin A1c;

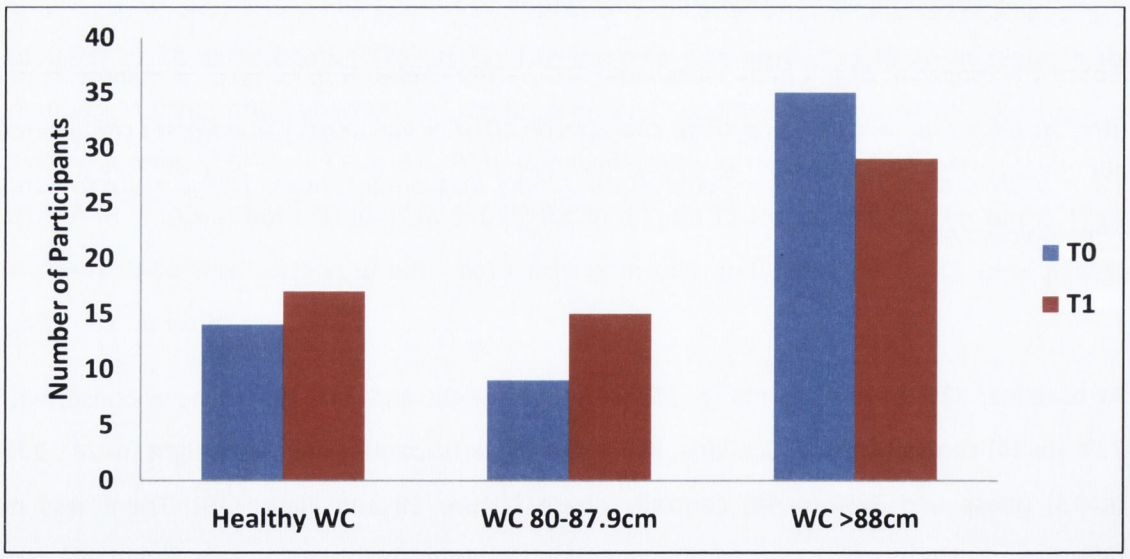
At baseline, 42% of participants (n=25) were overweight and 24% (n=14) were obese, with 72% (n=44) centrally obese. Similarly, at T1 39% of participants were overweight (n=24), 22% (n=13) obese and 72% (n=44) centrally obese (Figure 18 and Figure 19). There was no difference in the distribution of BMI categories ("overweight/obese" versus "healthy") over the study period (p=0.39).There was no change (p=1.00) in the percentage who were centrally obese at either assessment (n=44, (72%) at both).

Figure 18 BMI Classifications throughout Study IIa



Comparison of BMI categories at both assessments time-points (p=0.39)

Figure 19 Central Obesity Levels throughout Study IIa



Comparison of central obesity categories at both assessments time-points (p=1.00). Abb: WC = waist circumference.

As the primary analysis did not account for the influence of confounding variables, further analysis was completed to examine if the changes observed differed according to a number of baseline clinical and lifestyle characteristics including disease stage, adjuvant treatment, menopausal status, presence of the MetSyn at diagnosis and smoking status (Table 21). These characteristics have been previously shown to influence weight gain and change in body fat following adjuvant breast cancer treatment (Irwin et al., 2005a). All variables which demonstrated significant changes in the primary analysis were included with the exception of systolic blood pressure and HDL-C as these variables were potentially confounded by increased use of antihypertensive medication and concurrent hormonal therapy (Redig and Munshi, 2010).

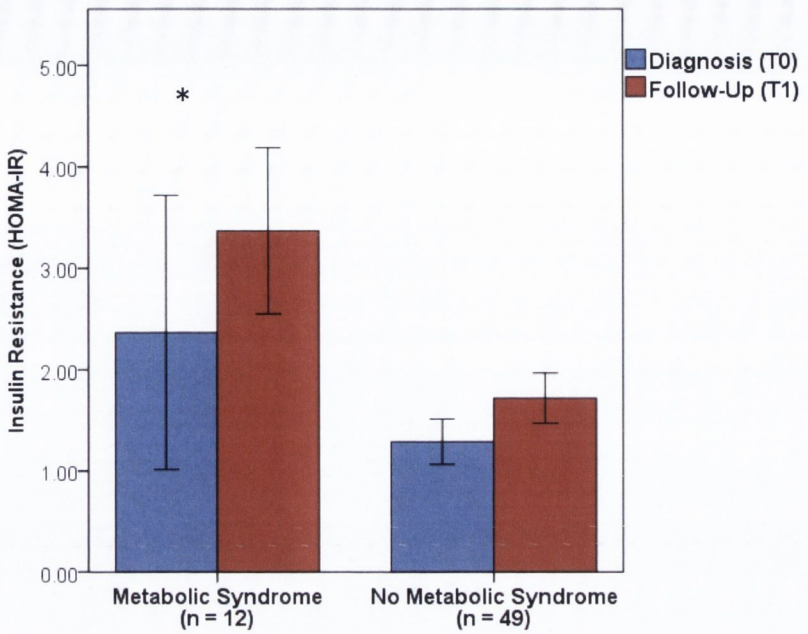
Participants who had a clinical diagnosis of the MetSyn at T0 experienced a significantly greater increase in both insulin (mean (SE) change 4.96 (1.98) $mU.L^{-1}$ vs. 2.26 (0.58) $mU.L^{-1}$, p=0.006) and insulin resistance (HOMA-IR) (1.09 (0.51) units vs. 0.13 (0.88) units, p=0.005) (Figure 20) compared to those who were metabolically healthy at T0. Similarly, smokers (T0) experienced a greater increase in both fasting insulin and HOMA-IR compared to non-smokers. Women who were premenopausal at T0 showed a greater increase in HbA_{1c} (0.19 (0.04) $mmol.mol^{-1}$) than those who were postmenopausal (0.04 (0.04) $mmol.mol^{-1}$, p=0.01) (Figure 21). Change in HOMA-IR did not differ between T0 menopausal groups, nor did the change in either HOMA-IR or HbA_{1c} differ according to clinical stage or adjuvant treatment. Changes in %BF did not differ across any baseline characteristic.

Table 21 Changes in Variables according to Baseline Characteristics

Baseline Characteristic		Fasting Insulin ($mU.L^{-1}$)		HOMA-IR		HbA_{1c} ($mmol.mol^{-1}$)		% BF (%)	
	n	Mean Change (SE)	p-value	Mean Change (SE)	p-value	Mean Change (SE)	p-value	Mean Change (SE)	p-value
Menopausal Status									
Premenopausal	31	2.8 (0.8)	0.73	0.6 (0.1)	0.75	0.1 (0.0)	0.01	1.3 (0.9)	0.92
Postmenopausal	30	2.5 (0.7)		0.5 (0.2)		0.0 (0.0)		1.4 (0.7)	
Disease Stage									
Stage I	19	3.7 (1.0)	0.91	0.8 (0.2)	0.88	0.1 (0.0)	0.59	1.4 (1.1)	0.62
Stage II	32	2.3 (0.6)		0.5 (0.1)		0.1 (0.0)		1.7 (0.8)	
Stage III	10	1.6 (2.0)		0.2 (0.5)		0.0 (0.0)		0.1 (1.3)	
Adjuvant Treatment									
CT (+/- RT)	10	3.0 (1.4)	0.58	0.7 (0.3)	0.63	-0.0 (0.0)	0.63	1.4 (1.3)	0.56
HT (+/- RT)	9	3.6 (0.7)		0.8 (0.2)		0.1 (0.1)		2.9 (1.0)	
CT + HT (+/- RT)	42	2.4 (0.7)		0.4 (0.1)		0.1 (0.0)		2.9 (1.0)	
Metabolic Syndrome									
Metabolic syndrome	12	4.9 (1.9)	0.006	1.0 (0.5)	0.005	0.1 (0.0)	0.99	1.0 (1.1)	0.74
No metabolic syndrome	49	2.2 (0.5)		0.4 (0.1)		0.1 (0.0)		1.5 (0.7)	
Smoking Status									
Smoker	9	7.4 (2.0)	0.009	1.6 (0.4)	0.02	0.1 (0.1)	0.71	2.7 (1.5)	0.31
Non-Smoker	52	1.9 (0.5)		0.4 (1.3)		0.1 (0.0)		1.1 (0.6)	

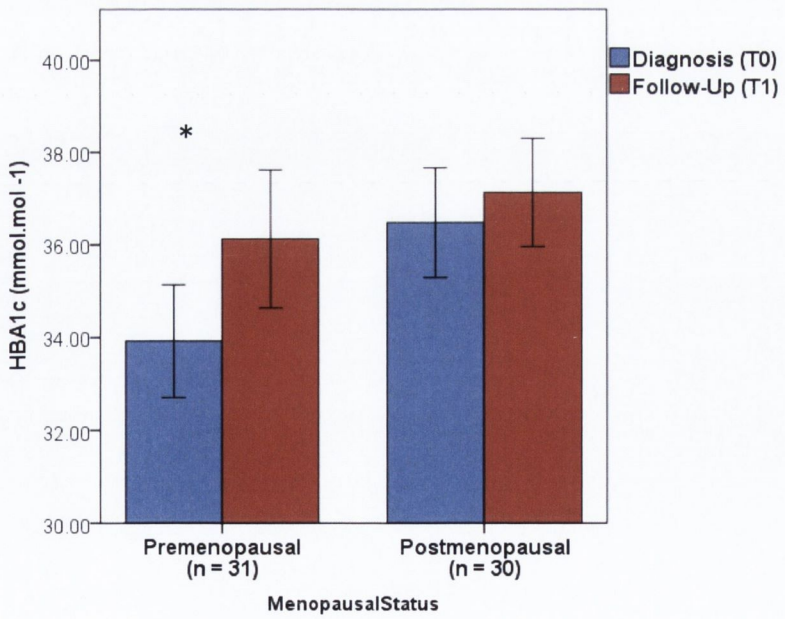
Data are displayed as mean change (standard error). Abb: CT = chemotherapy; RT = radiotherapy; HT = hormonal therapy; HOMA-IR = homeostatic model assessment index; HbA_{1c} = glycated haemoglobin A_{1c}; %BF = percentage body fat

Figure 20 Change in Insulin Resistance by Baseline Metabolic Syndrome Status



** Increases in insulin resistance was significantly higher in those who had the MetSyn at T0 versus those who didn't have the MetSyn (p=0.005).*

Figure 21 Change in HbA_{1c} by Baseline Menopausal Status



** Increases in HbA_{1c} was greater in those who were premenopausal at T0 versus those who were postmenopausal (p=0.01).*

4.5 Discussion Study IIa

The results of this study show that from the time of breast cancer diagnosis to completion of adjuvant treatment, patients with breast cancer with no other serious comorbidities demonstrated a significant deterioration in metabolic profiles, characterized by increases in fasting insulin and associated insulin resistance, accompanied by significant increases in HbA_{1c}. The proportion of participants presenting with the MetSyn also increased. While the study did not investigate predictors of metabolic deterioration, there was some preliminary evidence to suggest that those with baseline metabolic dysfunction, smokers and premenopausal women experienced the greatest deterioration in insulin-glucose markers.

The most striking changes observed were in measures of glucose metabolism with endogenous fasting insulin levels increasing significantly accompanied by an increase in HOMA-IR ($p<0.001$). Despite the observed increased fasting insulin levels, fasting glucose remained unchanged suggesting that insulin resistance had developed but that the pancreas was able to compensate sufficiently to maintain glucose homeostasis (ADA, 2012). However, the significant elevation in HbA_{1c}, the gold standard for measuring glycaemic control (Hanas and John, 2010) and a greater number of participants classified as hyperglycaemic at T1 (fasting glucose $\geq 5.6 mmol.L^{-1}$) (Alberti et al., 2009), provides some evidence of glucose intolerance. One previous study reported transient hyperglycaemia in 39 non-diabetic patients with breast cancer receiving dexamethaxone in addition to standard adjuvant chemotherapy regimens with six women developing impaired glucose tolerance (glucose 7.8-11.1$mmol.L^{-1}$) and eight with glucose intolerance within the diabetic range (glucose $>11.1 mmol.L^{-1}$) at treatment completion (non-fasting glucose) (Hickish et al., 2009).

While the deteriorations observed in measures of glucose metabolism were highly statistically significant there is a need however to consider them in the context of physiological significance. In the current study, mean fasting insulin increased from 6.88 $mU.L^{-1}$ (44.92 $pmol.L^{-1}$) at T0 to 9.26 $mU.L^{-1}$ (63.86 $pmol.L^{-1}$) at T1. The latter value is comparable to the highest quartile of insulin (69 (51.9 to 339.8 $pmol.L^{-1}$) reported by Goodwin et al., (2012), who found that compared to lowest quartile of insulin, patients with breast cancer in the highest quartile had a two-fold increased risk of distant recurrence (HR = 2.32 (95% CI, 1.39 to 3.86)) and almost a three-fold increase in mortality risk (HR=2.85 (95% CI, 1.48 to 5.50)). This

suggests that the increase observed in fasting insulin was sufficient to reach potentially prognostically meaningful levels. Results are similar for HOMA-IR. It should be noted however that Goodwin et al., (2012) measured fasting insulin at one time-point, shortly after breast cancer surgery, and therefore unlike the current study fasting insulin values were pre-adjuvant treatment. In contrast, results from the HEAL study, which measured insulin resistance approximately three years post diagnosis, reported no association between HOMA-IR scores and breast cancer outcome in women with fasting glucose ≤126 $mg.dL^{-1}$ (Duggan et al., 2011). In the current study, mean fasting glucose was 89.97 $mg.dL^{-1}$ at T0 and 89.43 $mg.dL^{-1}$ at T1. This result puts into question the prognostic significance of increases in HOMA-IR in this non-diabetic cohort. Nonetheless, even modest evidence of impaired glucose tolerance and dysmetabolism increase the risk of CVD in older women. Considering that CVD is a significant contributor to all-cause mortality following breast cancer (Nichols et al., 2009, Chapman et al., 2008, Patnaik et al., 2011) therapeutic management of established risk factors such as impaired glucose tolerance is recommended (Collins et al., 2007).

There are a number of potential mechanisms which may have contributed to the observed metabolic deterioration. Obesity is the most common underlying cause of insulin resistance (Hardy et al., 2012). In the current study, fasting insulin and HOMA-IR scores correlated with BMI at both T0 and T1. While weight gain during adjuvant breast cancer treatment is commonly reported (Demark-Wahnefried et al., 2001a) in the current study body weight and BMI remained stable, however there was a significant increase in %BF. While FFM did not change significantly, mean values decreased slightly, suggestive of sarcopenia, which is associated with a number of adverse cardiometabolic features including insulin resistance, chronic inflammation and abdominal adiposity (Dominguez and Barbagallo, 2007, Aubertin-Leheudre et al., 2006). Furthermore, waist circumference, characterising metabolically active visceral adipose tissue, remained above critical MetSyn thresholds (≥80cm) throughout the study. Visceral tissue promotes the development of insulin resistance through inflammatory and adipokine pathways (Chapter 1, section 1.3.1). Long-term abdominal adiposity is associated with the development an insulin resistant, pro-inflammatory environment characteristic of the MetSyn.

Insulin resistance and dysmetabolism are both known to increase with age (Pichard et al., 2008) and therefore in the absence of a control group, it is unclear whether the changes observed in this study are of similar or greater magnitude to healthy populations. Insulin resistance is rarely observed in premenopausal women, but emerges with the onset of the menopause due to estrogen deficiency (Carr, 2003, Kaaja, 2008). In a longitudinal analysis, Poehlman et al., (1995) reported an increase of 11 (9) $pmol.L^{-1}$ in fasting insulin in 18 healthy premenopausal women who traversed the menopause. In the current study a far greater mean increase of 2.73 (0.57) $mU.L^{-1}$ in fasting insulin (equivalent to 18.94 (3.93) $pmol.L^{-1}$) was observed. HbA_{1c} also increases by 0.4% between ages 40 and 70 years with normal aging (Pani et al., 2008). In the current study, a median increase of 4.49 (5.63) $mmol.mol^{-1}$ (equivalent to 0.1 (0.3)%) was observed suggesting that the increase observed in HbA_{1c} was comparable to normal age-related changes, albeit over a shorter time-frame. While a decline in insulin sensitivity may be considered a normal part of aging (Park et al., 2003), it is accompanied by increased chronic disease risk (Collins et al., 2007) and therefore remains a key therapeutic target.

4.5.1 Study Limitations

There are a number of limitations to this study which warrant discussion. Firstly, the inclusion of a relatively healthy cohort of breast cancer survivors, defined by the absence of significant comorbidity, may have resulted in selection bias. This decision was necessary to reduce the impact of known confounding factors on outcomes being measured. Those >70 years were excluded to reduce the impact of potentially unknown confounding factors. However, the included sample is representative of a group who would be suited to participation in exercise and weight loss interventions due to the lack of comorbidity. Therefore the presented results may provide a meaningful contribution to informing the design of future interventions.

The decision to re-assess this group of participants was made in retrospect and therefore the initial sample was not recruited with follow-up measures in mind, resulting in a number of limitations. Firstly, a large number of participants tested at T0 were unsuitable for testing at T1, thereby affecting the external validity of the study (Chapter 2, section 2.2.2). The presented results can only be applied to breast cancer survivors who are <70 years old and free from comorbidity and are not generalisable to a wider population of women following

breast cancer. Moreover, as participants did not consent originally to follow-up assessments, a relatively large proportion (29%) of suitable participants did not complete Study IIa due to absence of medical consent or refusal. Baseline comparison of those who did and did not participate demonstrated no differences however, suggesting that the presented results are applicable to this wider sub-cohort.

Secondly, as follow-up was unplanned, participants were only measured at two time-points; morning of surgery and again 2-5 years later meaning that the potential for collecting valuable data at key times during adjuvant treatment (e.g. at time-points during chemotherapy or at the start of hormonal therapy) was missed. Moreover, follow-up assessments were not completed at a standardised time post diagnosis or treatment completion leading to considerable sample heterogeneity. Finally, the current study was under-powered to measure change in variables according to baseline characteristics or to adjust results for to potentially confounding factors.

4.6 Conclusion

In the current study, participants demonstrated deteriorations in insulin, insulin resistance and MetSyn from the time of breast cancer surgery to post completion of adjuvant treatment. As the influence of dysmetabolism on prognosis is well-established there is a need for further investigation into the optimum timing of interventions to prevent metabolic decline. The results from the current study would suggest that interventions early in the cancer trajectory are needed to prevent deterioration in potentially prognostic variables. There is also a need to identify those at risk of metabolic decline. The results of the current study are consistent with others who found that breast cancer survivors were characterized by significant levels of central obesity (Buttros et al., 2012, Thomson et al., 2009). This raises the questions - what are the most important metabolic traits for investigation in this cohort? While dyslipidemia and hypertension (including their associated drug treatments) are central features of the current MetSyn definition, they may not be as predictive of breast cancer prognosis as glucose dysregulation. The results of this study may support the inclusion of a measure of insulin resistance in evaluations of dysmetabolism following breast cancer.

Chapter 5 Study IIb: Metabolic Syndrome in Breast Cancer Survivors

The Presentation of Metabolic Dysfunction in Breast Cancer Survivors and the Relationship with Energy Expenditure

Statement of Author's Contribution

The study concept and design were developed by the student Emer Guinan (EG), supervisor Dr. Juliette Hussey (JH), co-supervisor Ms. Elizabeth Connolly and medical oncologist Professor M John Kennedy (MJK). EG developed the testing protocol. Participant recruitment was completed by EG and facilitated by MJK. EG completed all outcome assessments, data analysis and data interpretation. EG was responsible for drafting Chapter 5 in this thesis and the subsequent manuscript. All authors approved the final version of the published manuscript.

5.1 Introduction

This chapter details the methods, results and discussion of the second part of the breast cancer survivors study in this thesis – Study IIb. The aim of Study IIb was to describe the characteristics of metabolic dysfunction in breast cancer survivors and the relationship between the components of metabolic dysfunction and habitual energy expenditure.

The metabolic consequences of obesity are well described (Despres and Lemieux, 2006, Galic et al., 2010). Metabolic dysfunction however does not always accompany obesity and the presentation of metabolic disturbance varies greatly among obese individuals (Messier et al., 2010). Furthermore, the classification of metabolically unhealthy has not been standardised, largely due to the ever-evolving definition of the MetSyn (Chapter 1, section 1.3.2). In breast cancer there is need to consider metabolic profiling in terms of those variables likely to be of greatest prognostic significance. Insulin resistance is arguably one of the most important features of metabolic dysfunction in relation to cancer due to the strong mitogenic effects of insulin on cancer cell growth (Hursting et al., 2007) and the substantial evidence linking hyperinsulinemia and insulin resistance to cancer prognosis (Duggan et al., 2011, Goodwin et

al., 2012). The results of Study IIa presented in Chapter 4 suggest a significant deterioration in measures of insulin-glucose metabolism following adjuvant breast cancer treatment. Equally, central obesity, characterising increased visceral fat accumulation, is associated with the secretion of many pro-tumor products including pro-inflammatory cytokines (IL-6, TNF-α), adipokines and sex hormones, particularly in postmenopausal women (Despres and Lemieux, 2006). Results from both Study I and Study IIa suggest a predominance of central obesity among breast cancer survivors. Despite these findings levels of metabolic dysfunction were relatively low in Study I.

As long-term obesity is essentially due to an imbalance between energy intake and energy output, Study IIb also examined the presentation of metabolic dysfunction in relation to energy expenditure (RMR and physical activity levels). As discussed in Chapter 1, physical activity is associated with improved breast cancer outcomes and is also a key factor in the development and management of the MetSyn (Grundy et al., 2005). Reductions in RMR may place certain individuals at an increased risk of weight gain (Bandini and Flynn, 2003) and has been suggested as one of the causal factors for weight gain during chemotherapy for breast cancer survivors (Chapter 1, section 1.2.3). RMR has also been shown to be altered in the presence of metabolic abnormalities (Weyer et al., 1999).

This study has been published in the Nutrition Journal (Appendix II)

Guinan, E.M., Connolly, E.M., Kennedy, M.J, Hussey, J. (2013) The Presentation of Metabolic Dysfunction and the Relationship with Energy Output in Breast Cancer Survivors: A Cross-Sectional Study. Nutrition Journal, 12:99

5.2 Objectives and Research Design

The overall aim of Study II was to examine the presentation of the MetSyn in breast cancer survivors who had completed adjuvant treatment with curative intent.

The specific objectives of Study IIb were:

- To describe the metabolic risk profile of breast cancer survivors who completed adjuvant therapy with curative intent.
- To investigate components of energy expenditure in breast cancer survivors and to examine associations between energy expenditure and metabolic parameters.
- To measure and classify the aerobic fitness levels of breast cancer survivors according to age and gender matched population data.

Study IIb was designed as a cross-sectional study. The limitations of this study design have been discussed in Chapter 2 (section 2.2.1).

5.3 Methods

5.3.1 Sampling and Recruitment

Recruitment for Study II was described in Chapter 4, section 4.3.1. In addition to the participant criteria stated for Study IIa, participants were excluded from completing the fitness test part of Study IIb if they were a) dependent on a mobility aid, b)if LVEF was <40% as measured by most recent MUGA. Those taking beta-blocker medication to manage hypertension were also excluded from completing the fitness test as the primary outcome measure used during the fitness test was heart rate. Beta blockers act by reducing heart rate and thus measurement would be inaccurate in these participants. The accuracy of RMR measurements can be affected by factors such as anxiety (Schmidt et al., 1996). Therefore, participants self-reporting claustrophobia or a reluctance to complete the RMR measurement which involved the canopy method were not required to compete this measurement.

5.3.2 Measures and Testing Protocol

As described in Chapter 4, section 4.3.2, participants attended for testing, following a 12 hour fast, during which all measures for Study II (Study IIa and Study IIb) were completed. The complete testing protocol for Study II can be found in Appendix IV. The background, validity and reliability of all measures have been described in Chapter 2.

The following measurements were completed for Study IIb in the listed order:

- **Standing height** was measured according to the procedures outlined in section 2.4.1.1.
- **Body composition**, including body weight, was measured using BIA according to the procedures outlined in section 2.4.1.1 and section 2.4.2.1.
- **Fasting blood samples** were drawn to measure insulin, glucose, HbA_{1c}, lipid profile and CRP as per the procedure outlined in section 2.5.7.1. Insulin resistance was estimated using HOMA-IR (section 2.5.6).
- Participants rested in a supine position during which the interview administered **Minnesota questionnaire** (section 2.3.1.5) was completed.
- **RMR** was measured according to the procedures outlined in section 2.6.3.1.
- **Resting blood pressure** was measured according to the procedures outlined in section 2.5.3.1.
- **Waist circumference** was measured according to the procedures outlined in section 2.5.2.1.
- **Aerobic fitness** was estimated using the Modified Bruce Treadmill protocol as per the procedures outlines in section 2.6.2.1. Following the baseline assessment aerobic fitness was classified as "poor", "fair", "average" or "good" according to age and gender matched normative data (Katch et al., 2011e) (Appendix XIII).
- Participants were provided with an **RT3 activity monitor** to wear for one week as per the protocol outlined in section 2.3.1.2.

5.3.3 Data Analysis

Data are presented as mean ± standard deviation for normally distributed data and as median ± interquartile range for non-normally distributed data. Correlations between energy output and metabolic variables were examined using PPMCC for normally distributed data and Spearman's rho for non-normally distributed data. The lowest detectable value for CRP was 1 $mg.L^{-1}$ and therefore results <1$mg.L^{-1}$ were assigned a value of 1$mg.L^{-1}$. Values >15$mg.L^{-1}$ were excluded as these results most likely represented an acute inflammatory event (Rifai and Ridker, 2001).

Over 70% of participants in both Study I and Study IIa were classed as centrally obese, i.e. had a waist circumference >80cm. However as described in Chapter 1 (section 1.3.2) there is a lack of consensus regarding the most appropriate cut-point for waist circumference (80cm vs. 88cm). Therefore, a secondary, post-hoc examination of participants in the current study (Study IIb) was completed to examine differences in metabolic profiles based on levels of central obesity (healthy waist circumference vs. waist circumference >80cm vs. waist circumference >88cm). The results of Study IIa suggested that insulin resistance may be an important feature of metabolic deterioration following adjuvant breast cancer treatment. In light of this, a fourth group, who were both insulin resistant and centrally obese were examined. Insulin resistance was defined by the 75th percentile of HOMA-IR of the participants being studied (HOMA-IR = 2.45) (Balkau and Charles, 1999). With the exception of one participant who had a waist circumference of 82.4cm, all women in Group 4 had a waist circumference >88cm. The four subgroups are described in Table 22.

Table 22 Study IIb: Sub-groups for Secondary Analysis

	Waist circumference	Insulin resistant
Group 1	<80cm	No
Group 2	80cm – 87.9cm	No
Group 3	≥88cm	No
Group 4	≥80cm	Yes

Anthropometric, metabolic and energy output variables were compared between the four groups using ANOVA. Significance was set at $p<0.05$. Post hoc analysis was completed using Tukey's HSD method when a significant group effect was observed. Kruskal-Wallis non-parametric ANOVA was used to compare distributions between non-parametric data and post hoc analysis was completed using a Mann-Whitney U test for comparison between pairs of group. Corrections were made for multiple comparisons using the Bonferroni correction ($p<0.01$).

5.3.3.1 Resting Metabolic Rate - Correction for Fat Free Mass

RMR ($kJ.day^{-1}$) was corrected for FFM using the following procedure according to the methods of Ravussin and Bogardus (1989). For a small sample size the following equation is recommended: RMR/(FFM + x-intercept)

- RMR was strongly and significantly correlated with FFM ($r=0.75$, $p<0.001$) as described by the following regression equation: RMR $kJ.day^{-1}$ = 310.53 + 114.39 (FFM (kg).
- The x-intercept of the line was calculated using the equation: $y = mx + c$, where $y = 0$, m = 114.39 (slope), c = 310.53 (y=intercept). The x-intercept was calculated as -2.71.[13]
- The following equation was used to adjust RMR for FFM: [RMR / (FFM + 2.71)]
- Adjusted RMR did not correlate with FFM ($r=0.003$; $p=0.985$) confirming that FFM had been factored out of RMR.

[13] FFM is underestimated by 2.71kg. Thus (FFM + 2.71kg) is a more accurate estimate of metabolically active tissue.

5.4 Results: Study IIb

Of the 70 participants recruited for Study II (section 4.3.1), one participant who was unwell on the day of testing and was later found to have a middle-ear infection was missing significant data and was therefore excluded from Study IIb. In total 69 participants (mean (SD) age 53.43 (9.39)) participated. Participant demographics and treatment details are shown in Table 23.

Table 23 Study IIb Participant Characteristics and Treatment Details

Characteristic	Mean (SD) / n (%)
Participant Demographics	
Age at diagnosis	50.2 (9.1) years
Age at follow-up assessment	53.3 (9.4) years
Time Since Diagnosis	3.1 (1.0) years
Menopausal status at diagnosis	
Premenopausal	37 (54)
Postmenopausal	32 (46)
Marital Status	
Married	48 (70)
Single	21 (30)
Smoking History	
Current smoker	9 (13)
Cancer Details	
Cancer Stage	
I	19 (28)
II	36 (52)
III	14 (20)
Estrogen Receptor Positive	56 (81)
Surgery	
Wide local excision	31 (45)
Mastectomy	38 (55)
Axillary Clearance	30 (44)
Chemotherapy	60 (87)
Radiotherapy	56 (81)
Hormone Therapy	
Tamoxifen	35 (51)
Aromatase Inhibitor	20 (29)
Biological Therapy	
Herceptin	8 (12)

Data are presented as mean (standard deviation) for continuous variables and as frequency (percentage) for categorical variables.

Similar to Study IIa, participants were treated with a combination of anthracycline and taxane based chemotherapy regimens including AC and taxol (n=20), TC (n=22), carboplatin and taxotere (n=2) and cyclophosphamide and doxorubicin (n=6). Almost 80% of the group were taking adjuvant hormonal therapy at the time of the measurements.

5.4.1 Data Normality

All variables were normally distributed with the exceptions of BMI, fasting insulin, fasting glucose, HOMA-IR, HbA_{1c}, TG, CRP, and RQ. Minutes spend in moderate and vigorous intensity activity by the RT3 were also non-parametric. Natural log transformations were applied to fasting insulin, HOMA-IR, TG, RQ, moderate intensity activity (RT3) and vigorous intensity activity (RT3). Non-parametric tests were used when dealing with BMI, fasting glucose, HbA_{1c} and CRP.

5.4.2 Metabolic Profile and Anthropometric Variables

5.4.2.1 All Participants

The metabolic profile for all participants is shown in Table 24. While the majority of participants were either overweight (41%) or obese (22%), over one third of the group (38%) had a healthy BMI. A large percentage (73%) were centrally obese and the MetSyn was present in 29% (n=20) participants.

Table 24 Study IIb Anthropometrics and Metabolic Profile

Characteristic	Mean (SD) / n (%)
Anthropometry	
Body weight (kg)	71.0 (13.4)
BMI ($kg.m^{-2}$)	27.1 (4.7)
BMI Categories	
Healthy weight	26 (38)
Overweight	28 (41)
Obese	15 (22)
Waist circumference (cm)	87.1 (11.8)
Central obesity (WC >80cm)	50 (73)
Percentage body fat (%)	36.1 (5.6)
Fat free mass (kg)	44.7 (5.3)

Characteristic	Mean (SD) / n (%)
Blood Pressure	
SBP (mmHg)	119.1 (13.0)
DBP (mmHg)	78.0 (8.1)
Hypertensive (BP >130/85mmHg)	20 (29)
Anti-hypertensive medication†	14 (20)
Lipid Profile	
TC ($mmol.L^{-1}$)	5.1 (0.9)
Dyslipidemia (TC > 5.2$mmol.L^{-1}$)	30 (44)
HDL-C ($mmol.L^{-1}$)	1.6 (0.4)
LDL-C ($mmol.L^{-1}$)	2.9 (0.9)
TG ($mmol.L^{-1}$)	1.2 (0.6)
Cholesterol medications†	4 (6)
Glucose Metabolism	
Fasting glucose ($mg.dL^{-1}$)	4.9 (0.5)
Fasting Insulin ($mU.L^{-1}$)	9.2 (4.5)
Hyperinsulinemia (>12$mU.L^{-1}$)	15 (22)
Insulin resistance (HOMA-IR)	2.0 (1.1)
HbA_{1c} ($mmol.mol^{-1}$)	36.1 (3.3)
Glucose medications†	0
Inflammatory Marker	
CRP ($mg.L^{-1}$)	1.4 (1.9)
Metabolic Syndrome	20 (29)

Data are displayed as mean (± standard deviation) for normally distributed variables and median (inter-quartile range) for non-normally distributed variables.

† Refers to the number of participants taking prescribed medication

Abb: BMI = body mass index; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; HOMA-IR = homeostatic model assessment index; HbA_{1c} = glycated haemoglobin A_{1c}; CRP = C - reactive protein

BMI showed moderate correlations with fasting insulin (rho=0.54; p<0.001) and HOMA-IR (rho=0.48; p<0.001). BMI was weakly correlated with HBA_{1c} (rho=0.26; p=0.04), fasting glucose (rho=0.26; p=0.03) and CRP (rho=0.29; p=0.02). Similarly, waist circumference showed a moderate-to-high correlation with fasting insulin (r=0.64; p<0.001), HOMA-IR (r=0.62; p<0.001) and CRP (rho=0.44; p<0.001). Waist circumference was weakly correlated with HBA_{1c} (rho=0.24; p=0.05) and fasting glucose (rho=0.24; p=0.02).

5.4.2.2 Secondary Analysis

Anthropometric and metabolic parameters of the four groups are shown in Table 25.[14] Women in Group 3 and Group 4 demonstrated significantly worse anthropometric measures, characterised by significantly higher body weight (p<0.001 vs. Group 1 and p<0.002 vs. Group 2), BMI (p<0.001 for both), waist circumference (p<0.001 for both) and %BF (p<0.001 for both) when compared to Group 1 and Group 2. FFM was significantly higher in both Group 3 (p=0.002) and Group 4 (p=0.001) compared to Group 1. Metabolic profiles were significantly worse in Group 4 than other groups characterised by significantly lower HDL-C (Group 4 vs. Group 1 p=0.02; vs. Group 2 p=0.008), elevated TG (Group 4 vs. Group 1 p<0.001; vs. Group 2 p=0.009), measures of insulin-glucose metabolism (fasting glucose, fasting insulin, HOMA-IR and HbA_{1c}, p<0.001 vs. all groups) and inflammatory status (Group 4 vs. Group 1 p<0.001; vs. Group 2 p=0.005; vs. Group 3 p=0.01). Metabolic profiles did not vary between non-insulin resistant groups.

[14] **Reminder:** Group 1: waist circumference <80cm
Group 2: waist circumference 80cm-87.9cm
Group 3: waist circumference >88cm
Group 4: centrally obese and insulin resistant

Table 25 Comparison of Anthropometric and Metabolic Variables across Groups

Characteristic	Group 1 (n=19)	Group 2 (n=16)	Group 3 (n=16)	Group 4 (n=18)
Demographics				
Age (years)	52.1 (11.6)	50.3 (8.5)	55.5 (9.4)	55.6 (6.7)
Time post diagnosis (years)	3.3 (0.9)	2.6 (0.9)	3.1 (0.8)	3.1 (1.2)
Anthropometry				
Body weight (kg)	59.7 (6.7)	66.2 (5.6)	79.5 (12.5)[a, b]	79.6 (13.8)[a, b]
BMI ($kg.m^{-2}$)	23.0 (1.8)	24.8 (1.7)[a]	30.2 (3.5)[a, b]	30.8 (5.0)[a, b]
BMI Categories				
Healthy weight	17 (90)	8 (50)	0	1 (6)
Overweight	2 (10)	8 (50)	10 (62)	8 (44)
Obese	0	0	6 (38)	9 (50)
Waist circumference (cm)	74.0 (4.6)	83.2 (2.5)[a]	95.1 (6.5)[a, b]	97.4 (10.5)[a, b]
Percentage body fat (%)	31.1 (3.6)	33.4 (3.0)	40.3 (3.0)[a, b]	40.1 (5.2)[a, b]
Fat free mass (kg)	40.9 (3.5)	44.0 (4.1)	47.2 (5.7)[a]	47.1 (5.3)[a]
Lipid Profile				
TC ($mmol.L^{-1}$)	5.2 (0.9)	5.3 (1.0)	4.6 (0.5)	5.3 (0.9)
Dyslipidemia (TC > $5.2mmol.L^{-1}$)	9 (47)	9 (56)	3 (19)	9 (50)
HDL-C ($mmol.L^{-1}$)	1.8 (0.4)	1.8 (0.5)	1.6 (0.3)	1.4 (0.4)[a, b]
LDL-C ($mmol.L^{-1}$)	2.9 (0.7)	3.1 (1.3)	2.3 (0.6)	3.1 (0.8)
TG ($mmol.L^{-1}$)	0.9 (0.4)	1.0 (0.5)	1.1 (0.4)	1.7 (0.8)[a, b]
Cholesterol medications	0	1 (6)	3 (19)	0

Characteristic	Group 1 (n=19)	Group 2 (n=16)	Group 3 (n=16)	Group 4 (n=18)
Blood Pressure				
SBP (mmHg)	114.7 (15.5)	117.0 (9.3)	119.0 (9.9)	125.9 (13.4)
DBP (mmHg)	77.2 (9.9)	75.6 (4.7)	78.5 (8.7)	80.5 (7.9)
Hypertensive (BP >130/85mmHg)	4 (21)	2 (13)	5 (31)	9 (50)
Anti-hypertensive medication	2 (10)	2 (13)	4 (25)	6 (33)
Glucose Metabolism				
Fasting glucose ($mg.dL^{-1}$)	4.7 (0.3)	4.8 (0.3)	4.8 (0.3)	5.3 (0.7)[a, b, c]
Fasting Insulin ($mU.L^{-1}$)	6.7 (1.8)	7.3 (2.2)	8.3 (0.3)	14.4 (5.3)[a, b, c]
Hyperinsulinemia (>12$mU.L^{-1}$)	0	0	1 (6)	14 (78)
Insulin resistance (HOMA-IR)	1.4 (0.4)	1.6 (0.4)	1.8 (0.4)	3.4 (1.3)[a, b, c]
HbA_{1c} ($mmol.mol^{-1}$)	35.2 (2.8)	35.2 (2.5)	35.7 (1.7)	38.3 (4.5)[a, b]
Glucose medications	0	0	0	0
Inflammatory Marker				
CRP ($mg.L^{-1}$)	1.5 (1.0)	1.8 (1.3)	2.0 (1.6)	4.9 (3.4)[a, b, c]
Metabolic Syndrome	0	3 (19)	5 (31)	12 (67)

Data are displayed as mean (± standard deviation) for normally distributed variables and median (inter-quartile range) for non-normally distributed variables. [a] *= significantly different from Group 1;* [b] *= significantly different from Group 2;* [c] *= significantly different from Group 3*

Abb: kg = kilogram; BMI = body mass index; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; HOMA-IR = homeostatic model assessment index; HbA_{1c} *= glycated haemoglobin* A_{1c}*; CRP = C - reactive protein*

5.4.3 Energy Output

5.4.3.1 All Participants

Energy output, including RMR and physical activity data, is shown in Table 26. Mean RMR values were 1297.53 (203.13) $kJ.day^{-1}$. Adjusted RMR demonstrated moderate-to-weak correlations with several metabolic variables including waist circumference (r=0.32; p=0.01), HOMA-IR (r=0.48; p<0.001), CRP (rho=0.31; p=0.02), HDL-C (r=-0.31; p=0.02), TG (r=0.34; p=0.009). Adjusted RMR did not correlate with measures of glucose metabolism (glucose or HBA_{1c}) or blood pressure.

Table 26 Study IIb Energy Output

Characteristic	Mean (SD) / n (%)
Resting Metabolic Rate	
Absolute RMR ($kJ.day^{-1}$)	1297.5 (203.1)
Adjusted RMR ($kJ.day^{-1}.kg^{-1}$)	114.4 (11.7)
RQ (VCO_2/VO_2)	0.7 (0.0)
Physical Activity	
RT3 Activity Monitor	
Sedentary ($min.day^{-1}$)	412.7 (100.3)
Light Intensity ($min.day^{-1}$)	367.2 (75.4)
Moderate Intensity ($min.day^{-1}$)	46.5 (40.0)
Vigorous Intensity ($min.day^{-1}$)	16.8 (27.0)
Moderate and Vigorous Intensity ($min.day^{-1}$)	60.4 (55.8)
Minnesota Questionnaire	
Light AMI ($MET\text{-}h.week^{-1}$)	0.0 (0.0)
Moderate AMI ($MET\text{-}h.week^{-1}$)	13.1 (11.9)
Vigorous AMI ($MET\text{-}h.week^{-1}$)	1.4 (6.0)
Total AMI ($MET\text{-}h.week^{-1}$)	20.1 (18.0)
Adherence to PA guidelines	
30 minutes 5 $days.week^{-1}$	17 (25)
150 $minutes.week^{-1}$	30 (44)

Data are presented as mean (± standard deviation) for normally distributed variables and as median (inter-quartile range) for non-normally distributed variables.

Abb: RMR = resting metabolic rate; RQ = respiratory quotient; VCO_2 = carbon dioxide produced; VO_2 = oxygen consumed; AMI = activity metabolic index; PA = physical activity

RT3 accelerometer output showed that participants spent 49% of waking hours sedentary, 44% engaging in light intensity activity and 7% engaging in either moderate or vigorous intensity activity. Data from the Minnesota questionnaire revealed that in the year prior to interview, on average participants spent just over 4 hours per week engaging in either moderate (3-6 METs) (13.17 (11.97) MET-h.week^{-1}) or vigorous (≥6 METS) (1.44 (6.02) MET-h.week^{-1}) intensity activity. Participants did not report spending any time engaging in light intensity (<3 METs) activity during the year. The most frequent activities completed were walking (for pleasure and to work) (59% of activity), dancing (including aerobics) (10%) and gardening (6%).

When the overall group was examined neither objective (RT3) nor subjective (Minnesota questionnaire) physical activity data correlated with any metabolic or anthropometric outcomes. In healthy cohorts, physical activity tends to correlate strongly with metabolic variables in postmenopausal women but in premenopausal women often no association is observed (Lynch et al., 2011a, Voskuil et al., 2001, Tworoger et al., 2007b). In the current study, the cohort examined was heterogeneous in terms of menopausal status due to the inclusion of women who were both pre- and postmenopausal at breast cancer diagnosis. Therefore, correlation analysis was repeated in only those aged ≥40 years at the time of diagnosis (n=61) as this group were most likely to experience early menopause following treatment (Torino et al., 2012, Goodwin et al., 1999b). In this sub-cohort objectively measured sedentary time was weakly associated with a number of anthropometric outcomes including waist circumference (r=0.27; p=0.04), BMI (r=0.27; p=0.04) and %BF (r=0.31; p=0.02) but not with fasting insulin, HOMA-IR or CRP. Similarly, objective moderate-to-vigorous intensity activity was weakly and inversely associated with waist circumference, BMI and %BF (r=-0.28; p=0.03 for all measures) only. Minnesota scores were not correlated with any anthropometric or metabolic variables in this sub-group.

5.4.3.2 Secondary Analysis

Energy output variables across the four groups are described in Table 27. Absolute RMR (kJ.day^{-1}) was significantly higher in Group 4 compared to all other groups (vs. Group 1 p<0.001; vs. Group 2 p=0.005; vs. Group 3 p=0.05). This result remained significant when RMR was adjusted for FFM (kJ.day^{-1}.kg^{-1}) (Group 4 vs. Group 1 p=0.02; vs. Group 2 p=0.01; vs. Group 3 p=0.008). Neither objective nor subjective habitual activity varied between groups.

Table 27 Comparison of Energy Output across Groups

Characteristic	Group 1 (n=19)	Group 2 (n=16)	Group 3 (n=16)	Group 4 (n=18)
Resting Metabolic Rate				
Absolute RMR ($kJ.day^{-1}$)	4884.5 (619.3)	5232.7 (438.6)	5484.2 (625.0)	6190.9 (959.4)[a, b, c]
Adjusted RMR ($kJ.day^{-1}.kg^{-1}$)	111.7 (12.5)	112.9 (7.6)	110.5 (11.7)	122.3 (10.7)[a, b, c]
RQ (VCO_2/VO_2)	0.7 (0.0)	0.7 (0.0)	0.7 (0.0)	0.7 (0.0)
Physical Activity				
RT3 Activity Monitor				
Sedentary ($min.day^{-1}$)	374.7 (86.5)	414.0 (104.1)	456.3 (98.8)	412.8 (103.9)
Light Intensity ($min.day^{-1}$)	390.1 (87.5)	346.3 (55.7)	346.9 (85.7)	380.2 (61.2)
Moderate Intensity ($min.day^{-1}$)	56.4 (57.5)	47.4 (42.1)	34.9 (18.6)	45.4 (27.5)
Vigorous Intensity ($min.day^{-1}$)	25.2 (42.3)	20.3 (20.9)	8.9 (10.8)	11.5 (18.1)
Moderate and Vigorous Intensity ($min.day^{-1}$)	71.1 (80.4)	67.7 (57.0)	43.8 (22.1)	57.0 (41.3)
Adherence to PA guidelines				
30 minutes 5 $days.week^{-1}$	6 (32)	5 (31)	3 (19)	3 (17)
150 $minutes.week^{-1}$	9 (47)	10 (63)	6 (38)	5 (28)
Minnesota Questionnaire				
Light AMI ($MET\text{-}h.week^{-1}$)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Moderate AMI($MET\text{-}h.week^{-1}$)	14.0 (13.1)	16.7 (18.8)	12.3 (9.5)	13.7 (9.0)
Vigorous AMI ($MET\text{-}h.week^{-1}$)	2.8 (6.4)	1.0 (2.9)	2.0 (7.6)	0.4 (6.9)
Total AMI ($MET\text{-}h.week^{-1}$)	24.4 (17.3)	20.1 (21.3)	16.3 (15.6)	15.1 (18.8)

Data are presented as mean (± standard deviation) for normally distributed variables and as median (inter-quartile range) for non-normally distributed variables. [a] *= significantly different from Group 1;* [b] *= significantly different from Group 2;* [c] *= significantly different from Group 3 Abb: RMR = resting metabolic rate; RQ = respiratory quotient;* VCO_2 *= carbon dioxide produced;* VO_2 *= oxygen consumed; AMI = activity metabolic index; PA = physical activity*

5.4.4 Estimated Aerobic Fitness

In total, 65 participants completed the submaximal fitness test. Fitness levels were classed as poor, fair, average, good or excellent based on population normative data (Appendix XIII) (Katch et al., 2011e). The median (IQR) predicted VO_2max for the group was 16.26 (10.47) $ml.kg.^{-1}min^{-1}$. In total, 35% (n=23) of participants were classed as having poor fitness levels, 45% (n=29) were classed into the fair fitness category, 15% (n=10) had average fitness levels and only 3 participants (5%) were in the good category (Figure 22). The distribution of fitness categories across groups studied is illustrated in Figure 23. The three participants with "good" fitness were in Groups 1 (n=1) and 2 (n=2). The numbers with poor and fair fitness were similar across all group (Poor fitness: Group 1 n=4, Group 2 n=6, Group 3 n=7, Group 4 n=6; Fair fitness Group 1 n=9, Group 2 n=5, Group 3 n=6, Group 4 n=9). No participant in Group 4 had either average or good fitness levels.

Figure 22 Study IIb Estimated Aerobic Fitness

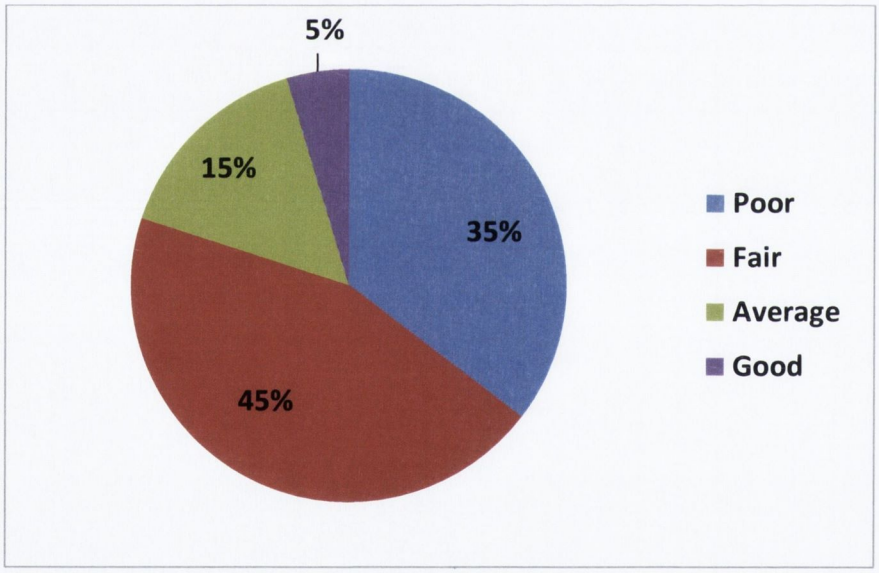
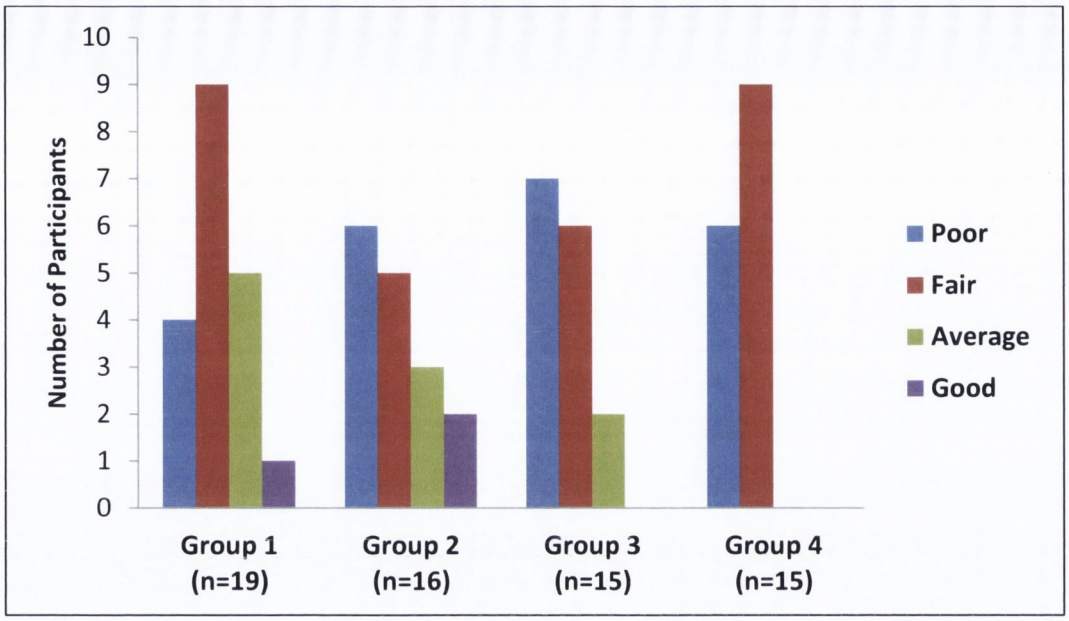


Figure 23 Estimated Aerobic Fitness by Group



5.5 Discussion Study IIb

The results from this descriptive analysis of metabolic characteristics in survivors of breast cancer 2-5 years post adjuvant treatment are not dissimilar to those described in Chapter 3, section 3.4.3. In both analyses, despite both obesity and central obesity being dominant features, there was minimal evidence of metabolic dysfunction as characterised by insulin resistance or chronic low grade inflammation. The overall prevalence of the MetSyn (29%) was also lower than previously reported in similar cohorts (54.8%) (Thomson et al., 2009). Thus a secondary analysis was conducted in an attempt to identify clinically and prognostically significant characteristics. Generally, a measure of insulin sensitivity has been used to distinguish between metabolically healthy and unhealthy obese groups (Brochu et al., 2001, Stefan et al., 2008, Succurro et al., 2008). This approach was adopted in the current study in addition to subdividing the cohort by the level of central obesity.

Results from the secondary analysis suggest that breast cancer survivors who are both centrally obese and insulin resistant are characterised by a higher degree of metabolic dysfunction when compared to women who are centrally obese in the absence of insulin resistance (Table 25). Metabolic dysfunction was characterised by dyslipidemia, glucose dysmetabolism, low grade inflammation and a higher prevalence of the MetSyn. In the

secondary analysis, dysmetabolism was accompanied by higher absolute and adjusted RMR levels but was not associated with differing habitual physical activity levels (Table 27). The results of the current study are consistent with others which have demonstrated altered lipid-lipoprotein profile, inflammatory status and measures of glucose-insulin homeostasis when central obesity exists concurrently with insulin resistance (Nieves et al., 2003, Piche et al., 2005). In these studies, participants who were central obesity and not insulin resistant were characterised by metabolic profiles that are similar to lean controls

In the present study inflammatory status was measured by CRP, which is secreted from the liver in response to pro-inflammatory cytokines (TNF-α and IL-6). As described in Chapter 1, pro-inflammatory cytokines are secreted from the visceral adipose tissue in response to infiltration by macrophages to expanding adipose tissue. Additionally, they act on the liver to stimulate gluconeogenesis, resulting in increased production of hepatic glucose and consequently increased pancreatic secretion of insulin leading to the development of insulin resistance (Hauner, 2005, Kershaw and Flier, 2004). Therefore in the current study, CRP values suggestive of low-grade inflammation (4.98 (3.46) $mg.L^{-1}$)[15] were observed in those who were insulin resistant. These results are comparable to those reported by Thomson and colleagues (2009) who described a mean high sensitivity CRP of 5.1 (5.3) $mg.L^{-1}$ in an overweight cohort of breast cancer survivors. In the current study, CRP was weakly correlated with BMI and moderately correlated with waist circumference. This is consistent with others who reported increasing CRP with increasing adiposity in breast cancer survivors (Pierce et al., 2009b).

Chronic inflammation may also adversely influence lipid-lipoprotein profiles resulting in dyslipidemia (Kershaw and Flier, 2004). Consequently, in the current study HDL-C was significantly lower and TG significantly higher in the insulin resistant group compared to all other groups (Table 25). There is a lack of consensus regarding the presentation of dyslipidemia in obese, insulin resistant adults. Nieves and colleagues (2003) reported in insulin resistant, non-obese individuals, the presentation of dyslipidemia could be explained by differing levels of visceral fat accumulation. In contrast, Piché and colleagues (2005) suggested that variations in the presentation of dyslipidemia in centrally obese adults was driven by

[15] CRP >3$mg.dL^{-1}$ is indicative of chronic low-grade inflammation (Grundy et al., 2009)

insulin resistance. In the current study, only those who were insulin resistant showed evidence of dyslipidemia, however causality cannot be inferred.

It should be acknowledged that the HOMA-IR scores observed in this study (mean 2.09 (range: 0.47 – 6.36) were lower than observed in similar cohorts for example the HEAL study which reported mean HOMA-IR scores of 2.55 (range: 0.25 – 40.16) (Duggan et al., 2011). The HEAL study is a multicentre, multiethnic trial based in the United States of America. To the authors' knowledge, the current study is the first to examine metabolic characteristics in an Irish cohort of breast cancer survivors. One of the limitations of this cohort is a lack of diversity variables such as BMI scores. The mean BMI of participants in the current study was 27.02 (range 19.7-39.9) $kg.m^{-2}$ compared to 27.3 (range 16.2 – 53.3) $kg.m^{-2}$ in those involved in HEAL (Duggan et al., 2011). While the mean values are comparable, the range and maximum values was much smaller in the current study. As obesity is the predominant underlying cause of insulin resistance (Hardy et al., 2012), the lower HOMA-IR scores observed in the current study may be attributed to lower range of BMI values. The prevalence of obesity in Ireland is increasing steadily (Morgan et al., 2008), albeit at a slower rate than observed in North America (WHO, 2000). Nonetheless, the metabolic and physiological health consequences of obesity in Ireland are becoming increasingly evident (National Task Force on Obesity Report 2005) and there is a need for intervention to prevent further decline. While the observed rates of dysmetabolism may be lower than observed internationally, they remain a key therapeutic target.

As discussed in Chapter 1 section 1.2.4, the treatment of obesity requires management of both energy intake and energy expenditure. One of the hypothesised pathways linking physical activity to improved postmenopausal breast cancer outcome is through reductions in adiposity (WCRF/AICR, 2007). Associations between various domains of physical activity and anthropometric measurements have been shown previously in postmenopausal breast cancer survivors (Lynch et al., 2010, Irwin et al., 2005b). In the current study, objective physical activity was correlated with anthropometric variables (BMI, waist circumference, %BF) but only in those ≥40 years old at diagnosis. This group were most likely to experience chemotherapy induced menopause (Torino et al., 2012, Goodwin et al., 1999b), however as

menopausal status was not objectively measured, it cannot be stated that this group are postmenopausal.

A relationship between physical activity and metabolic markers was not observed in the current study. This is in contrast other studies in breast cancer survivors who reported correlations between physical activity and several metabolic variables including fasting insulin (Lynch et al., 2010), HOMA-IR (Lynch et al., 2010), CRP (Pierce et al., 2009b), leptin (Irwin et al., 2005b), IGF-I (Irwin et al., 2005b)and IGFBP-3 (Irwin et al., 2005b). Furthermore habitual physical activity levels did not vary between groups in the secondary analysis. Sedentary behaviour was prevalent across each of these groups representing 50% (Range: 44% in Group 1 to 54% in Group 3) of waking hours (Table 27).In contrast, moderate and vigorous intensity activity accounted for only 7% of waking hours (Range: 5% in Group 3 to 10% in Group 1) with less than one-third of any group achieving recommended physical activity guidelines. It could be suggested that the high percentage of sedentariness made it difficult to identify differences between equally sedentary groups in this small sample. Recent findings from our research group comparing objectively measured physical activity levels in cancer survivors to a matched healthy population demonstrated no differences in sedentary time or participation in moderate or vigorous intensity exercise between the cancer patients and healthy controls (Broderick, 2012). The problem of inactivity and sedentary behaviour observed in the current study reflects low physical activity levels in both cancer survivors and in the population in general. There is a need for interventions to aim to decrease sedentary behaviour in addition to increasing activity time. The implementation of such interventions remains to be established but would probably involve lifestyle and behavioural modification.

RMR comprises the largest component of energy expenditure and therefore is an essential determinant of energy balance. Mean RMR levels (1297.53 (203.13) $jK.day^{-1}$ (equivalent to 1297.53 (203.13) $kcal.day^{-1}$ in the current study were comparable to those reported previously in a similar cohort (1300 (183.9) $kcal.day^{-1}$) (Thomson et al., 2009). In addition, both absolute and adjusted RMR were significantly higher in the insulin resistant group compared to all others and demonstrated moderate-to-weak correlations with a number of metabolic variables. These results are consistent with others which report that adjusted RMR is typically increased in individuals with T2DM relative to healthy counterparts (Huang et al., 2004, Bitz et

al., 2004). Weyer and colleagues (1999) suggested that increases in RMR occur early in the development of T2DM in conjunction with the development of progressive metabolic abnormalities including an increase in gluconeogenesis and increased hepatic glucose productions. In contrast, there is a lack of consensus as to whether RMR is increased or decreased in individuals with clinically defined MetSyn compared to metabolically healthy counterparts (Soares et al., 2011, Buscemi et al., 2007). Despite the exclusion of individuals with T2DM from the current study, results are consistent with the development of underlying glucose dysregulation. In contrast, non-insulin resistant groups with lower RMR values may be at risk of continued weight gain (Bandini and Flynn, 2003).

One of the strengths of the PEACH trial was exercise prescription that was graded according to baseline fitness levels (Table 8). Estimated aerobic fitness in the current study was similar to that observed in the PEACH trial in that the majority of participants were classed as having "poor" or "fair" fitness levels (Katch et al., 2011e). Lower cardiorespiratory fitness is observed in individuals with the MetSyn (Lee et al., 2010). In the current study, while the results are purely descriptive, the numbers class as having "average" or "good" fitness decreases with increasing waist circumference and metabolic abnormalities (Figure 23). The aerobic fitness results from the current study may be used to inform exercise prescription in future exercise trials.

5.5.1 Study Limitations

The limitations of Study II in relation to sampling and selection bias have been discussion in Chapter 4 section 4.5.1. As stated previously however, the population studied represent a group that are suitable for exercise intervention and therefore as stated previously results may be used to inform therapeutic targets for future interventions. It should be acknowledged however that the secondary analysis performed in Study IIb was post-hoc in nature and therefore should be interpreted with caution as results are unadjusted for confounding factors.

This study could also be criticised for not including a matched control sample of non-breast cancer survivors. There is a need to consider the value of comparison to a healthy group. Traditionally, rehabilitation has focused on return to "normal" function and baseline levels. Population statistics however, suggest that "normal" is characterised by obesity (WHO, 2000), inactivity (Hallal et al., 2012) and sedentariness (Lynch et al., 2011a); factors which are all associated with reduced breast cancer outcome and will contribute to metabolic decline. Therefore it is highly likely that the metabolic characteristics presented in this study are comparable to population norms. In today's society however population norms are not suitable rehabilitative goals for optimising patient outcomes following cancer treatment. Therefore the challenge with rehabilitating cancer survivors is the need for them to adopt lifestyle behaviours which far exceed pre-diagnosis levels. It is argued that comprehensive evaluation of metabolic presentation to inform exercise prescription in this population is of more value than comparison to a matched control group.

5.6 Conclusion

The results of this study are consistent with others which demonstrate a high prevalence of obesity, central obesity and inactivity in breast cancer survivors. Despite this there was limited evidence of metabolic dysfunction. In a secondary analysis, breast cancer survivors who were both insulin resistant and centrally obese presented with a number of metabolically unhealthy features. In contrast, despite increasing levels of central obesity, breast cancer survivors without concurrent insulin resistant displayed similar metabolic profiles to lean participants. These results suggest that insulin resistance may be a key rehabilitative target. The level of inactivity this entire cohort of breast cancer survivors is concerning. In breast cancer survivors, a comprehensive assessment of metabolic dysfunction and energy expenditure may be useful for informing the design and therapeutic targets of physical activity interventions.

Chapter 6 Study III: The *BRCA* Study

A Descriptive Analysis of Modifiable Risk Factors in Unaffected *BRCA1* and *BRCA2* Gene Carriers

Statement of Author's Contribution (Chapter 6 (Study III))

The idea for the review presented in section 6.3 was developed by the student Emer Guinan (EG) and supervisor Dr. Juliette Hussey (JH). The search protocol was developed by EG. The search was completed initially by EG and verified by JH. Data analysis and interpretation was completed by EG. Co-supervisor Ms. Elizabeth Connolly (EC) provided medical advice regarding interpretation of the data. EG was responsible for drafting section 6.3.

The subsequent prospective study design and concept was developed by EG, JH, EC, associate professor in the department of Surgery Dr Jacintha O'Sullivan and statistician Dr Kathleen Bennett (KB). The prospective study protocol was developed by EG with contributions from postdoctoral researcher in the department of surgery Dr Sarah McGarrigle (SMcG) and clinical nutritionist Dr Laura Healy (LH). Participant recruitment was completed by EG in association with EC and the BreastCare surgical and nursing teams. All outcome assessments were completed by EG. EG was responsible for interpretation of body composition, metabolic syndrome and physical activity data. SMcG was responsible for DNA processing and analysis and for measurement of DNA telomere length. LH was responsible for assessment and analysis of dietary outcomes. KB completed the sample size calculation and provided statistical advice. Data analysis and interpretation presented in Chapter 6 was completed by EG. EG was responsible for drafting Chapter 6 and for the published study protocol. All authors approved the final version of the published study protocol.

6.1 Introduction

Study III provides the baseline descriptive analysis of a multidisciplinary prospective longitudinal study, which will be completed over the coming 10 years, examining the relationship between modifiable and predictive risk factors for breast cancer in unaffected *BRCA1* and *BRCA2* gene carriers. The study design for the prospective study was developed by the author of this thesis in conjunction with other members of the breast research multidisciplinary team. Complete accrual and completion of all follow-up assessments is beyond the scope of this thesis. In this thesis, results refer to baseline assessments completed

on those recruited from the St. James's hospital site for the prospective study. The following sections will describe the background to the development of the prospective cohort study protocol. This will include a discussion of international *BRCA* cohort studies which are currently ongoing (section 6.2) and a systematic literature review examining the current knowledge of the role of modifiable risk factors for *BRCA*-related breast cancer risk (section 6.3). The aims and objectives, methods, results and discussion of results presented in this thesis will commence at section 6.4.

6.2 Modifying *BRCA*-Related Breast Cancer Risk

As described in Chapter 1, section 1.1.2.2, women who are identified as carriers of the deleterious mutation in either one of the breast cancer genes, *BRCA1* or *BRCA2*, have up to an 80% risk of developing breast cancer and a 60% risk of ovarian cancer development. Management of this group involves intensive annual screening and prophylactic risk reducing surgery. Such surgeries confer the greatest reduction in risk however bilateral mastectomy is not appealing to all, particularly younger mutation carriers, and bilateral oophorectomy is only suitable for women beyond childbearing years. Increased understanding of the role of modifiable breast cancer risk factors may have important implications for breast cancer prevention and management in this cohort.

In recent years there has been increased penetrance of *BRCA* related breast cancer compared to previous cohorts of *BRCA* mutation carriers (Milne et al., 2008, Tryggvadottir et al., 2006, Evans et al., 2008), suggesting that environmental or lifestyle factors may modify risk in this cohort with genetic predisposition. A number of international collaborations have been established to gather information from multi-national, multicentre trials which are collecting data on genetic modifiers of breast cancer risk in both affected and unaffected[16] *BRCA* mutation carriers (Table 28). In most of these trials the primary outcomes are genetic modifiers and markers of DNA damage. Lifestyle measures are also being collected using standardised questionnaires primarily focusing on reproductive breast cancer risk factors. Information on exposure to x-ray radiation, weight history, physical activity levels and dietary

[16] The term "affected" implies that individuals were affected by breast cancer. The term "unaffected" implies that individuals were unaffected by breast cancer.

intake are being collected in this manner. This collaborative approach facilitates sufficient sample size for meaningful data analysis.

While several collaborations are based in North America and Australia, both The Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) and the International *BRCA1/2* Carrier Cohort Study (IBCCS) have strong input from European centres. The Epidemiological Study of Familial Breast Cancer (EMBRACE) study, which has an accrual target of 7500 affected and unaffected *BRCA1/2* carriers, is recruiting from 16 centres across the UK and Ireland. In the Netherlands the Hereditary Breast and Ovarian Cancer Study (HEBON) is a retrospective cohort study with prospective follow-up and is using self-reported, retrospective methods to examine differences in anthropometric (Manders et al., 2011) and physical activity (Pijpe et al., 2010) measures in relation to cancer risk. Other contributors to CIMBA include the Modifiers and Genetics in Cancer (MAGIC) study (USA), the Genetic Modifiers of cancer risk in *BRCA1/2* mutation carriers (GEMO) study (France / USA) and the Gene Etude Prospective Sein Ovaire (GENEPSO) study (France). A full list of contributors to CIMBA can be found at http://ccge.medschl.cam.ac.uk/consortia/cimba/groups/groups.html.

Table 28 Collaborative Cohort Studies

Study Title	Population	Aims and Measures
The International *BRCA1/2* Carrier Cohort Study (IBCCS) (http://www.ibccs.nl/Home/tabid/55/language/en-US/Default.aspx) Goldgar et al., (2000)	• Collaborative European prospective study • Known *BRCA1/BRCA2* carriers • Affected and unaffected carriers • Includes 14 collaborative members examining modifiers of hereditary breast cancer risk.	**Aims:** To precisely estimate the age, sex and site-specific cancer risk due to *BRCA*-mutation; to determine the importance of known reproductive factors on risk; to determine the efficacy of prophylactic surgery and other screening / prevention strategies; to create an ongoing registry of gene carriers. **Outcomes:** Standardized lifestyle questionnaire; biological samples
The Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) (http://www.kconfab.org/Index.shtml) Osborne et al., (2000)	• A research resource based in Australia and New Zealand. • *BRCA* mutation positive families with two or more carriers.	**Aim:** To collect biological specimens and data on familial breast and ovarian cancer for use in research projects worldwide. **Outcomes:** Standardized lifestyle questionnaire and blood sampling
The Breast Cancer Family Registry (Breast CFR) (http://www.cfr.epi.uci.edu/) John et al., (2004)	• Collaboration of six research groups in North America (USA and Canada) and Australia • Known *BRCA1/BRCA2* carriers • Affected and unaffected carriers • Accrual: 12,000 families	**Aim:** To understand genetic and environmental factors contributing to familial cancer risk. **Outcomes:** Lifestyle questionnaire including weight history and physical activity, self-administered FFQ, 30ml blood sample from participants with a history of breast cancer.
The Consortium of investigators of Modifiers of *BRCA1/2* (CIMBA) (http://ccge.medschl.cam.ac.uk/consortia/cimba/index.html) Chenevix-Trench et al., (2007)	• A collaborative group of researchers examining genetic modifiers of cancer risk in *BRCA*-mutation carriers. • Includes over 50 collaborative members examining modifiers of hereditary breast cancer risk.	**Aim:** To calculate sufficient sample size to evaluate genetic modifiers of *BRCA1/2* breast cancer risk. **Outcomes:** Standardized lifestyle questionnaire; biological sampling

Abb: FFQ = Food Frequency Questionnaire

6.3 Systematic Literature Review

While considerable data is being collected from the above mentioned collaborative cohort studies on markers of DNA damage and reproductive factors related to breast cancer risk, there is a need for clarity on the evidence available regarding the role of modifiable lifestyle-related risk factors in this cohort. A systematic literature review was undertaken to review the evidence examining the association between established modifiable lifestyle risk factors (physical activity, body composition, metabolic dysfunction and dietary intake) and *BRCA*-associated breast cancer risk. Although dietary contribution to breast cancer risk is beyond the scope of this thesis, the topic was included for review due to the inter-relationship with weight gain and body composition.

6.3.1 Methods

Eligibility Criteria

Cohort or case-control studies examining the impact of anthropometric, dietary, metabolic and / or physical activity outcomes on *BRCA*-related breast cancer risk were considered for inclusion. Anthropometric outcomes included current weight, weight history or history of weight change. Metabolic outcomes included presence of the MetSyn (or its individual components) or related conditions such as insulin resistance or T2DM. Dietary intake included total energy intake and individual dietary components such as alcohol consumption.

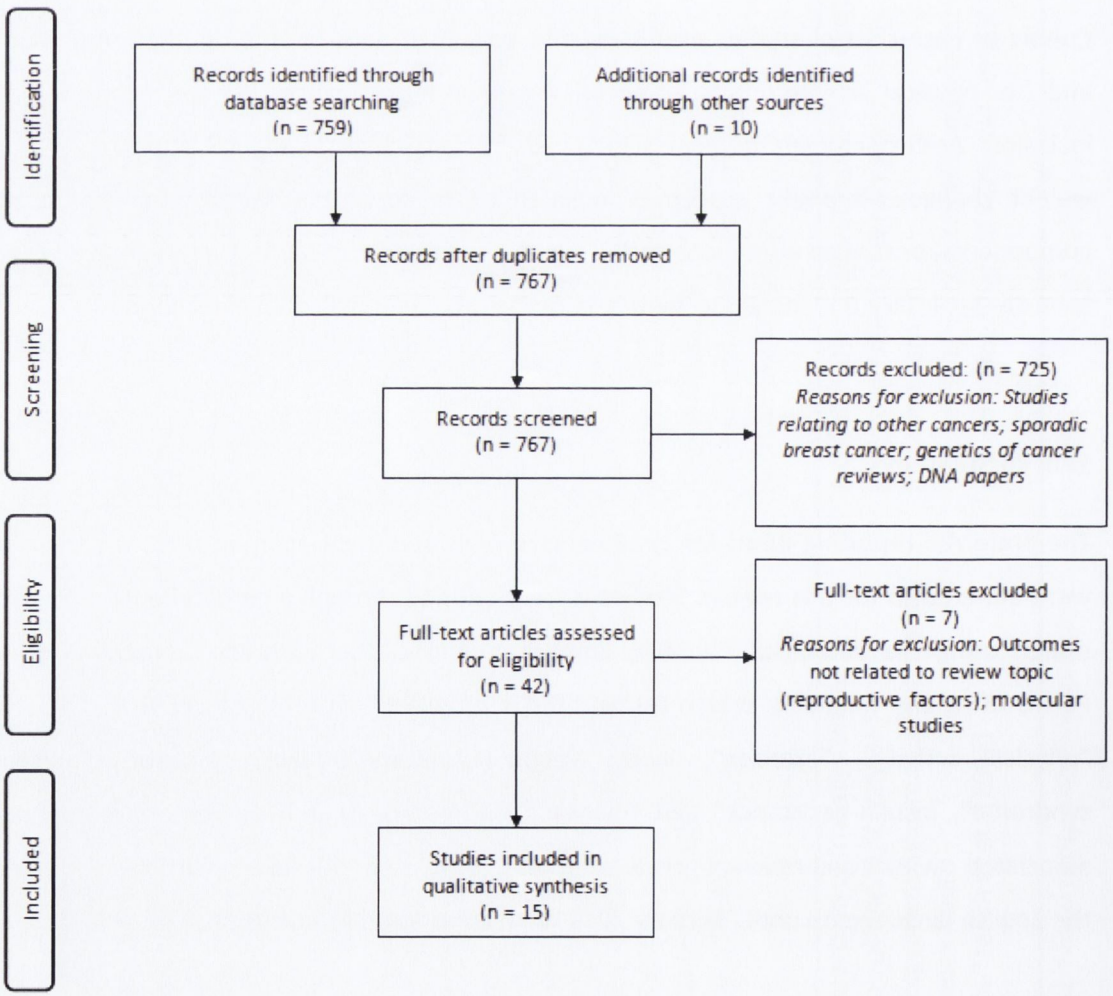
Search Strategy

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were adhered to for this review. Studies were identified through a comprehensive electronic search using the databases PubMed, Embase, SciVerse, the Cochrane Library, AMED and PEDro using the following search terms: "*BRCA* mutation"; "breast cancer risk", "lifestyle", "physical activity", "exercise", "body weight", "dietary intake", "alcohol", "metabolic syndrome", insulin resistance" and "diabetes". A manual search of the reference lists of associated reviews and relevant articles was also completed. All suitable articles published in the English language up until February 2013 were considered for inclusion.

6.3.2 Results

The search strategy identified 767 potentially suitable articles. When inclusion and exclusion criteria were applied 15 studies remained for review. The search strategy is shown in the PRISMA diagram (Figure 24). Three studies reported on physical activity outcomes (King et al., 2003, Nkondjock et al., 2006b, Pijpe et al., 2010), six on anthropometric outcomes (Chang-Claude et al., 1997, King et al., 2003, Kotsopoulos et al., 2005, Nkondjock et al., 2006b, Manders et al., 2011, Moorman et al., 2010), one on metabolic outcomes (Bordeleau et al., 2011) (specifically T2DM) and nine examining components of dietary intake including total energy intake (Nkondjock et al., 2006b, Nkondjock and Ghadirian, 2007, Ghadirian et al., 2009), coffee consumption (Nkondjock et al., 2006a) and alcohol intake (Dennis et al., 2010, McGuire et al., 2006, Moorman et al., 2010, Dennis et al., 2011).

Figure 24 PRISMA Diagram



Study Designs and Participant Characteristics

Eight case-control designs, five case-only studies and two retrospective cohort studies were reviewed. With the exception of the study by Nkondjock et al., (2007) where a group of non-*BRCA* carriers within the control group were included, all case-control studies reviewed compared *BRCA* carriers with a history of breast cancer (cases) to *BRCA* carriers who were unaffected by breast cancer (controls). In four studies, cases and controls were matched by mutation (*BRCA1/BRCA2*), year of birth (within one year) and country of residence (multi-national trials) (Nkondjock et al., 2006a, Dennis et al., 2010, Kotsopoulos et al., 2005, Bordeleau et al., 2011). The study by Bordeleau and colleagues (2011) included a second unmatched analysis of cases (i.e. all affected by breast cancer) with and without a history of T2DM. In all other case-control analyses participants were unmatched (Nkondjock et al., 2006b, McGuire et al., 2006, Nkondjock and Ghadirian, 2007, Lecarpentier et al., 2011). All five case-only studies included individuals with a history of breast cancer; two studies included only *BRCA* carriers (King et al., 2003, Chang-Claude et al., 1997) while three others included both *BRCA* carriers and non-*BRCA* carriers with breast cancer. Moorman et al., (2008) aimed to match each *BRCA* carrier to two non-*BRCA* carriers by both age (+/- 4 years) and treatment centre. Two reports, both taken from the HEBON cohort, used a retrospective cohort design with prospective follow-up (Manders et al., 2011, Pijpe et al., 2010). Participants included *BRCA*-carriers with and without a history of breast cancer and activity questionnaires used gathered information on the previous 10 years.

Six studies reported results from collaborative efforts which included participants recruited from multi-national sites, mainly Australia and North America (USA and Canada) (Dennis et al., 2010, McGuire et al., 2006, Bordeleau et al., 2011, Kotsopoulos et al., 2005, Nkondjock et al., 2006a, Moorman et al., 2010). Five other studies included homogenous groups with similar genetic backgrounds associated with increased incidence of *BRCA* mutations including French-Canadians (Nkondjock and Ghadirian, 2007, Nkondjock et al., 2006b, Ghadirian et al., 2009, Dennis et al., 2011) and Ashkenazi Jews (King et al., 2003). Finally, four studies recruited from single countries namely Germany (Chang-Claude et al., 1997), France (Lecarpentier et al., 2011) and the Netherlands (Manders et al., 2011, Pijpe et al., 2010).

With the exception of one study (Nkondjock and Ghadirian, 2007), in all unmatched case-control analyses cases were significantly older than controls (Nkondjock et al., 2006b, McGuire et al., 2006, Lecarpentier et al., 2011). In contrast, in three case-only studies, *BRCA* carriers were more likely to be younger than non-*BRCA* patients with breast cancer (Moorman et al., 2010, Ghadirian et al., 2009, Dennis et al., 2011). Menopausal status at the time of study interview was reported by five studies (Nkondjock et al., 2006a, Dennis et al., 2010, Dennis et al., 2011, Manders et al., 2011, Pijpe et al., 2010), where the majority of participants were premenopausal (range 48% (Dennis et al., 2011) to 85% (Manders et al., 2011). In all other studies, mean age at menarche and menopause were reported however the percentage of the cohort who were postmenopausal at the time of interview was not provided. The following sections will discuss results relating to modifiable measures of interest (physical activity, body composition, metabolic dysfunction and dietary intake).

Physical Activity and *BRCA*-related Breast Cancer

Two cohort studies (King et al., 2003, Pijpe et al., 2010) and one case-control study (Nkondjock et al., 2006b) reported on the associations between physical activity and *BRCA*-related breast cancer risk. In all studies physical activity was assessed subjectively. King and colleagues (2003) classified activity as having participated in teenage sports activities ("yes" or "no" response). Nkondjock et al., 2006 and Pijpe et al., 2010 both completed physical activity interviews using detailed questionnaires however neither the name or the validity of questionnaires used in either study were reported.

King et al., (2003) found that participation in teenage sports activities was associated with delayed breast cancer onset for all genetic mutations associated with breast cancer risk ($p=0.025$), specifically in women with *BRCA1/2* mutations ($p=0.034$). Nkondjock et al., 2006 reported no difference in physical activity levels (previous two years) between unaffected *BRCA*-mutation carriers (controls: n=48) and *BRCA* carriers with a history of breast cancer (cases: n=89) for total physical activity levels (controls 29.6±21.9 MET-h.week^{-1}; cases 30.8±23.8 MET-h.week^{-1}) and found no association between history of *BRCA*-related breast cancer and history of either total ($p=0.91$), moderate ($p=0.40$) or vigorous ($p=0.56$) weekly activity participation.

Pijpe et al., (2010) examined physical activity in relation to participation in lifetime sports activity. In this cohort study 79% (n=172) of cases reported "ever" participating in sports activity, 72% (n=152) engaging in sports prior to the age of 30 and 49% (n=106) after the age of 30. Participation in moderate intensity (11.0-22.7 MET-h.week^{-1}) sports activity was associated with a significant decreased risk of breast cancer compared to both never participating in sports (HR=0.64, 95% CI, 0.38 to 1.06) and to engaging in light intensity (<11.0 MET-h.week^{-1}) activity (HR=0.59, 95% CI, 0.36 to 0.95). Participation in high intensity (≥22.7 MET-h.week^{-1}) activity did not convey greater risk reduction. A dose-dependent relationship was observed for higher levels of activity participation prior to age 30 ($HR_{\text{(moderate versus light MET-h.week-1)}}$ = 0.60, 95% CI, 0.3 to 0.96; $HR_{\text{(high versus light MET-h.week-1)}}$ = 0.58, 95% CI, 0.35 to 0.94, p-trend = 0.053). Participation in sports after aged 30 was associated with decreased breast cancer risk (HR=0.63, 95% CI, 0.44 to 0.91) in a non-dose dependent manner. Lean individuals who participated in sports after aged 30 experienced greater reduction in risk when compared to their obese counterparts (Lean HR =0.58, 95% CI, 0.38 to 0.88; Heavy HR=0.75, 95% CI, 0.49 to 1.15). Results did not vary by either menopausal status or *BRCA* mutation type.

Body Composition and *BRCA*-related Breast Cancer

The association between body composition and/or weight change and *BRCA*-related breast cancer risk was examined by three cohort studies (Chang-Claude et al., 1997, King et al., 2003, Manders et al., 2011) and two case-control studies (Kotsopoulos et al., 2005, Nkondjock et al., 2006b). In all studies participants were asked to self-report weight and height in addition to either a retrospective recall of weight at particular ages or history of weight change. No study measured current weight or height objectively in a clinical or research setting.

Two studies reported no association between body weight measures as characterised by current body weight (Chang-Claude et al., 1997), weight in the year prior to diagnosis (Moorman et al., 2010) or weight at age 18 (Moorman et al., 2010) and breast cancer risk. In contrast, King et al., (2003) reported delayed onset breast cancer in those who were a healthy body weight (versus overweight or obese) at menarche (p=0.017) and who were a lighter weight at aged 21 (p=0.021). Similarly, a pilot case-control analysis (n=137) by Nkondjock et al., 2006 found that age at maximum BMI attainment, adjusted for physical activity, age and total energy intake was directly associated with increased breast cancer risk (OR=2.980, 95%

CI, 1.01 to 8.36, p=0.046). Maximum weight gain from aged 18 (OR=4.64, 95% CI, 1.52 to 14.12, p=0.011) and aged 30 (OR=4.11, 95% CI, 1.46 to 11.56, p=0.013) were both significantly associated with increased risk (Nkondjock et al., 2006). Similar, yet contrasting results were reported in a larger (n=1073 pairs) matched case-control study where weight loss of ≥10lbs between age 18 and 30 was associated with significantly reduced breast cancer risk between ages 30 and 49 (OR=0.47, 95% CI, 0.28 to 0.79), particularly in *BRCA1* carriers who had ≥2 children (OR=1.44, 95% CI, 1.01 to 2.04) (Kotsopoulos et al., 2005).

While Manders and colleagues (2011) did not report any significant associations between anthropometric measures and breast cancer risk in their overall cohort (n=719), trends varying by menopausal status were observed. Premenopausal breast cancer risk was non-significantly but inversely associated with BMI at aged 18 (HR $_{\text{BMI 18.2-22.49 kg.m-2 vs. 22.5-24.9 kg.m-2}}$=0.83, 95% CI, 0.47 to 1.44; HR $_{\text{BMI 18.2-22.49 kg.m-2 vs. ≥25 kg.m-2}}$ =0.13, 95% CI, 0.13 to 1.27) and with increasing current BMI (HR $_{\text{BMI 18.2-22.49 kg.m-2 vs. 22.5-24.9 kg.m-2}}$ =0.87, 95% CI, 0.53 to 1.42; HR $_{\text{BMI 18.2-22.49 kg.m-2 vs. ≥25 kg.m-2}}$ =0.75, 95% CI, 0.43 to 1.31). In contrast, higher current body weight (>72kg) was associated with a two-fold increased risk of postmenopausal breast cancer (HR=2.10, 95% CI, 1.23 to 3.59). Non-significant direct associations with breast cancer risk were also observed for current BMI ≥25 $kg.m^{-2}$ (HR=1.46, 95% CI, 0.86 to 2.51), adult weight gain ≥5kg (HR=1.56, 95% CI, 0.85 to 2.87) and relative adult weight gain ≥20% (HR=1.60, 95% CI, 0.97 to 2.63).

Metabolic Dysfunction and *BRCA*-related Breast Cancer

Only one case-control study (n=3026 pairs) examined the association between any element of metabolic dysfunction and *BRCA*-related breast cancer risk, namely self-reported presence or absence of T2DM (Bordeleau et al, 2011). In the year before breast cancer diagnosis there was no difference in the presence of T2DM between cases (4.3%) and controls (2.8%) (p=0.10). The annual risk of T2DM developing over a 15 year period was increased in all (affected and unaffected) *BRCA*-carriers with a BMI ≥25$kg.m^{-2}$, but was higher for those with a history of breast cancer with a significant increase in the number of new onset cases of T2DM either at or following diagnosis (OR=2.0, 95% CI, 1.4 to 2.8, p=0.0001).

Dietary Intake and *BRCA*-related Breast Cancer

The associations between various aspects of dietary intake, including alcohol consumption, coffee intake and total energy intake, have been examined in nine studies; six case-control studies and three case-only cohort studies. All three studies examining dietary intake used interview administered FFQs to assess dietary intake over the past year (Nkondjock et al., 2006, Nkondjock et al., 2007) or in the year prior to diagnosis (Ghadirian et al., 2009). Total energy intake, adjusted for age, maximum lifetime BMI and physical activity was directly associated with increased breast cancer risk (OR=2.76, 95% CI, 1.10 to 7.02, p=0.026) (Nkondjock et al., 2006b). Further analysis on the same cohort found that adjusted diet quality scores (highest vs. lowest quartile), as assessed by the DQI-R (OR=0.35, 95% CI, 0.12 to 1.02, p=0.034) and CHEI (OR=0.18, 95% CI, 0.05 to 0.68, p=0.006) scores were associated with increased breast cancer risk. Adjusted fruit and vegetable diversity has also been shown to be associated with decreased cancer risk (OR= 0.27, 95% CI, 0.10 to 0.80, p=0.03) (Ghadirian et al., 2009).

With the exception of Moorman and colleagues (2010) who recorded alcohol use as either "yes" or "no", all studies completed a comprehensive assessment alcohol consumption patterns which included alcohol type, volume consumption and duration of drinking (years). Conflicting results have been reported. Two studies reported no associations between greater alcohol consumption and increased cancer risk for either *BRCA1* (OR=1.06, 95% CI, 0.73 to 1.52) or *BRCA2* (OR=0.66, 95% CI, 0.45 to 0.97) carriers (McGuire et al., 2006) or by smoking status (Lecarpentier et al., 2011). Moorman et al., (2010) suggested that alcohol had a weaker effect on *BRCA1* breast cancer risk (n=283) compared to non-*BRCA* carriers (n=894)) (interaction RR=0.65, 95% CI, 0.48 to 0.90). While Dennis et al., (2010) found no association between alcohol consumption with *BRCA2* breast cancer risk (odds ratio (OR) =1.00, 95% CI, 0.71 to 1.41) an inverse association was observed with *BRCA1* breast cancer risk (OR=0.82, 95% CI, 0.70 to 0.96) and increased wine consumption (p=0.01). With the exception of wine, Dennis et al., (2011) found that greater alcohol consumption was associated with higher breast cancer risk with *BRCA2* mutations (OR=2.15, 95% CI, 1.03 to 4.49) but not with *BRCA1* mutations (OR=0.38, 95% CI, 0.08 to 1.81).

One matched case-control study (n=845 pairs) reported a significant trend (p=0.02) towards reduced breast cancer risk with increasing consumption of caffeinated coffee (adjusted for parity, smoking, oral contraceptive use, alcohol use and BMI). No association was observed for decaffeinated coffee (p=1.00). When results were stratified by mutation status, the protective effect of coffee consumption (≥6 cups.day^{-1}) was observed in *BRCA1* (n=652 pairs) carriers (p=0.009) and not *BRCA2* (n=193 pairs) carriers (p=0.84) (Nkondjock et al., 2006a).

6.3.3 Discussion

This review provides a summary of the current evidence examining the influence of established modifiable breast cancer risk factors on *BRCA*-related breast cancer risk. The results provide evidence that healthy lifestyle practices during younger years may confer some protection over cancer occurrence in later life. Participation in moderate intensity sports activity during teenage and early-adult years was associated with decreased or delayed breast cancer risk (King et al., 2003, Pijpe et al., 2010). Lighter weight during teenage years and weight loss between ages 18 and 30 were both associated with decreased breast cancer risk during later life suggesting that *BRCA*-carriers can reduce future cancer risk at a young age (King et al., 2003, Kotsopoulos et al., 2005). The negative impact of weight gain from both aged 18 and aged 30 on breast cancer risk was also observed highlighting the detrimental consequences of unhealthy lifestyle choices during early adulthood (Nkondjock et al., 2006b). Not surprisingly, greater total energy intake, which will promote excess weight gain, conveyed higher breast cancer risk (Nkondjock et al., 2006b) while greater consumption of fruit and vegetables was inversely associated with cancer risk (Ghadirian et al., 2009). In sporadic breast cancer, greater alcohol consumption was the only component of dietary intake that was strongly and positively associated with increased breast cancer risk in both pre- and postmenopausal women (WCRF/AICR, 2007). Among *BRCA* mutation carriers however there was a lack of consensus regarding the association between alcohol consumption and breast cancer risk and conflicting evidence regarding the relationship with each mutation (Dennis et al., 2010, Dennis et al., 2011).

One of the primary concerns with the studies reviewed was the methods used to collect the variables of interest. All studies relied heavily on self-report, retrospective methods of data collection, with some merely collecting "yes"/"no" style responses with no details on intensity

or volume of the outcome in question (Bordeleau et al., 2011, King et al., 2003, Moorman et al., 2010). In large epidemiological studies, information on habitual physical activity levels is most often collected using self-reported quantitative history questionnaires. There are a large number of physical activity tools available for this purpose which have been validated for cancer research (http://appliedresearch.cancer.gov/tools/paq/paqrefs.html - accessed 15.02.2013), however it is unclear which tools were employed to assess physical activity in the studies reviewed (Pijpe et al., 2010, Nkondjock et al., 2006b) making it difficult to have confidence in the validity of the physical activity collection methods used. It should be acknowledged that all self-report methods are limited due to the reliance on participant recall and subjective interpretation of activity intensity, frequency etc., which often results in inaccurate and exaggerated reporting of actual physical activity levels, particularly among groups that are overweight (Noonan and Dean, 2000).

Equally, adult weight history and dietary intake are inherently reliant on subjective methods for data collection. None of the studies reviewed supplemented historical body composition data with objective measurement of current body weight. In particular, self-reported BMI must be interpreted with caution due the tendency for individuals to overestimate height and underreport weight, leading to a greater cumulative underestimation of BMI (Engstrom et al., 2003). The majority of studies used validated FFQs to measure dietary intake, generally in the year prior to diagnosis. While all methods of measuring dietary intake are limited due to their subjective nature and heavy reliance on participant accuracy (Chapter 2, section 2.6.1), FFQ are widely considered the best methods to explore dietary habits in the past year. Care should be taken however when interpreting data from FFQs where greater time has elapsed between the year to which the assessment referred (normally the year pre-diagnosis) and the interview. Both Ghadirian et al., (2009) and Dennis et al., 2011 concentrated on the year prior to diagnosis, however the mean time between diagnosis and interview in the study by Dennis and colleagues (2011) was 3.1 years (range <1month-24.7 years) while Ghadirian and colleagues (2009) did not provide this information.

Metabolic dysfunction was measured by one study by self-reported presence or absence of T2DM (Bordeleau et al., 2011). No objective evaluation of either fasting glucose or HbA_{1c} was included. The prevalence of undiagnosed T2DM in the United States has been consistent

across NHANES reports in recent years (Harris et al., 1998, Cowie et al., 2006, Cowie et al., 2010), representing up to 20% of total T2DM. The prevalence of undiagnosed T2DM increases with increasing age (Cowie et al., 2010), obesity (Gregg et al., 2004) and sedentariness (Dunstan et al., 2004). There is a clear need for a study using objective measures of dysmetabolism from pre-breast cancer diagnosis in this cohort for an accurate reflection of prevalence of metabolic abnormalities.

While two studies describe a positive association between teenage sports participation and decreased breast cancer risk, there is a need to examine domains of physical activity other than sports. Lynch and colleagues (2011b) identified a number of domains of activity associated with decreased postmenopausal breast cancer risk including recreation and household (21% decreased risk), transport by walking or cycling (18%) and activity related to occupation (13%) (Chapter 1, section 1.4.3). There is also increasing evidence of the detrimental influence of excess sedentary behaviour on chronic disease risk, including cancer (Lynch, 2010). A comprehensive assessment of all domains of physical activity, including sedentariness, is required and if possible objective rather than subjective methods of data collection should be employed.

It is well established that while overweight and obesity increase the risk of sporadic postmenopausal breast cancer, an inverse relationship is observed with premenopausal breast cancer (Friedenreich, 2001, Ballard-Barbash, 1994). Despite this only one study stratified results by menopausal status (Manders et al., 2011). Moreover the study by Manders et al., (2011) and was in fact the only study measuring body composition outcomes to describe the menopausal status of their cohort (King et al., 2003, Chang-Claude et al., 1997, Kotsopoulos et al., 2005, Nkondjock et al., 2006b, Moorman et al., 2010). As observed in sporadic breast cancer, Manders and colleagues (2011) reported an inverse relationship between increasing BMI and premenopausal breast cancer and a direct relationship with postmenopausal breast cancer. There is a need to examine breast cancer risk in terms of menopausal status. In addition, there is a need for studies to include a measure of visceral abdominal fat, as surgically induced menopause resulting from prophylactic bilateral salpingo-oophorectomy will result in changes in regional fat distribution which can have significant metabolic consequences (Michelsen et al., 2009).

Research into the protective effects of modifiable lifestyle risk factor on sporadic breast cancer risk has increased considerably in the past number of years. Investigations into the role of such modifiable risk factors in hereditary or genetically predisposed breast cancer are not as advanced as reflected in the studies reviewed. Going forward, there is a need for prospective, longitudinal studies which follow unaffected *BRCA* mutation carriers through pre-breast cancer years ultimately to a point if or when breast cancer occurs. While a number of large cohort studies and collaborative groups, such as those listed in Table 28, plan to prospectively measure modifiable risk factors for breast cancer risk in this cohort, the methodological issues with outcome measures related to the measurement of lifestyle factors (which generally are secondary measures in these large studies) may reduce the validity of results. To the authors knowledge there is no study currently objectively measuring body composition and physical activity in unaffected *BRCA*-mutation carriers. While blood samples are being collected and stored, non-fasting measurements make it impossible to potentially measure metabolic variables such as insulin, glucose or lipid profiles.

A prospective longitudinal protocol was developed to examine the potential of modifiable risk factors to reduce cancer risk in this high risk cohort. The protocol was developed as part of a multidisciplinary team involving breast care, physiotherapy, clinical nutrition, molecular medicine and statistics. The protocol has been published in BMC Cancer which can be found in Appendix II. Briefly, the protocol describes a 10 year prospective study, aiming to recruit 350 unaffected *BRCA1/2* carriers and measure a range of modifiable lifestyle (physical activity, body composition, dietary and metabolic) and predictive (markers of DNA damage) factors related to breast cancer risk. Objective assessments will be completed at three time-points (baseline, two years and five years) and subjective data will be collected annually by questionnaire. Objective data collection methods will include accelerometry (physical activity), BIA (body composition) and fasting blood samples (metabolic screening). Three-day food diaries will be used to measure dietary intake. Data collection has commenced at St. James's hospital and at the National Centre for Medical Genetics at Our Lady's Children's Hospital Crumlin. The following section will describe the methods and baseline demographics of the cohort of participants recruited at the time of thesis submission.

6.4 Study III: Objectives and Research Design

The overall aim of Study III was to investigate the presentation of modifiable breast cancer risk factors in unaffected *BRCA1* and *BRCA2* mutation carriers.

The specific objectives of Study III relating to this thesis were:

- To describe the metabolic risk profile, including body composition of *BRCA* mutation carriers who have been unaffected by cancer.
- To examine the physical activity levels and to assess adherence to physical activity guidelines among unaffected *BRCA* mutation carriers.
- To examine associations between selected metabolic markers with body composition and physical activity in unaffected *BRCA* mutation carriers.

Study III was designed as a prospective longitudinal study, however the results presented are from a cross-sectional analysis of baseline data. The characteristics of observational study designs have been discussed in Chapter 2, section 2.2.1

6.5 Methods

6.5.1 Sampling and Recruitment

Recruitment commenced in September 2011. The first number of this defined cohort of participants was recruited from family risk and genetics clinics at St. James's hospital and the National Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin. Potentially suitable participants were identified in advance of clinics by research and nursing teams. Participants were provided with an information leaflet (Appendix III) during their medical appointment and if they wished to receive more information they were invited to approach a research representative present at the clinic.

Women who met the following study criteria were eligible to participate: a) genetically tested and identified as carriers of the deleterious mutation in either one of the *BRCA* genes, *BRCA1/2* and who do not have a history or either breast or ovarian cancer, b) aged 18 years or more, c) able to understand English, d) willing to travel to the study site for measurements. Participants were excluded for the following reasons: a) history of cancer or evidence of active

disease (exception: non-melanoma skin cancer), b) confirmed pregnancy or history of childbirth in the preceding 6 months (all assessment were completed a minimum of 6 months postpartum), c) any medical co-morbidity that would preclude the ability to participate in the study, d) dependence on a mobility assistive device, e) participants who at the local investigators discretion (usually genetics or breast care nurse) were not deemed appropriate e.g. very upset and emotional regarding finding of *BRCA* gene mutation, family, work or transport issues that would make participation difficult.

6.5.2 Measures and Testing Protocol

All measurements were completed at the Exercise Laboratory at the Discipline of Physiotherapy, Trinity Centre for Health Sciences, St. James's Hospital. Baseline measures, as outlined, were completed during one 60 minute session, following a 12 hour fast. The complete assessment protocol for Study III can be found in Appendix IV. The background, validity and reliability of all measures used in this study have been described in Chapter 2.

The following measurements were completed for Study III in the listed order:

- **Standing height** was measured according to the procedures outlined in section 2.4.1.1.
- **Body composition**, including body weight, was measured using BIA according to the procedures outlined in section 2.4.1.1 and section 2.4.2.1.
- **Fasting blood samples** were drawn to measure insulin, glucose, HbA_{1c}, lipid profile and CRP as per the procedure outlined in section 2.5.7.1. Insulin resistance was estimated using HOMA-IR (section 2.5.6).
- Participants rested in a seated position during which the interview administered **Minnesota questionnaire** and **Tecumseh questionnaire** (section 2.3.1.5) were completed
- **Resting blood pressure** was measured according to the procedures outlined in section 2.5.3.1.
- **Waist circumference** was measured according to the procedures outlined in section 2.5.2.1.
- Participants were provided with an **RT3 activity monitor** to wear for one week as per the protocol outlined in section 2.3.1.2.

6.5.3 Data Analysis

Data was analysed using SPSS version 18.0 software (SPSS, Inc., Evanston, IL). Distributions were checked for normality using the K-S normality test. Descriptive statistics are presented as mean ± standard deviation for normally distributed data and as median ± interquartile range for non-parametric data. Insulin resistance was defined by the 75th percentile of HOMA-IR of the participants being studied (HOMA-IR = 2.68) (Balkau and Charles, 1999). Comparison of metabolic and physical activity measures between mutation type (*BRCA1* vs. *BRCA2*) were performed using independent sample t-tests for normally distributed data and Mann Whitney U test for non-normally distributed data. Correlations between anthropometric and physical activity measures and selected metabolic variables were carried out using PPMCC for normally distributed data and Spearman's Rank Correlation test for non-normally distributed data. Statistical significance was set at $p<0.05$.

6.6 Results

6.6.1 Participant Characteristics

Recruitment for Study III commenced in September 2011. Of the 83 potentially suitable participants identified at St. James's hospital, 60 consented to participate in this study. This represents a 72% participation rate of eligible participants presenting to the hospital. Participation was higher among those recruited from family risk clinics (86%) than from newly diagnosed *BRCA* mutation carriers recruited from genetics clinics (72%). While recruitment is underway at the National Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin, no participants have been tested to date. Participant demographics and selected breast cancer risk factors are detailed in Table 29.

6.6.2 Data Normality

The following variables were not normally distributed: body weight, %BF, FFM, muscle mass, waist circumference, systolic blood pressure, fasting insulin, fasting glucose, insulin resistance, HbA_{1c}, HDL-B, LDL-C, TG and CRP. All Minnesota questionnaire and Tecumseh questionnaire data were non-normal and non-parametric tests were used. RT3 measured vigorous intensity activity was also non-normal. When log transformations were applied the following variables became log-normal: weight, waist circumference, insulin, TG and HOMA-IR.

Table 29 Study III Participant Characteristics

Characteristic	Mean (SD) / n (%)
Demographics	
Age	42.8 (9.1) years (range 25.9-64.1)
***BRCA* Mutation Type**	
BRCA 1	21 (35)
BRCA 2	39 (65)
Marital Status	
Married	44 (73)
Single	16 (27)
Smoking History	
Current Smoker	16 (27)
Ex-Smoker	21 (35)
Never Smoked	23 (38)
Exposure to Environmental Smoke	
Yes	12 (20)
No	48 (80)
Risk Reducing Surgery	
BSO	30 (50)
Mastectomy	0
Reproductive Characteristics	
Mean age at menarche	13.0 (1.8)
Menopausal Status	
Premenopausal	26 (43)
Postmenopausal	34 (57)
Parity	
Nulliparous	14 (23)
≥1	46 (77)
Oral contraceptive use	
Ever	25 (42)
Never	35 (58)
Hormone Replacement therapy	
Yes	4 (7)
No	56 (93)
Weight History	
Birth Weight (kg)	3.1 (0.8)
Weight at Menarche (kg)	52.7 (8.1)
Weight at 18 (kg)	61.1 (11.6)
Weight at 21 (kg)	62.6 (12.8)
Weight at 30 (kg)	69.1 (13.1)
Weight at 40 (kg)	71.3 (15.3)

Data are presented as mean (standard deviation) for continuous variables and as frequency (percentage) for categorical variables.

6.6.3 Metabolic Profile

The metabolic profiles of all participants and group comparisons based on type of mutation are shown in Table 30. Overall, 40% (n=24) of the cohort were overweight and 35% (n=21) were obese. Over three-quarters (77%) of the cohort were centrally obese (waist circumference >80cm). Fifteen participants (25%) had a clinical diagnosis of the MetSyn characterised mainly by central obesity (n=46), dyslipidemia (n=37 (HDL-C<1.3 $mmol.mol^{-1}$ n=9; TG<1.7 $mmol.mol^{-1}$ n=12; cholesterol medications n=16)) and hypertension (BP >135/85 n=9; BP medications n=5) (Figure 25). Metabolic profiles, diagnosed only from baseline data, did not differ between *BRCA1* and *BRCA2* mutation carriers.

Table 30 Study III Anthropometrics and Metabolic Profile

Characteristic	Total (n=60)	*BRCA1* (n=21)	*BRCA2* (n=39)	p-Value*
Anthropometry				
Body weight (kg)	74.3 (19.7)	74.0 (23.7)	77.1 (16.8)	0.83
BMI ($kg.m^{-2}$)	28.9 (6.3)	28.5 (7.39)	29.1 (6.5)	0.74
BMI Categories				
Healthy weight	15 (25)	6 (29)	9 (23)	
Overweight	24 (40)	8 (38)	16 (41)	
Obese	21 (35)	7 (33)	14 (36)	
Waist circumference (cm)	86.2 (17.9)	88.1 (16.5)	90.0 (13.3)	0.38
Central obesity	46 (77)	13 (62)	33 (85)	0.06
Percentage body fat (%)	38.1 (9.7)	36.0 (7.6)	38.7 (7.3)	0.50
Fat free mass (kg)	47.6 (5.7)	48.4 (5.9)	47.2 (6.1)	0.83
Blood Pressure				
SBP (mmHg)	111.0 (12.0)	113.9 (8.4)	111.0 (10.0)	0.96
DBP (mmHg)	78.0 (6.8)	76.5 (6.8)	78.6 (9.0)	0.22
Hypertensive (BP >130/85mmHg)	9 (15)	3 (14)	6 (15)	1.00
Anti-hypertensive medication†	6 (10)	1 (5)	5 (13)	0.41
Lipid Profile				
TC ($mmol.L^{-1}$)	4.8 (0.7)	4.9 (0.9)	4.8 (0.7)	0.57
Dyslipidemia (TC > 5.2$mmol.L^{-1}$)	19 (32)	7 (33)	12 (31)	0.84
HDL-C ($mmol.L^{-1}$)	1.7 (0.5)	1.6 (0.6)	1.7 (0.5)	0.77
LDL-C ($mmol.L^{-1}$)	2.6 (1.0)	2.6 (1.2)	2.6 (0.9)	0.60
TG ($mmol.L^{-1}$)	0.9 (0.6)	0.9 (0.9)	1.0 (0.6)	1.00
Cholesterol Medications†	7 (12)	2 (10)	5 (13)	1.00

Characteristic	Total (n=60)	*BRCA1* (n=21)	*BRCA2* (n=39)	p-Value*
Glucose Metabolism				
Fasting glucose ($mg.dL^{-1}$)	4.6 (0.4)	4.6 (0.4)	4.7 (0.5)	0.27
Fasting Insulin ($mU.L^{-1}$)	8.9 (7.1)	8.3 (5.8)	10.6 (5.4)	0.35
Hyperinsulinemia (>12$mU.L^{-1}$)	19 (32)	5 (24)	14 (36)	0.34
Insulin resistance (HOMA-IR)	1.7 (1.4)	1.7 (1.1)	2.3 (1.4)	0.27
Insulin Resistant (HOMA-IR >2.7)	16 (27)	4 (19)	12 (31)	0.33
HbA_{1c} ($mmol.mol^{-1}$)	35.0 (4.0)	35.0 (3.0)	35.4 (3.2)	0.81
Glucose medications†	1 (2)	0	1 (3)	1.00
Inflammatory Marker				
CRP ($mg.L^{-1}$)	1.5 (1.6)	1.3 (1.3)	1.6 (2.0)	0.48
Metabolic Syndrome	15 (25)	3 (14)	12 (31)	0.16

Data are presented as the mean (standard deviation) for normally distributed continuous variables, as median (interquartile range) for non-parametric continuous variables and as frequency (percentage) for categorical variables.

**p values comparing BRCA1 to BRCA2 groups*

† Refers to the number of participants taking prescribed medication

Abb: BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; HOMA-IR = homeostatic model assessment index; HbA_{1c} = glycated haemoglobin A_{1c}; CRP = C – Reactive Protein.

Figure 25 Study III Distribution of Metabolic Features

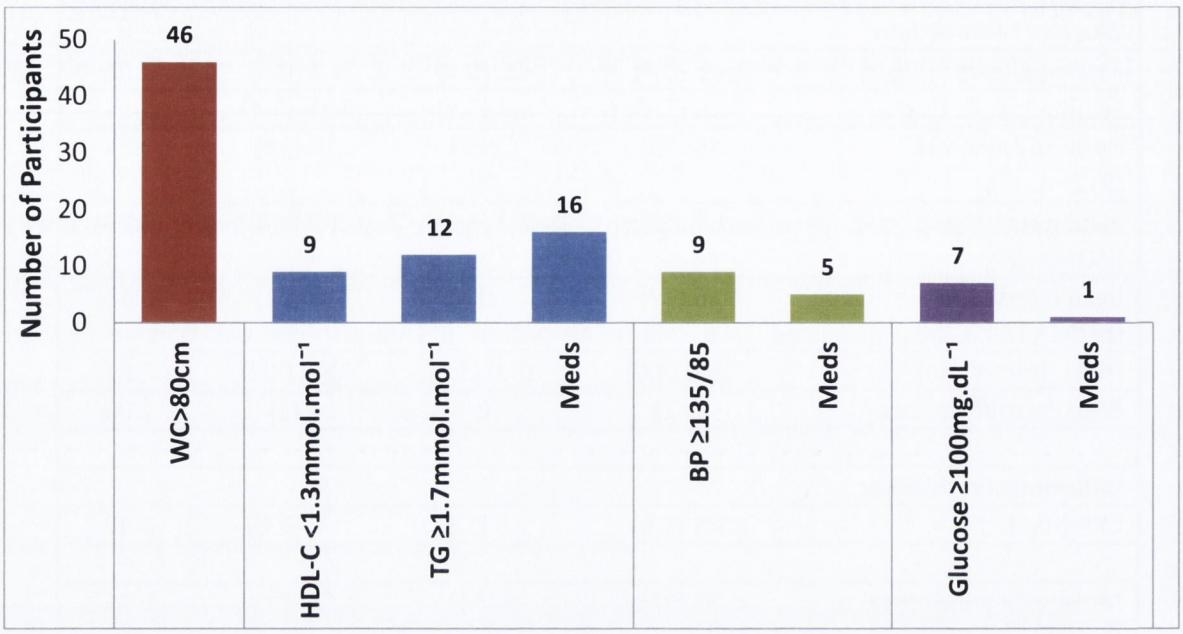


Abb: WC = waist circumference; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; BP = blood pressure; Meds = medication.

6.6.4 Physical Activity Levels and Adherence to Physical Activity Guidelines

Output from physical activity measures is shown in Table 31. The results from the Tecumseh questionnaire are also presented. The Tecumseh questionnaire was introduced into the study protocol following testing of the first 33 participants. A significant percentage (63%) of this initial cohort was working outside the home and therefore an assessment of occupation-related physical activity would be useful. An attempt was made to retrospectively gather data by posting the questionnaire to all initial participants. Of the 33 questionnaires that were posted, only eight were completed and returned. Of the remaining 25 unreturned questionnaires, seven participants self-reported not working outside the home during the initial interview. Therefore, occupation-related physical activity data is not collected from 18 participants. Of the 42 participants with occupation-related data, 22 were working in jobs outside the home (mean hours 34.84 (9.24) (range 5-48) hours.week^{-1}) for a mean of 42.95 (11.42) (range 12-51) weeks.year^{-1}. Activity scores were adjusted for weeks spent on holiday or on maternity leave during the year.

Table 31 Study III Physical Activity Data

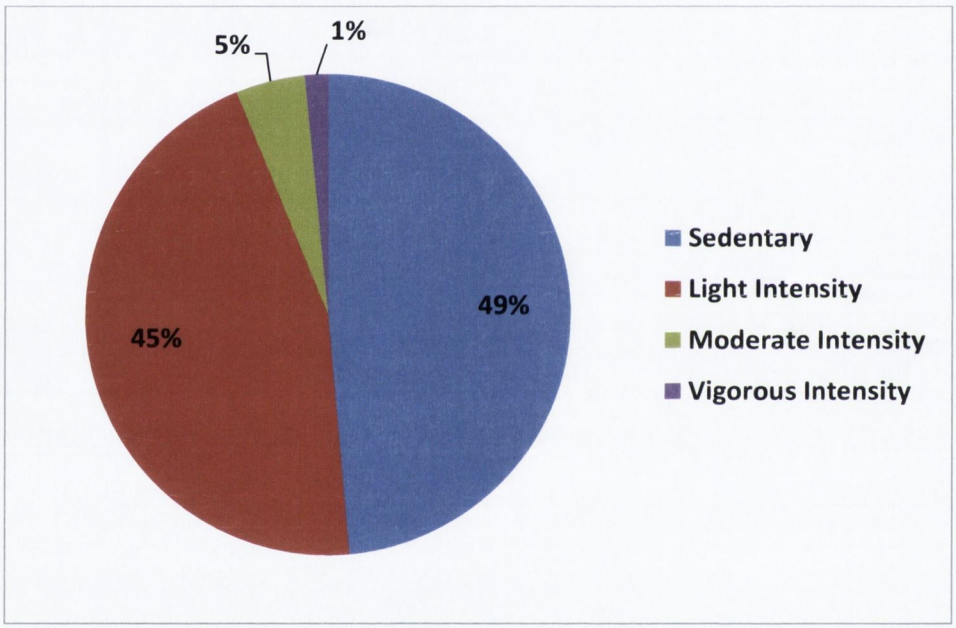
Activity Domain	Total (n=60)	*BRCA1* (n=21)	*BRCA2* (n=39)	p-value
Objective Physical Activity				
RT3 Activity Monitor				
Sedentary (min.day^{-1})	415.6 (99.0)	414.6 (96.0)	416.1 (101.6)	0.95
Light (min.day^{-1})	388.0 (82.5)	400.4 (387.9)	382.2 (79.1)	0.45
Moderate (min.day^{-1})	40.1 (14.8)	37.8 (16.5)	41.2 (14.0)	0.43
Vigorous (min.day^{-1})	10.8 (18.3)	5.7 (11.5)	15.5 (12.6)	0.05
Moderate and vigorous (min.day^{-1})	53.9 (23.8)	47.7 (26.3)	56.8 (22.3)	0.19
Physical Activity Guidelines				
30 minutes 5 days.week^{-1}	4 (7)	1 (5)	3 (8)	1.00
150 minutes.week^{-1}	22 (37)	3 (14)	19 (49)	0.02
Subjective Physical Activity				
Minnesota Questionnaire				
Light (MET-h.week^{-1})	0	0	0	1.00
Moderate (MET-h.week^{-1})	10.8 (12.0)	9.5 (8.2)	12.1 (12.6)	0.28
Vigorous (MET-h.week^{-1})	5.2 (12.9)	4.5 (10.8)	5.5 (16.1)	0.49
Total (MET-h.week^{-1})	18.1 (14.6)	15.5 (14.9)	18.3 (16.1)	0.12
Tecumseh Questionnaire*				
Sedentary (MET-h.week^{-1})	32.9 (21.8)	39.1 (25.4)	28.6 (23.2)	0.35
Light (MET-h.week^{-1})	0.0 (0.5)	0.0 (0.0)	0.0 (5.7)	0.22
Moderate (MET-h.week^{-1})	0.0 (16.5)	0.0 (38.9)	0.0 (15.1)	0.83
Vigorous (MET-h.week^{-1})	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.23
Total (MET-h.week^{-1})	52.1 (22.4)	54.0 (30.0)	47.5 (32.4)	0.17

Data are presented as mean (± standard deviation) for normally distributed variables and as median (inter-quartile range) for non-normally distributed variables.

** Total n=22; BRCA1 n=9; BRCA2 n=13*

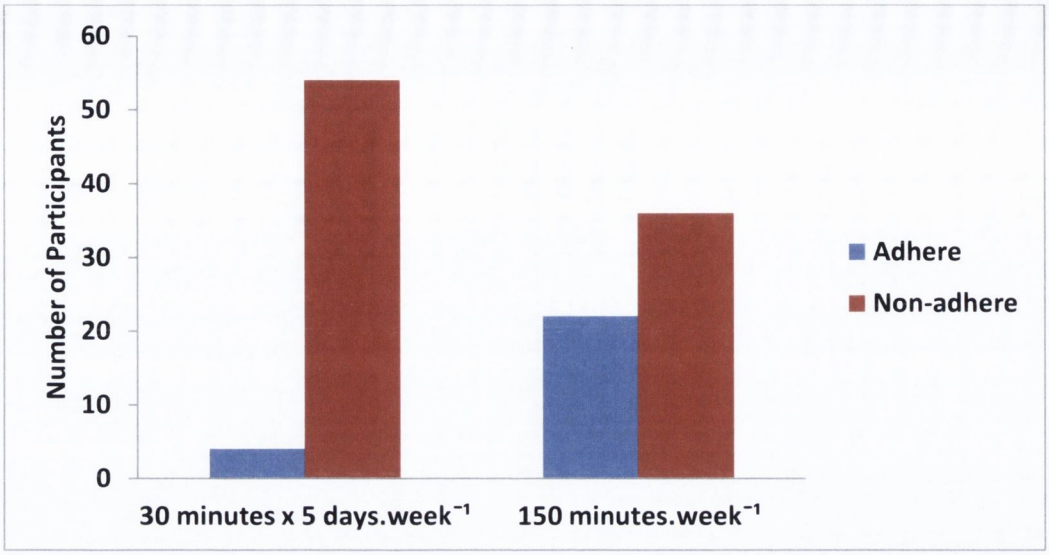
Objective physical activity results show that participants spent 49% of waking hours sedentary (73.75 (17.33) MET-h.week^{-1})[17], 45% of time engaging in light intensity activity (135.83 (28.89) MET-h.week^{-1}) and 6% of waking hours engaging in either moderate (23.41 (8.66) MET-h.week^{-1}) or vigorous (14.45 (13.27) MET-h.week^{-1}) intensity activity (Figure 26). Only 7% (n=4) participants were adhering to recommended physical activity guidelines (30 minutes x 5 days.week^{-1}). When defined as 150 minutes.week^{-1}, 37% (n=22) of participants were achieving recommended levels, which was significantly higher among *BRCA2* carriers (p=0.02) (Figure 27).

Figure 26 Percentage Time Spent in each Activity Domain



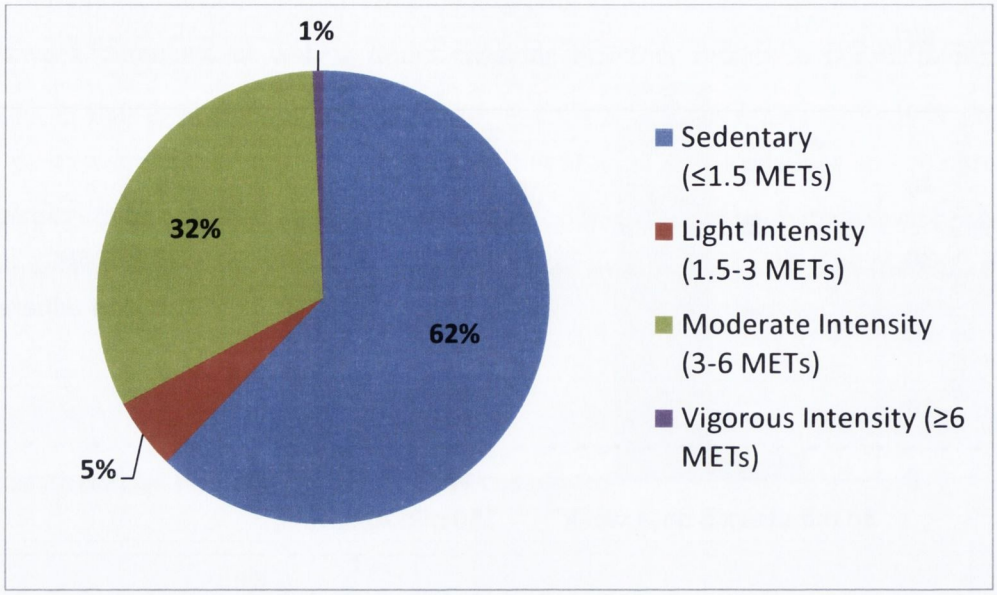
[17] Calculated as: Sedentary MET-h.week^{-1} = (1.5 METs)*((minutes.day^{-1}in activity)/60)*7). The same formula was applied to calculated light (3.0 METs), moderate (5.0 METs) and vigorous (9.0 METs) MET-h.week^{-1} based on the MET intensities recommended for the Godin Leisure Time Exercise Questionnaire (Chapter 2, section 2.3.1.4).

Figure 27 Adherence to Physical Activity Guidelines



Results from the Minnesota questionnaire shows that in the year prior to interview, participants spent 10.85 (12.08) MET-h.week^{-1} engaging in moderate intensity (3-6 METs) activity and 5.27 (12.91) MET-h.week^{-1} engaging in vigorous intensity (≥6 METs) activity, which is equivalent to approximately 4 hours moderate to vigorous intensity activity per week. No light intensity leisure time activities were reported. A diverse range of activities were recorded including walking (27% of total activity), dancing (including aerobics) (16%), health club exercise (11%), jogging / running (8%), painting and decorating (7%), swimming (pool and beach) (6%) and gardening (6%). Physical activity related to occupation (Tecumseh questionnaire) was mainly sedentary (≤1.5 METs), representing 62% of total occupational activity. Almost one-third (32%) of occupation-related activity was of a moderate intensity (3-6 METs), while light (1.5-3 METs) and vigorous (≥6 METs) represented less than 6% of activity completed (Figure 28).

Figure 28 Percentage Time Spend in each Domain of Occupational Physical Activity



6.6.5 Correlation Analysis

Waist circumference (Log waist circumference) was moderately and significantly correlated with a number of metabolic variables including insulin (r=0.49; p<0.001), HOMA-IR (r=0.52; p<0.001), glucose (rho=0.29; p=0.023), HbA_{1c} (rho=0.28; p=0.03), CRP (rho=0.52; p<0.001), systolic blood pressure (rho=0.32; p=0.012), diastolic blood pressure (r=0.32; p=0.013) and TG (r=0.43; p=0.001). Other components of the lipid profile including TC (r=0.16; p=0.24), HDL-C (rho=-0.23; p=0.08) and LDL-C (rho=0.19; p=0.15) were not correlated with waist circumference. BMI also displayed slightly weaker, yet significant, correlations with a number of the above variables including insulin (r=0.403; p=0.001), HOMA-IR (r=0.428; p=0.001), glucose (r=0.286; p=0.03), CRP (rho=0.57; p<0.001), systolic blood pressure (r=0.34; p=0.008), diastolic blood pressure (r=0.319; p=0.013) and TG (r=0.331; p=0.01). There were no correlations between BMI and HbA_{1c} (r=0.206; p=0.118) or other variables in the lipid profile including TC (r=0.106; p=0.419), HDL (rho=-0.206; p=0.114) or LDL-C (rho=0.194; p=0.137). There were no correlations between selected physical activity outcomes (RT3 Sedentary, RT3 moderate/vigorous and/or Minnesota total AMI) and metabolic variables.

6.7 Discussion Study III

The descriptive analysis of the anthropometric and metabolic traits and physical activity habits of *BRCA1* and *BRCA2* mutation carriers who are unaffected by cancer suggest that in line with population norms, overweight and sedentariness are prominent characteristics. In relation of anthropometrics, 40% of participants were overweight, 35% obese and 77% were centrally obese. Moreover data from all physical activity sources indicate a predominance of sedentariness ranging from 49% of objectively measured waking hours to 62% of occupation-related physical activity data. 25% were diagnosed with the MetSyn and 27% were classed as insulin resistant. A range of metabolic features were directly and significantly associated with selected anthropometric measures but not with physical activity output, suggesting a stronger influence of body composition on metabolic variables.

The results of the physical activity analysis are comparable to reported population norms. For example, 39% of Irish adult women (aged 45+) in the SLÁN survey were overweight and 32% were obese (objectively measured values) (Morgan et al., 2008). Interestingly, in the SLÁN report, there was a substantial discrepancy between self-reported and measured BMI whereby respondents tended to underestimate BMI, resulting in almost 41% of overweight women classifying themselves as healthy and 43% of those who were obese classifying themselves as overweight. This reinforces the issues with retrospective weight recall which have been previously used by studies examining anthropometric variables in *BRCA* mutation carriers as discussed in section 6.3.3 and highlights the need for prospective objective BMI classification to fully evaluate potential risk associations.

As expected, dysmetabolism was not a prominent feature of this cohort of essentially healthy women. The observed prevalence of MetSyn at 25% is similar to the percentage of participants in SLÁN presenting with a clustering of metabolic risk factors (18-48% depending on variables considered) and also similar to prevalence rates for MetSyn reported worldwide (Cameron et al., 2004). Direct associations were however observed between a number of metabolic features and anthropometric measures including BMI and waist circumference. Three-quarters of participants tested were overweight or obese and slightly more (77%) centrally obese. In the absence of metabolic disturbance or comorbidity, being overweight is associated with increased mortality (Greenberg, 2012). In a large, 10 year prospective study of

186 women aged 40-93, overweight women who were diagnosed with breast cancer during routine screening services experienced up to a 57% increase in mortality (Moore et al., 2008). While there is conflicting evidence regarding the benefit of weight loss on mortality (Harrington et al., 2009, Poobalan et al., 2007), there is a suggestion that overweight and obese individuals who are physically active following weight loss experience reduced mortality (Ostergaard et al., 2010).

In the current study, both self-reported and objective physical activity data are presented. Interestingly, greater total MET-h.week^{-1} were reported by the RT3 versus the Minnesota questionnaire for both moderate (RT3 23.41 (8.66) MET-h.week^{-1} vs. Minnesota 10.85 (12.08) MET-h.week^{-1}) and vigorous (RT3 14.45 MET-h.week^{-1} vs. Minnesota 5.27 (12.91) MET-h.week^{-1}) intensity activity. This discrepancy may be due to a number of factors including the different time-frames being measured (past week vs. past year), the difference between subjective and objective measurement techniques and issues related to inaccurate recall of past year activity. It should be noted however that the high total MET-h.week^{-1} recorded by the RT3 refer to every minute spent in activity during the week of measurement and not necessarily bouts of activity contributing to time spent exercising. Analysis of these 10 minute bouts when examining adherence to physical activity guidelines portrays a different description of objective activity levels, with only four participants (7%) achieving 30 minutes of moderate or vigorous intensity activity five days per week. The issue of flexibility within public health guidelines is highlighted, whereby when the guideline was interpreted as 150 minutes of moderate and vigorous intensity activity per week, with no constraints on days, a far greater number of participants (n=22) were exercising to recommended levels. In individuals with cardiovascular and metabolic risk factors, short bouts of regular activity are recommended for greatest benefits (Lee et al., 2004), however, in non-symptomatic women longer durations of exercise performed over less days may be more appropriate for incorporating into busy lives. This issue remains to be clarified in current public health guidelines (Garber et al., 2011).

Modern living involving desk-based occupations, motorised transport and mechanical methods of performing previously manual tasks, is thought to make a significant contribution to the degree of inactivity and sedentariness observed in society (Speakman and Selman, 2003). In the current study, results from the Tecumseh questionnaire are consistent with

these concerns, with 62% of occupational-related physical activity classed as sedentary by respondents. While it should be noted that these results refer to only 22 participants who were in employment outside of the home, when compared to those confirmed as not working outside of the home, mean sedentary time was higher in those in outside employment (439.23 (97.78) minutes.day^{-1}) versus those working within the home (382.62 (88.63) minutes.day^{-1}), although the difference did not reach significance (p=0.06). Sedentary behaviour is a significant contributor to chronic disease risk (Lynch, 2010) and therefore potentially a crucial target for disease prevention in this cohort.

While a case-control analysis comparing *BRCA* mutation carriers to non-carriers, was not completed results of the current study are consistent with others reporting that women with increased hereditary or genetic breast cancer risk are no more likely to engage in healthy lifestyle habits than the general population (Ochoa et al., 2010, Madlensky et al., 2005). Similar results are observed in individuals at increased familial risk for colon cancer (Burton et al., 2010, Martinez-Ochoa et al., 2012). The results from this profiling analysis of anthropometric, metabolic and physical activity breast cancer risk factors in this unique cohort suggest that they are an overweight, sedentary but metabolically healthy group. While the findings are comparable to population statistics, this should be interpreted in the context of the current worldwide obesity epidemic and not considered satisfactory. A number of modifiable targets for breast cancer risk management were identified. The results of the ongoing prospective study will indicate if these characteristics are predictive of breast cancer occurrence in this cohort.

Chapter 7 Discussion

7.1 Introduction and Main Findings

The association between physical activity and breast cancer control outcomes has been well established (Chapter 1, section 1.4.3 and 1.4.4). These protective effects of physical activity are hypothesised to occur through alterations in a number of obesity-related biological pathways including sex hormones, measures of inflammation and measures of insulin-glucose homeostasis (Ballard-Barbash et al., 2012, Neilson et al., 2009). The aim of this thesis was to investigate the interactions and inter-relationships between these pathways and physical activity in two high risk groups – breast cancer survivors and carriers of the deleterious mutation in either of the *BRCA* genes, *BRCA1* or *BRCA2*. The main findings of this thesis are outlined in the following sections. Study I and Study II, which focused on survivor groups, will be discussed first followed by Study III which examined *BRCA*-mutation carriers.

At the time the studies presented in this thesis commenced, the role of physical activity in breast cancer prevention was the most studied cancer control outcome. While there was some data from large-scale studies with long-term follow-up on the role of physical activity in breast cancer survival prior to 2009 (Holmes et al., 2005, Holick et al., 2008, Irwin et al., 2008), there has been a steady increase in the number of publications in the short time since then (Sternfeld et al., 2009, Chen et al., 2011, Bertram et al., 2011, Irwin et al., 2011b). Ballard-Barbash and colleagues (2012) published the most comprehensive review to date examining physical activity, biomarkers and disease outcome in cancer survivors. The review concluded that there is considerable potential for physical activity to be used as an adjunct to breast cancer treatment, but that the evidence in this regard remained preliminary.

In order to develop therapeutic exercise prescription aimed at improving outcome following breast cancer, information on causality and dose-response from RCTs of exercise training is required. The results of the literature review presented in Chapter 1 (section 1.5.1), highlights the paucity of trials available examining these metabolic outcomes and suggested that unlike interventions that have been completed in non-breast cancer populations (Frank et al., 2005, Friedenreich et al., 2012, Friedenreich et al., 2011, Irwin et al., 2003b), exercise trials in breast cancer survivors overall did not demonstrate changes in key metabolic outcomes.

In the PEACH trial (Chapter 3) a graded exercise intervention of moderate intensity, deemed appropriate for influencing metabolic biomarkers and anthropometric outcomes was prescribed. Analysis of baseline data demonstrated that a significant proportion of participants were overweight (50%) or obese (23%) and/or centrally obese (73%), but there was minimal evidence of dysmetabolism characterised by either insulin resistance or low grade inflammation. Objective physical activity data demonstrated that the majority of waking hours were spent sedentary (52%) and that there was poor adherence to physical activity guidelines. No changes in anthropometric, metabolic or physical activity outcomes were observed following the 8-week aerobic intervention. A sub-group analysis of those with highest adherence to the supervised exercise protocol (>90% adherence) demonstrated a significant decrease in waist circumference ($p<0.05$) and a significant increase in subjectively measured "total weekly" physical activity ($p=0.005$).

Study II was undertaken to examine metabolic parameters in a group of previously profiled breast cancer survivors. Adjuvant treatment is associated with numerous side-effects which may contribute to metabolic decline, potentially complicating exercise prescription in this cohort. The objectives of Study II were two-fold; i) to examine changes in metabolic variables from the time of diagnosis to treatment completion, and ii) to profile the metabolic characteristics of breast cancer survivors. In Study IIa, a significant deterioration in measures of insulin-glucose homeostasis from breast cancer diagnosis through to completion of adjuvant therapy was demonstrated. This deterioration was characterised by increases in fasting insulin ($p<0.001$), HOMA-IR ($p<0.001$) and HbA_{1c} ($p=0.001$) and occurred in the absence of any significant change in body weight, BMI or in the percentage of participants classed as centrally obese. The profile of participants in Study IIb was similar to that of Study I, in that a high percentage of overweight (41%), obesity (22%) and central obesity (73%) was observed and while dysmetabolism was present it was not excessive. A secondary analysis, sub-dividing the group by levels of central obesity and the presence or absence of clinically defined insulin resistance identified multiple risk factors in the insulin resistant group (reduced HDL-C, elevated TG, glucose dysmetabolism and raised inflammatory status). Metabolic profiles of those who were centrally obese only (waist circumference >80cm or >88cm) were not significantly different from lean, healthy participants.

Objective physical activity data from Study IIb showed a predominance of sedentary behaviour (49%) and low adherence to physical activity guidelines (n=17; 25%). There were no differences in habitual physical activity patterns between groups studied in the secondary analysis in Study IIb and physical activity did not demonstrate significant correlations with selected biomarkers. In contrast, both absolute and adjusted RMR was significantly higher in those who were insulin resistant versus all other groups ($p<0.05$). Adjusted RMR correlated with a number of metabolic features including waist circumference, HOMA-IR, CRP, HDL-C and TG. These results are consistent with others which describe an increased RMR in the presence of glucose dysregulation (Weyer et al., 1999, Bitz et al., 2004). In summary, the results of Study II suggest a significant decline in insulin resistance during the course of adjuvant treatment and that insulin resistance in survivorship may be a key determinant of metabolic dysfunction. In contrast, central obesity alone was not associated with dysmetabolism. Habitual physical activity levels were low regardless of obesity or metabolic presentation. RMR appeared raised in those with glycaemia. In the absence of glycaemia, RMR was lower, which may contribute to future weight gain (Bandini and Flynn, 2003). These results may be useful in informing the metabolic targets and potential challenges of future exercise interventions in this cohort.

In Study III, unaffected *BRCA*-mutation carriers were examined. The results of the systematic review presented in Chapter 6, section 6.3 suggest that there is potential for lifestyle factors to modify breast cancer risk in this cohort, however investigations to date have been limited due to retrospective subjective data collection methods. Furthermore, as described in Chapter 1, section 1.2.3 and 1.4.5 significant changes in body composition and physical activity can occur following breast cancer diagnosis. Therefore care should be exercised in case-control studies involving *BRCA* mutation carriers with a history of cancer so as not to allow the anthropometric, metabolic and activity changes that occur post diagnosis to confound results. There is clearly a need for prospective studies using objective measurement techniques for physical activity and anthropometry in unaffected carriers from pre-cancer years. The prospective study design (Appendix II) arose from the results of the systematic review. In this thesis the baseline characteristics of the cohort are presented. This study is the first to objectively measure anthropometric, physical activity and metabolic breast cancer risk factors in non-symptomatic *BRCA*-mutation carriers (age range 25.9 to 64.1 years). High levels of obesity (40% overweight, 35% obese) and central obesity (77%) were observed. Furthermore,

sedentary behaviour (49% of waking hours) and poor adherence to physical activity guidelines (7% adhering) were recorded objectively. Results are currently limited by the cross-sectional study design however multiple risk factors were identified. It is hoped that the results of the prospective study will determine if these features confer higher breast cancer risk.

7.2 Analysis of key points

7.2.1 Rehabilitation in the Cancer Context

The ultimate goals of rehabilitation are to promote movement, treat disability and restore normal function (Terlouw, 2007). Over the last century however there has been a paradigm shift in what is considered "normal" or what is required for "function". In recent years, technology has developed rapidly, replacing the need for manual labour at work and in the home (Speakman and Selman, 2003). Modern society is now highly automated and can facilitate individuals who are very disabled to work and function independently.

Rehabilitation of cancer patients needs to be considered in the context of societal norms. For both breast and colon cancer patients, who now experience five–year survival rates of >50% (National Cancer Registry, 2012) outcomes can be further improved by maintaining a healthy body weight and being physically active. On measurement these groups are often as active as their healthy peers and demonstrate levels of overweight and obesity similar to population norms (Chapter 1, section 1.4.5). In work from our research group, 100 breast and colon cancer patients wore the RT3 activity monitor for one week prior to their initial outpatient medical oncology appointment (Broderick, 2012). During this appointment, physicians assigned a performance score using the Eastern Cooperative Oncology Group Performance Status to reflect activity levels during the same week. The majority of participants were assigned a score of 0 (fully active, able to carry out all pre-disease performance without restriction) or 1 (restricted in strenuous activities only). Accelerometer data however demonstrated that over 50% of waking hours were spent sedentary. These results suggest that societal and even medical interpretation of "fully active" is not consistent with "sufficiently active" for health benefits.

Public health recommendations and guidelines for BMI and physical activity are well established (Garber et al., 2011, WHO, 2000). Despite these guidelines, globally, high rates of overweight (35% of adults worldwide), obesity (12%) and inactivity (31%) are reported (Hallal et al., 2012, WHO, 2000). Therefore, when analysing the anthropometric characteristics and habitual physical activity levels of those both at high risk of cancer and those post cancer treatment, there is a tendency to consider them in terms of population norms. Population norms however do not reflect public health recommendations and are not sufficient for health benefits. With this in mind, the rehabilitation of cancer patients following treatment and the pre-habilitation of healthy individuals in the prevention of chronic disease must not aim to achieve "normal" or "functional" levels of activity and body size, but aim beyond that to behaviours that are recommended for health benefits.

There are several challenges to rehabilitation in the cancer context. Crucially, in today's society it involves changing behaviours and lifestyle habits which in any population will be difficult. The following discussion will examine how the results from this thesis may inform rehabilitation strategies in terms of i) physical activity; ii) obesity and metabolic dysfunction; iii) considerations for targeted interventions.

7.2.2 Sedentary Time versus Physical Activity Guidelines

Excessive sedentary behaviour and poor adherence to physical activity guidelines were prominent features of all three studies presented in this thesis. The percentage of time spent engaging in sedentary behaviour represented approximately half the waking day in both Study IIb and Study III (49%) and was slightly higher in Study I (52%). Sedentary behaviour did not change or decrease in Study I despite the implementation of a physical activity intervention (Chapter 3, Figure 15 and Figure 16, page 138). While cumulatively, participants in all cohorts studied engaged in ≥30 minutes of moderate and vigorous intensity activity per day, this represented <7% of total activity during waking hours, and when examined in the context of exercise bouts (≥10 minutes), was insufficient to contribute to weekly physical activity guidelines (see Chapter 2, section 2.3.1.2 for analysis of adherence to physical activity guidelines). These results are consistent with those from the HEAL study (Irwin et al., 2004) and the NHANES (Lynch et al., 2010), which suggest that breast cancer survivors spend the majority of time sedentary and demonstrate poor adherence to recommended physical

activity guidelines. They are also consistent with population statistics which suggest that even among healthy adults, less than one third of the population are sufficiently activity (Hallal et al., 2012, Morgan et al., 2008) and over 50% of the waking day is spent sedentary (Lynch et al., 2011a, Matthews et al., 2008).

Sedentary behaviour characterises activity that involves little or no movement or physical activity, with an energy expenditure of ≤1.5 METs such as prolonged sitting or lying (Lynch, 2010, Ainsworth et al., 2011). Modern lifestyle contributes significantly to the degree of sedentary behaviour observed at population level related to increased use of motorised transport, desk based occupations and sedentary-style recreational activities such as computer use, electronic devices including iPads and video-games (Gorely et al., 2007, Speakman and Selman, 2003). The contribution of occupation to sedentary behaviour was demonstrated in Study III, where 62% of occupational-related activity was deemed sedentary (Chapter 6, section 6.6.4). Sedentary behaviour is distinct from physical inactivity in that the latter implies that physical activity guidelines are not being achieved (Lynch, 2010, Marshall et al., 2010). Thus an individual can exercise to recommended physical activity guidelines but spend the remainder of the day sedentary. An independent association exists between the amount of time spent sedentary and overall metabolic risk, even in those who exercise to recommended physical activity guidelines (Owen et al., 2010, Thorp et al., 2011, Matthews et al., 2012). Objectively measured and subjectively reported sedentary time are both associated with a number of metabolic risk factors including elevated waist circumference, high BMI, hyperinsulinemia and raised inflammatory status in both healthy postmenopausal women and postmenopausal breast cancer survivors (Lynch et al., 2010, Lynch et al., 2011a, Pierce et al., 2009b) and therefore reducing sedentary behaviour has potential as a key cancer control strategy and therapeutic target (Lynch, 2010).

The studies in this thesis were greatly strengthened by the inclusion of accelerometry measured sedentary time and physical activity. The majority of self-report tools examine activities completed and therefore studies measuring physical activity by subjective means have not traditionally measured sedentary behaviour nor differentiated it from light activity (Pate et al., 2008). Objectively measured sedentary behaviour was a particularly novel aspect of the PEACH trial (Chapter 3). In the systematic review presented in Chapter 1, section 1.5.1,

two interventions, those by Ligibel and colleagues (Ligibel et al., 2008, Ligibel et al., 2009b) and Irwin and colleagues (Irwin et al., 2009a, Irwin et al., 2009b), reported increases in activity versus baseline activity levels, however, did not account for change, or lack-of change, in sedentary behaviour.

There is a concern that prescribed exercise interventions may displace normal activity patterns and sedentary behaviour may persist or increase to compensate for time spent exercising. Therefore it is difficult to draw conclusions regarding the effectiveness of exercise training interventions if sedentary time is not considered (Pate et al., 2008). The challenges associated with implementing an exercise programme following adjuvant breast cancer treatment, such as adherence and ongoing medical issues, were experienced in the PEACH trial. Physical activity interventions in survivorship traditionally aim to increase activity to a levels consistent with public health recommendation, therefore require cancer survivors to exercise to level that is far greater than current population norms and likely to greatly exceed pre-diagnosis activity habits. The challenge of changing lifestyle behaviours in this group is further confounded by disease morbidity. The debilitating side-effects of cancer treatment such as cancer-related fatigue may continue long past treatment completion, thus directly contributing to the cycle of inactivity and sedentary behaviour. Therefore, there is a role for holistic rehabilitation strategies in cancer survivorship that involve active participation in exercise prescription in addition to behavioural and lifestyle modification.

In terms of public health and disease risk management, physical activity recommendations focus on encouraging individuals to exercise to a minimum amount of moderate intensity activity and while sedentariness is discouraged, there is limited specific guidance in this regard. In paediatric populations, the Canadian Sedentary Behaviour Guidelines recommends restricting recreational screen time to ≤2 hours.day^{-1}, limiting sedentary based (motorised) transport, limiting sitting time and reducing time spent indoors (Tremblay et al., 2011). Cancer survivors are specifically advised to avoid inactivity (Schmitz et al., 2010). The WCRF/AICR report (2007) recommends that the proportion of the population that is sedentary should be halved every 10 years. There is a need however for specific guidance in this regard. Clarity within public health recommendations on limiting bouts of sedentary behaviour would guide exercise prescription and lifestyle rehabilitation in the management of chronic disease.

Physical activity was measured objectively in this thesis using the RT3 activity monitor. The RT3 was a triaxial monitor which captured acceleration in three planes using an in-built sensor, thus representing the most advanced type of accelerometer (see Chapter 2, section 2.3.1.1). There are however a number of limitations associated with the RT3 which may have limited its ability to accurately measure sedentary behaviour. For example the device is unable to measure physical activity during water-based activities and also underestimates the energy cost of uphill or isometric activities, thus contributing to an overall under-estimation of actual activity levels. In contrast, some studies have suggested that as with a number of activity monitors, the RT3 can be inclined to underestimate sedentary behaviour leading to a overestimation of time spent in light intensity activity (Hiremath and Ding, 2009, Rothney et al., 2008). Furthermore, there is no cut-point to define sedentary behaviour using the RT3. In the absence of a validated cut-point sedentary behaviour is often defined as ≤100 counts per minutes in accelerometer analysis (Healy et al., 2011). This approach was adopted in this thesis however the validity of the cut-point point in relation to the RT3 remains to be established. Objective physical activity data was supplemented by use of questionnaires to capture physical activity during a typical week (Godin) or during the past year (Minnesota questionnaire and Tecumseh questionnaire) across both recreational (Godin and Minnesota questionnaire) and occupational (Tecumseh questionnaire) activity domains. These activity domains are identified as the two most likely to contribute to reduced postmenopausal cancer risk (Lynch et al., 2011b).

Adherence to recommended physical activity levels was poor across all studies. As described in Chapter 2, section 2.3.1.2, adherence to physical activity guidelines was defined as moderate intensity completed on both ≥30 minutes.day^{-1} on ≥5 days.week^{-1} and 150 minutes.week^{-1}. Currently, there is insufficient evidence to recommend ≥30 minutes.day^{-1} on ≥5 days.week^{-1} over 150 minutes.week^{-1} completed over an undefined number of days in healthy individuals. The latter pattern of activity, often labelled the "weekend warrior", may not be effective in those with known CVD risk factors and is associated with an increased risk of injury (Kruger et al., 2007, Lee et al., 2004). In both definitions it is recommended that activity contributing to activity guidelines be accumulated in bouts of ≥10 minute duration (Garber et al., 2011), however there is limited evidence to support this advice (Murphy et al., 2009). There is evidence that moderate-to-vigorous intensity activity completed in a "non-

bout" fashion may also be beneficial for treating obesity and associated measures of dysmetabolism (Loprinzi and Cardinal, 2013, Strath et al., 2008).

It should be acknowledged however that the method used to define adherence to physical activity guidelines in this thesis was quite conservative, as both moderate and vigorous intensity activity minutes treated equally within each block (≥ 10 minutes) of activity. This is consistent with methods used in the NHANES (Tucker et al., 2011). The NHANES used an additional method of treating each vigorous minute of activity within each ≥10 minute period as the equivalent of two moderate intensity minutes. This method was not employed in this thesis due to the small percentage of vigorous activity recorded (<3%) and the findings of Tucker and colleagues (2011) which demonstrated very little difference between the two methods in a much larger cohort. Nonetheless, the conservative method used may have resulted in an underestimation of adherence to physical activity guidelines.

Historically women demonstrate poor adherence to physical activity programmes, such as cardiac rehabilitation programmes, citing barriers such as lack of transport and lack of social support (Daly et al., 2002). Furthermore, changes in physical activity patterns often accompany significant life events for women such as having children or developing an illness (Brown et al., 2009). Poor adherence may be more pronounced in breast cancer survivors who experience debilitating disease and treatment-related side-effects, further contributing to the challenges of physical activity rehabilitation.

7.2.3 Obesity versus Metabolic Dysfunction

Overweight, obesity and central obesity were prominent features of all cohorts studied in this thesis. The percentage overweight ranged from 41% in Studies II and III to 50% in Study I, while levels of obesity ranged from 23% in Studies I and II to 35% in Study III. Rates of central obesity (waist circumference >80cm) spanned from 73% of participants in Study I and II, to 77% of participants in Study III. The problem of obesity in breast cancer survivors has been described previously (Thomson et al., 2009, Irwin et al., 2005b, Chlebowski et al., 2002) and reflects the increasing prevalence of obesity worldwide (Popkin and Gordon-Larsen, 2004).

There are many adverse consequences of obesity in cancer. Obesity is a well-established risk factor for several cancers, including postmenopausal breast cancer (Chapter 1, 1.2.2). While obesity is thought to protect against premenopausal breast cancer development, treatment of the obese patient with breast cancer in the adjuvant setting is challenging. Chemotherapy dosage, which is based on total body surface area, is more difficult to prescribe in obese individuals (Griggs et al., 2012) and there is evidence that adjuvant hormonal therapy with either Tamoxifen or AIs, may be less effective in those with obesity (Sestak et al., 2010). Furthermore, obesity in survival and weight gain during adjuvant treatment are both associated with adverse breast cancer outcomes (Berclaz et al., 2004, Caan et al., 2012) and thus weight loss is recommended to improve prognosis (Chlebowski et al., 2002). In particular BMI is a significant predictor of all-cause mortality (Berclaz et al., 2004). CVD is the largest contributor to all-cause mortality following breast cancer (Nichols et al., 2009, Chapman et al., 2008, Patnaik et al., 2011) and therefore management of obesity and other established CVD risk factors is a key rehabilitative target. Women who are obese at diagnosis demonstrate greatest reductions in physical activity levels during adjuvant treatment (Irwin et al., 2003a, Irwin et al., 2004), thereby increasing the risk of co-existing CVD risk factors. Moreover, obesity is the largest contributor to dysmetabolism (Hardy et al., 2012), thus management of obesity and prevention of weight gain may serve to reduce or prevent metabolic decline. Therefore there is a role for obesity is a key modifiable risk factor at several stages throughout the cancer trajectory.

Obesity, particularly visceral adiposity, is associated with numerous metabolic complications including hyperglycaemia, hyperinsulinemia, chronic low-grade inflammation, dyslipidemia and hypertension which play a central in the pathogenesis of several diseases (Chapter 1, section 1.3.1). As observed in this thesis however, obesity is not always accompanied by dysmetabolism and there is increasing evidence of a "metabolically healthy but obese" (MHO) phenotype, who exhibit favourable metabolic profiles even in situations of severe obesity (Primeau et al., 2011, O'Connell et al., 2010). Characteristics of MHO individuals include normal glycaemic control, low inflammatory status, raised HDL-C, reduced TG and lower anthropometric measures as compared to metabolically unhealthy counterparts (Karelis et al., 2005, Succurro et al., 2008, Brochu et al., 2001). The prognostic implications of the MHO phenotype are unclear, with several reports suggesting that mortality risk is similar to that of lean, healthy individuals (Hamer and Stamatakis, 2012, Durward et al., 2012, Calori et al.,

2011). Participants studied in this thesis were predominantly overweight (BMI 25.0 to 29.9 $kg.m^{-2}$) and not generally characterised by severe obesity (BMI ≥40 $kg.m^{-2}$) (n=2 participants in Study III). Therefore it is unclear if the cohorts studied experienced the protection of the MHO phenotype or if levels of overweight and obesity were simply lower than that associated with metabolic disturbance.

Physical activity plays an important role in the management of obesity, particularly of visceral fat deposits. In this thesis, over 70% of each cohort was classed as centrally obese. Aerobic exercise has been shown to be more effective than diet alone at targeting visceral fat (Kay and Fiatarone Singh, 2006, Ross et al., 2004, McTiernan, 2004, Ismail et al., 2012). Conversely, an increase in visceral fat deposits is observed in control groups who remain sedentary during exercise intervention periods (Slentz et al., 2005).Therefore reducing visceral fat through physical activity is a critical component of breast cancer risk management and one of the key biological targets for physical activity in cancer control (Neilson et al., 2009). Estrogen deficiency following menopause is associated with increased central fat accumulation (Carr, 2003, Kaaja, 2008) and therefore surgical oophorectomy in *BRCA* mutation carriers and ovarian toxicity following adjuvant chemotherapy, both of which are associated with early-onset menopause, make management of central obesity particularly challenging in the cohorts studied.

There is increasing evidence of a relationship between dysmetabolism and breast cancer outcome (Goodwin et al., 2012, Duggan et al., 2011, Pierce et al., 2009a). While not all obese individuals are metabolically unhealthy, there is a need to identify individuals with evidence of dysmetabolism to manage these risk factors. In the breast cancer context, confounding factors related to menopausal status and differences in adjuvant treatment regimens may contribute to a diverse presentation of dysmetabolism, thus making targeted exercise prescription difficult. There is a lack of consensus regarding the definition of "metabolically unhealthy" and there is a need to consider metabolic screening in the context of clinical and prognostic relevance. The results in this thesis were strengthened by a comprehensive assessment of metabolic dysfunction which incorporated the recommendations from the consensus statement on MetSyn (Alberti et al., 2009), a measure of chronic low-grade inflammation, insulin resistance and the gold standard measure of glycaemic control, HbA_{1c}. Visceral obesity

and insulin resistance are both considered core components of the MetSyn and are inter-related with several other measures of dysmetabolism including low-grade inflammation and altered adipokines (Chapter 1, section 1.3.1). The results from Study II (Chapter 4 and Chapter 5) in this thesis suggested that insulin resistance may be an important determinant of overall dysmetabolism and a feature of metabolic decline following adjuvant treatment. In Study IIb, individuals with insulin resistance presented with a clustering of adverse metabolic markers. While individually, each of the risk factors identified in the insulin resistant group is associated with adverse breast cancer outcomes, the combined risk may be more powerful (Alberti et al., 2005). Limitations of the presented metabolic profiling include analysis of standard CRP as opposed to high sensitivity CRP and the absence of adipokine analysis. While these measures were beyond the score of this thesis, blood samples from all studies are in storage at -80°C with the intention of completing these analyses in the future. Future work examining the alterations in high sensitivity CRP and adipokine status during the cancer experience is warranted.

7.2.4 Targeted Exercise Interventions

An abundance of evidence now exists to suggest that regular lifetime physical activity conveys a protective effect over breast cancer development (Chapter 1, section 1.4.3) and that physical activity undertaken following breast cancer diagnosis is associated with improved disease outcome (Chapter 1, section 1.4.4). The ultimate goal however is to design interventions and prescribe exercise which will influence surrogate markers of breast cancer risk with the aim of reducing occurrence and/or disease-related outcomes including mortality and disease recurrence.

In terms of breast cancer prevention, a number of year-long aerobic exercise programmes, specifically targeting biomarkers of breast cancer risk in overweight, sedentary postmenopausal women have yielded promising results (Frank et al., 2005, Irwin et al., 2003b, Friedenreich et al., 2012, Friedenreich et al., 2011). The results of these interventions have led to the design of the BETA trial (Breast Cancer and Exercise Trial in Alberta) which is currently ongoing and will examine the volume of exercise required to influence breast cancer risk in postmenopausal women by comparing a year-long high volume protocol to a moderate volume protocol (http://www.beta-trial.com/index.html (accessed 28.01.2012)). The long-

term results of the prospective study associated with Study III in this thesis (Appendix III) will provide important information regarding the role of modifiable risk factors in carriers of the deleterious mutation in the *BRCA* gene, thus potentially providing justification for extending such interventions to high risk groups with the aim of managing cancer risk.

In relation to cancer survival, an intervention to improve outcome following colon cancer is currently underway in the United States and Canada. The Colon Health and Life-long Exercise change (CHALLENGE) trial aims to examine the effect of a three-year exercise programme on disease-free survival following chemotherapy for stage II-III colon cancer (Courneya et al., 2008a). Trials of this nature in breast cancer are still in the exploratory phase. The prognostic benefits of weight management and physical activity following breast cancer are particularly observed in relation to all-cause mortality (Berclaz et al., 2004, Holmes et al., 2005). Therefore management of inactivity, obesity and dysmetabolism following cancer needs to be considered in the context of chronic disease risk management, particularly CVD, in addition to breast cancer-specific outcome. The results of the systematic review presented in Chapter 1, section 1.5.1 demonstrated that the majority of studies of interventions in breast cancer survivors reported no effects on various metabolic biomarkers. Similarly, the intervention in the PEACH trial (Chapter 3) did not lead to any significant changes in outcomes measured. The following paragraphs will discuss how lessons learned from the PEACH trial and subsequent results from Study II may inform the design and targets for future interventions following breast cancer.

A unique aspect of the PEACH trial was the inclusion of breast cancer survivors within a defined survivorship period. The "time since diagnosis" of participants in trials reviewed in Chapter 1, section 1.5.1 ranged from one year to over 20 years. While the accepted definition of a cancer survivor spans from the time of diagnosis through the balance of an individual's life (http://www.canceradvocacy.org (accessed 31.07.2012)), the needs of cancer survivors change over time with recovery and resumption of normal life. Therefore, group intervention at a common time post diagnosis may be most beneficial. The PEACH trial was implemented when participants were 2-6 months post chemotherapy to coincide with the recommended "rehabilitation period" (Chapter 1, Figure 4, page 35, Courneya and Friedenreich, 2001). The experience from the PEACH trial however would suggest not all breast cancer survivors appear

ready for such a demanding intervention so early in their recovery as adherence to the protocol was poor (per-protocol analysis excluded 10/26 participants). Results from Study IIa however demonstrate significant deterioration in measures of glucose metabolism within the first five years post diagnosis, thus advocating the need for intervention early in the cancer trajectory to prevent metabolic decline. The most appropriate time for intervention remains to be established however timing will require balance between the ability of patients to adhere to the prescribed protocol and the need for early intervention to optimise health outcomes.

The results from Study IIb provided considerable information regarding the presentation of obesity and dysmetabolism in this cohort. It was evident from metabolic profiling in Study I (section 3.4.3) and subsequently in Study IIb (section 5.4.2) that the cohorts of breast cancer survivors under examination in this thesis were characterised by overweight, obesity and central obesity but while dysmetabolism was present, it was not excessive. These results question the need for interventions to improve metabolic variables which were already within healthy ranges and the potential for improvement following intervention to be detected. The sub-analysis of Study IIb, while limited by its post-hoc design, suggested two distinct group – i) overweight and metabolically healthy and ii) obese and metabolically unhealthy. The latter group, characterised by a clustering of metabolic risk factors, seem the obvious one to target for intervention. Further evidence of metabolic dysfunction was provided by a higher RMR, which is often raised in the presence of glycaemia (Weyer et al., 1999), compared to metabolically healthy groups. The benefits of an intervention to manage glucose dysregulation in this homogenous cohort are likely to be clearly demonstrated.

The predominant characteristic of participants in this thesis however was obesity, particularly central obesity. Long-term successful weight loss from diet and exercise interventions is difficult to attain. Frequently, individuals lose weight in the initial rehabilitation period however failure to modify lifestyle behaviours for sustained weight loss often results in weight regain (Katch et al., 2011a). The task of reversing unhealthy lifestyle habits which promote weight gain is particularly challenging in a society where the obesity epidemic continues to flourish and activity levels continue to decline. Nonetheless, there is a need for weight management strategies to commence when individuals are overweight and not when the

problem reaches obese levels. As obesity levels increase, the potential for successful weight loss through either diet or exercise interventions decreases (Katch et al., 2011a). As the severity of obesity increases, the need for pharmaceutical or surgical intervention increases, as does the incidence of associated morbidity (Kral, 2001).

The rehabilitation challenges of obesity are similar to the challenges faced in the management of physical inactivity and sedentary behaviour. Increasing activity and reducing body size to levels that greatly exceed what is considered "normal" by population standards require life-style modification and behavioural change. There is potential for health professionals working in cancer rehabilitation to learn from the well-established cardiac rehabilitation model (Schmitz, 2011). Cardiac rehabilitation involves four phases of intervention which spans from in-patient (acute phase post cardiac surgery or cardiac event) to an out-patient rehabilitation programme and subsequent independent exercise (Taylor et al., 2002). The goals of cardiac rehabilitation include decreasing morbidity related to cardiac disease and modifying established CVD risk factors for secondary prevention. In the cancer setting, activity and weight management advice from the time of diagnosis and throughout adjuvant treatment may help prevent weight gain, reductions in physical activity levels and subsequent metabolic decline, thus optimising patient function. Post treatment exercise commencing with a graded home-walking programme (phase 2 cardiac rehabilitation) and progressing to a structured exercise programme (phase 3 cardiac rehabilitation) would provide the gradual introduction to exercise that was missing from the PEACH trial. Phase 3 in cardiac rehabilitation involves a 6-8 week progressive exercise intervention which includes educational sessions from all members of the multi-disciplinary team to address disease-specific issues and concerns including medical and pharmacological advice, the benefits of exercise and perceived barriers to exercise, dietary advice and psychology to manage debilitating disease side-effects. The benefits of such a model in cancer rehabilitation need to be considered in the overall management of morbidity following breast cancer in addition to management of established risk factors for chronic disease.

The majority of exercise interventions conducted in breast cancer survivors to date have been aerobic in nature, with some elements of resistance training. It needs to be acknowledged however that, in relation to obesity and metabolic markers, interventions have not been as

successful as in non-cancer cohorts and therefore there is a need to explore alternative forms of training. One form of aerobic training that has not been examined cancer cohorts is high intensity interval training (HIT). HIT involves short bursts of aerobic exercise at high intensities (90-95% VO_2max) following by a short rest period involving lower intensity exercise recovery (Earnest, 2008). While overall the workload / volume of exercise is similar to that of continuous aerobic training, HIT facilitates periods of anaerobic exercise which may convey greater benefits for cardiometabolic parameters (Kessler et al., 2012). Short bursts of exercise followed by rest intervals allow even untrained individuals to exercise at a vigorous intensity (Tjonna et al., 2008, Wisloff et al., 2007) and may encourage breaks in sedentary behaviour (Macfarlane et al., 2006).

The beneficial effects of HIT have been shown to be similar to, and in some incidences superior to, traditional continuous aerobic training protocols in terms of improvements in VO_2max (Rognmo et al., 2004) (Wisloff et al., 2007, Tjonna et al., 2008), anthropometric measures including body weight, fat mass and waist circumference (Tjonna et al., 2008, Stensvold et al., 2012), and cardiometabolic parameters including blood pressure, inflammatory markers and insulin sensitivity (Babraj et al., 2009, Tjonna et al., 2008, Metcalfe et al., 2012, Little et al., 2011, Hood et al., 2011, Kessler et al., 2012, Munk et al., 2011). Improvements in insulin sensitivity have been demonstrated repeatedly following HIT in both sedentary adults (Babraj et al., 2009, Metcalfe et al., 2012, Hood et al., 2011) and those with the MetSyn (Tjonna et al., 2008). In addition, a number of studies have reported improvements in skeletal muscle markers of metabolic capacity including an increase in the GLUT-4 proteins following HIT in both sedentary adults (Hood et al., 2011) and individuals with T2DM (Little et al., 2011). HIT has been shown to be safe and effective in clinical cohorts including those the MetSyn (Tjonna et al., 2008), coronary artery disease (Rognmo et al., 2004), T2DM (Little et al., 2011) and heart failure (Wisloff et al., 2007). The potential role for HIT in cancer cohorts needs to be explored.

In summary, there is huge potential for physical activity to play a meaningful role in optimizing morbidity and mortality following breast cancer. The study of exercise interventions is central to determining optimal exercise prescription. The results from this thesis suggest that key targets for intervention include sedentary behaviour, inactivity and obesity. The management

of risk factors for secondary disease including CVD should be considered. The benefits of exercise on metabolic variables may be particularly beneficial in those with a clustering of metabolic abnormalities. There is great potential for the application of the cardiac rehabilitation model to cancer rehabilitation and for novel forms of exercise training such as HIT to be explored. Crucially, there is a need for rehabilitation to promote health behaviours and to work beyond current population norms and focus on public health recommendations.

7.3 Critical Analysis of this Work

In Chapter 2, the strengths and limitations of methods used and study designs employed were presented. As physical activity was the key focus of the thesis, this was measured primarily using accelerometry and supplemented using self-report questionnaires. All questionnaires are limited in that they rely on participant recall and accurate reporting of activity. The questionnaires used in this thesis were specifically chosen as they captured energy expended from physical activity over the preceding year, a timeframe not captured by the RT3 activity monitor and for their emphasis on domains of activity specifically related to breast cancer risk as identified by Lynch and colleagues (2011b) including recreational and household activity (Minnesota questionnaire) and occupation-related activity (Tecumseh questionnaire). The Tecumseh questionnaire was used to measure occupation-related physical activity over the preceding 12 months in the *BRCA* cohort. The application of this questionnaire in conjunction with the related Minnesota questionnaire ensured a thorough evaluation of yearly activity in all activity domains.

The Tecumseh questionnaire was not used for Study IIb. This decision was made based on an observation by staff working with the cohort that a large percentage of the cohort being tested would not have returned to work at the time of the follow-up evaluation. There is very little data available describing return-to-work rates among breast cancer survivors. While one review concluded that between 75 and 85% of patients with breast cancer return to work, these estimates come from four studies, three of which were completed during the 1970s and 1980s (Hoving et al., 2009). There was no data on the numbers at work 18 months following diagnosis, which represented the group under study in Study IIb. In hindsight however we observed that 54% (n=37) of participants tested for Study IIb were working at the time of the

assessment and therefore an evaluation of occupation-related physical activity would have been useful.

Overweight and obesity were measured by BMI and visceral central adiposity was measured by waist circumference. While both methods demonstrate certain limitations (see Chapter 2, section 2.4.1), they are used widely in both the clinical and research setting and are recommended in the assessment of chronic disease risk (WHO, 2011). Body composition was measured using BIA, which has been shown to be a valid measure (see Chapter 2, section 2.4.2). The BIA system used in this thesis was more advanced than other models due to the incorporation of 8 electrodes to facilitate segmental measurement and multi-frequency electrical levels to measure both intra- and extra-cellular water (Volgyi et al., 2008, Tanita, 2005), however the lack of precision and accuracy compared to measurements taken by DEXA or MRI limits the use of BIA for assessing change in components of body composition in longitudinal studies (Ward, 2012). In the longitudinal analysis in Study IIa both body weight and BMI remained stable ($p=0.30$ and $p=0.80$ respectively) as did FFM ($p=0.82$), while there was a significant increase in %BF ($p=0.03$). Sarcopenia is associated with numerous cardiometabolic abnormalities including insulin resistance and inflammation (Aubertin-Leheudre et al., 2006, Dominguez and Barbagallo, 2007) and is reported to develop with adjuvant breast cancer treatment even in those who remain weight stable (Demark-Wahnefried et al., 2001a, Del Rio et al., 2002, Campbell et al., 2007). While a significant increase in %BF was reported in Study IIa, the use of BIA limited the ability to accurately evaluate the development of sarcopenia, which may have contributed to the increases observed in measures of glucose metabolism.

The relationship between physical activity and metabolic dysfunction was a primary interest in this thesis. Associations between physical activity and metabolic parameters in Study IIb were only observed in women >40 years of age at diagnosis and not when the entire cohort was examined, while no such associations were identified in Study III. These results are most likely due to menopausal influences and the decision to include both pre- and postmenopausal women in both the survivor and *BRCA* groups requires discussion. While physical activity correlates strongly with metabolic markers in postmenopausal women (Lynch et al., 2011a), in premenopausal women often no association has been found (Tworoger et al., 2007b, Voskuil

et al., 2001). The data available to-date in terms of cancer risk refers almost exclusively to postmenopausal women (WCRF/AICR, 2007). The biological model suggested by Neilson and colleagues (2009) (Chapter 1, Figure 5, page 43) is proposed in relation to postmenopausal risk. It is well-established that obesity is only a risk factor for postmenopausal breast cancer and may in fact protect against premenopausal breast cancer development (WCRF/AICR, 2007).

In this thesis, menopausal status in both cancer survivor studies (Study I and Study II) was not defined. Both cohorts were within five years of diagnosis and as described in Chapter 1 section 1.1.4 accurately distinguishing between chemotherapy amenorrhea and chemotherapy induced menopausal within this time period is challenging (Soules et al., 2001) and further complicated as the majority of participants were taking concurrent hormonal therapy. It is suggested that women aged ≥40 years at diagnosis are more likely to experience chemotherapy-induced menopause than younger women (Torino et al., 2012, Goodwin et al., 1999b). Therefore when this cohort were examined separately in Study IIb associations between objectively measured physical activity and anthropometric variables were observed that were not evident when the total cohort was studied. While current knowledge of how physical activity influences breast cancer outcomes extends almost exclusively to postmenopausal women, there is a need to develop understanding of associations with younger women, who will potentially experience more side-effects due to greater amounts of adjuvant treatment and are more likely to experience long-term morbidity. This need is reflected by the inclusion of breast cancer survivors aged ≥18 years, therefore not excluded by menopausal status, in both the HEAL cohort study (Irwin et al., 2003a) and the proposed Alberta Moving Beyond Breast Cancer (AMBER) cohort study (Courneya et al., 2012). The sample size in both the HEAL study (n=834) and the proposed accrual target for the AMBER study (n=1500) greatly exceeds the numbers recruited for the studies in this thesis. It could be argued that results of the presented survivor studies may have been different if samples were restricted to those who were confirmed as postmenopausal.

Breast cancers arising from *BRCA* mutations, particularly those arising from *BRCA1*, are predominantly ER-negative, with only 27% of *BRCA*-related breast cancers reported as being ER-positive, compared to 96% of sporadic breast cancers (Loman et al., 1998). It is interesting

however that tumours arising due to mutations in these genes develop in hormone sensitive tissues such as the mammary glands and the ovaries as opposed to organs such as the endometrium. Reduced exposure to endogenous steroid hormone levels through reproductive factors such as later onset menarche, pregnancy, earlier menopause have been associated with reduced breast cancer risk while increased breast cancer risk is observed in those taking the oral contraceptive pill or HRT (Pepe et al., 2012, Noruzinia et al., 2005). Ongoing trials examining the risk reducing benefits of Taxomifen as a chemopreventive agent for *BRCA*-associated breast cancer, suggest a 13% reduction in *BRCA1* and 27% in *BRCA2* mutation carriers (Duffy and Nixon, 2002). While both *BRCA1* and *BRCA2* mutations are associated with ER-negativity, there is a suggestion that the likelihood of *BRCA1* mutation carriers developing ER-positive breast cancer increases with increasing age, which is most likely associated with the menopausal transition (Mavaddat et al., 2012, Tung et al., 2010). Conversely, *BRCA2* mutation carriers are more likely to present with ER-positive tumours throughout life, however the likelihood of ER- and triple-negative tumours occurring may increase slightly with age (Mavaddat et al., 2012). Therefore there is potential for physical activity and weight management to modify breast cancer risk in *BRCA* mutation carriers via hormone sensitive pathways, even if hormone sensitive breast cancer is not a predominant feature in this group.

Study II included elements of post-hoc design and analysis which may have introduced some bias to the results presented. The post-hoc nature of the sub-group analysis in Study IIb is inherently limited. Study IIa was not originally designed for follow-up measurements and therefore subjects were not retested at a standardised time. The advantage of this type of study design is the absence of the "Hawthorn effect" whereby participants, aware that their body composition or metabolic measurement will be measured again, may attempt to influence results by changing their behaviour. Limitations however include issues such an inadequate sample size, initial recruitment of participants for a cross-sectional study that would not be suitable for follow-up analysis and post-hoc statistical analysis which may introduce bias and therefore limit interpretation of study results. These issues were the drivers for the design of the prospective longitudinal study in Study III. One of the limitations of short-term PhD research is a lack of time to complete larger-scale or long-term projects. The results of the systematic review in Chapter 6 clearly demonstrate the need for a longitudinal analysis of the effects of modifiable risk factors on *BRCA*-related breast cancer risk however such a study is clearly beyond the scope of a PhD. The decision was therefore

taken to design a longitudinal analysis which will be completed over the coming years. While this limits the data that can be presented in this thesis, restricting it to a cross-sectional analysis of just those participants recruited through St. James's hospital, the foundations have been laid for a study that will be adequately powered and in the long-run will provide novel, meaningful information regarding breast cancer risk in this cohort.

Compared to larger trials in North America examining some of the questions presented in this thesis, the sample sizes in the studies presented were relatively small. Much of the work completed in the cancer survivor cohorts in Study I and Study II was exploratory in nature, completed on samples of convenience from St. James's hospital. While this cohort is somewhat representative of the population nationally, there is a bias towards the inclusion of urban dwelling over rural dwelling participants due to transport issues and the added inconvenience of a 12 hour fast. The information gathered from these studies was collected with the future intention of designing a comprehensive exercise intervention that is suitably powered and multi-centred.

7.4 Future Research

There is potential for future research arising from the results presented in this thesis. While designing and completing a further exercise intervention was beyond the scope of this thesis, clearly the results from both studies within Study II, support the development of an exercise intervention to target surrogate biomarkers of breast cancer outcome. The results of Study I and Study II advocate the need for a trial early in the cancer trajectory. Baseline metabolic screening may be useful for designing targeted rehabilitation goals. Exercise interventions that have been completed to date have not been successful in this regard and therefore more novel methods of exercise training, such as HIT, need to be explored. There is a need however to examine the safety and feasibility of this form of training in cancer survivor cohorts. Furthermore, there is potential for cancer rehabilitation to apply the cardiac rehabilitation model which may serve to prevent health decline and optimise patient function during treatment, in addition to a rehabilitation programme that incorporates elements of behavioural and lifestyle change. The results from the PEACH trial in particular support the need for objective measurement of both physical activity and compliance with the prescribed exercise intensity to monitor adherence.

7.5 Conclusion

Breast cancer survivors and *BRCA*-mutation carriers are faced with the stark reality that their risk of breast cancer, including recurrence, greatly outweighs that of the general population. Despite the burden of this knowledge, the cohorts studied in this thesis do not appear to engage in healthier lifestyle behaviours such as being physically active or ensuring a healthy body composition. Physical activity guidelines were not being achieved however there is a need to clarify the interpretation of these guidelines with regards to activity patterns and sedentary behaviour. The role for physical activity in the prevention of *BRCA*-related breast cancer has yet to be established.

In breast cancer survivors, despite the growing evidence of a relationship between physical activity and cancer outcomes, physical activity interventions have thus far failed to demonstrate a significant impact on surrogate markers of breast cancer risk. There is a need to consider these results in the context of patient-specific characteristics including metabolic presentation, habitual physical activity patterns and ongoing disease and treatment related side-effects. A holistic approach to rehabilitation such as used in the cardiac rehabilitation model may be beneficial.

These results add to the accumulating evidence that is being gathered with the intention of informing exercise interventions aimed at targeting surrogate markers of breast cancer risk and disease outcome. There is considerable scope for targeted exercise prescription to act as an adjunct to traditional breast cancer prevention and treatment strategies. Due to the complex nature of cancer and its treatment physical activity should be considered within the wider context of disease side-effects and patient presentation. Further research into the challenges of prescribing exercise in the cancer control context is warranted.

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APPENDICES

Appendix I: Letters of Ethical Approval

Ethical Approval Study I

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

SJH/AMNCH Research Ethics Committee Secretariat
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Ms. Emer Guinan
Department of Physiotherapy
Trinity Centre
St. James's Hospital
James Street
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March 4th 2010

Please quote this reference in any follow up to this letter: 2010/03/05 Chairman's Action

Re: Effects of an Individually Prescribed Exercise Programme versus Usual Care on the Cardiovascular Risk Profile in a Population of Breast Cancer Survivors: An Exploration Study.

Dear Emer,

Thank you for your recent submission of the above proposal to the SJH/AMNCH Research Ethics Committee.

The Chairman, having reviewed the proposal, has given ethical approval on behalf of the Committee.

Yours sincerely,

Mr. Dan Lynch
Secretary
SJH/AMNCH Research Ethics Committee

Ethical Approval Study II

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

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Ms. Emer Guinan
Physiotherapy Postgraduate Student
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Dublin 8

March 30th 2011

REC reference: 2011/11/03

(Please quote REC reference and EudraCT number on all correspondence)

Re: The Metabolic Risk Profile of Breast Cancer Survivors – Are There Long-Term Differences Related to Adjuvant Treatment?

Dear Ms. Guinan,

Thank you for your recent communication which you sent in response to the Committee's letter of March 3rd 2011.

The Vice-Chairman of the Committee has reviewed your response and has given ethical approval on behalf of the Committee.

Full ethical approval is now in place for this study.

Yours sincerely,

p Cathie O'Neill

Ms. Ursula Ryan
Secretary
SJH/AMNCH Research Ethics Committee

Ethical Approval Study III

Ethical approval for Study III was obtained as an amendment to Study II.

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

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August 2nd 2011

REC reference: 2011/29/02

(Please quote REC reference and EudraCT number on all correspondence)

Re: The Metabolic Risk Profile of Breast Cancer Survivors – Are there Long-Term differences Related to Adjuvant Treatment

Dear Ms. Guinan,

Thank you for your recent submission of an amendment which you submitted for review and approval by the SJH/AMNCH Research Ethics Committee.

The Vice-Chairman of the Committee has reviewed your submission and has given ethical approval on behalf of the Committee.

Yours sincerely,

Ms. Ursula Ryan
Secretary
SJH/AMNCH Research Ethics Committee

Appendix II: Publications Relating to this Work

Systematic Review: Physical Therapy Reviews

Systematic Review

Exercise training in breast cancer survivors: a review of trials examining anthropometric and obesity-related biomarkers of breast cancer risk

Emer M. Guinan[1], Elizabeth M. Connolly[2], Juliette Hussey[1]

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[2]Department of Surgery, St James's Hospital and Trinity College, Dublin, Ireland

Background: Substantial observational evidence exists which supports a role for physical activity in improving breast cancer prognosis. Biological pathways linking physical activity to prognosis include alterations in obesity-related biomarkers involving chronic low-grade inflammation, adipokines, and markers of insulin resistance. Exercise interventions, with these biomarkers as end-points, may be beneficial for improving breast cancer outcomes.
Objective: To conduct a systematic literature review, investigating the effect of exercise interventions on anthropometric variables and related biomarkers of cancer risk in breast cancer survivors.
Methods: The preferred reporting for systematic review and meta-analysis (PRISMA) guidelines were followed. A comprehensive literatures search was conducted using the databases PubMed, Embase, SciVerse, the Cochrane Library, AMED, and PEDro, for articles published in English up to June 2012. Exercise interventions, both randomized and non-randomized, examining a range of biomarkers of cancer risk were included.
Results: Thirteen articles, representing nine exercise interventions were included — seven randomized controlled trials (RCT) and two non-randomized trials. A number of trials reported improvements in anthropometrics (percentage body fat, body mass index, and waist / hip circumference). Three trials reported changes in insulin-like growth factor (IGF)-I and IGF-II, and insulin-like growth factor binding protein (IGFBP)-3. There were no reported changes in insulin, glucose, insulin resistance, adipokines or inflammatory markers.
Conclusions: More robust RCTs are required to fully elucidate the effect of exercise training on biomarkers of breast cancer risk and determine the role of physical activity as an adjunct to breast cancer treatment as a means of reducing breast cancer recurrence and improving mortality.

Keywords: Breast cancer, Exercise training, Biomarkers, Body composition, Physical activity

Introduction

Obesity and lifetime physical inactivity are well-established risk factors for postmenopausal breast cancer[1,2] and are also associated with poorer prognosis.[3–5] Obesity at diagnosis is associated with poorer survival and increased breast cancer recurrence.[6] Furthermore, every 5-kg weight gain after diagnosis is associated with a 12% increase in all-cause mortality and a 13% increase in breast cancer specific mortality, independent of prior menopausal status, body mass index (BMI) or smoking habits.[3]

Women who are physically active following diagnosis show improved breast cancer outcomes. Up to a 35% reduction in all-cause mortality has been reported by a number of large epidemiological studies, including the Nurses' Health Study[7] (n=2987), the Life after Cancer Epidemiology study[8] (n=1970) and the Shanghai Breast Cancer Survival Study[9] (n=4826). Similarly, the Women's Healthy Eating and Living study[10] (n=2361) reported a 35% reduction in mortality among breast cancer patients who adhered to recommended physical activity (PA) guidelines following diagnosis and in the Women's Health Initiative[11] (n=4643) a 33% reduction in all-cause mortality was observed in survivors exercising to ≥9 metabolic equivalent-hours (MET-h)/week, even if they were sedentary prediagnosis. Breast cancer-specific outcomes also benefit from habitual physical activity. The Nurses' Health Study[7] reported a 26%

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DOI 10.1179/1743288X12Y.0000000057

reduction in breast cancer recurrence for ≥24 MET-h/week versus <3 MET-h/week activity and Chen *et al.*[9] reported a 41% reduction in breast cancer specific mortality in the first three years post diagnosis with ≥8.3 MET-h/week activity.

There are a number of biological mechanisms through which PA may exert its protective effects including alterations in obesity-related biomarkers involving chronic low-grade inflammation, adipokines, markers of insulin resistance and circulating sex hormones.[12–14] Adipose tissue is responsible for the secretion of these factors and therefore the effect of PA on body fat, in particular visceral fat, is of critical importance.[15] The Healthy Eating Activity and Lifestyle (HEAL) study (n=1200), a multicentre prospective cohort study examining the role of lifestyle factors on postmenopausal breast cancer prognosis, has reported lower C-peptide and leptin levels and higher insulin-like growth factor (IGF)-1 and insulin like-growth factor binding protein (IGFBP)-3 levels in women in the higher quartile of PA (>13.3 MET-h/week)[16] while elevated markers of inflammation [C-reactive protein (CRP) and serum amyloid A] were associated with decreasing PA levels.[17] Elevated CRP and serum amyloid A, high levels of insulin resistance and low adiponectin concentrations have been associated with reduced survival in this cohort.[18,19]

However, limited information can be elucidated from observational studies. While associations between PA and established biomarkers of cancer risk are well reported, exercise interventions with biomarkers as end-points are required to fully evaluate the role of PA in modifying these variables and to establish information on dose–response. Such interventions may convey the benefits of improved survival and reduced risk of recurrence. Exercise interventions have been shown to improve many of these biomarkers, which also serve as risk factors for cardiovascular disease and type II diabetes, in various populations including overweight and obese women[20,21] and those with the metabolic syndrome.[22]

A recent systematic review by Ballard-Barbash *et al.*[14] concluded that physical activity was associated with reduced all-cause and breast cancer specific mortality and that exercise interventions may have a role in improving biomarkers of cancer risk among a range of cancer survivor populations, with particular emphasis on disease outcome. The current systematic review aims to expand on the conclusions of Ballard-Barbash *et al.*,[14] by focusing on the physical activity parameters prescribed by exercise interventions to stimulate changes in cancer risk biomarkers and anthropometric variables, specifically in breast cancer survivors. Breast cancer survivors are a unique group and face challenges to exercise, which may not be applicable to other cohorts, including weight gain and changes in body composition following adjuvant therapy,[23] low PA levels,[24,25] side-effects of ongoing hormone therapy including joint pain or menopausal symptoms,[26] early menopause,[27] persistent cancer-related fatigue,[28] reduced arm/shoulder mobility,[29] and psychological challenges related to alterations in body image.[30]

Methods

Eligibility criteria

Studies which examined the effects of exercise interventions in patients with breast cancer who had completed all adjuvant treatment and were showing no signs of recurrent or progressive disease were reviewed. Studies where participants continued to take endocrine therapy during the intervention period were included. Studies were considered if they included a structured exercise programme based on aerobic and/or resistance exercise, fully-supervised, partially supervised or non-supervised. Interventions where another intervention type such as diet or pharmacological interventions were combined with exercise were excluded. Exercise interventions which included non-specific exercise protocols based on stretching, Tai Chi, yoga or dance were excluded. Due to the small number of published studies both randomized and non-randomized trials of exercise training were included.

Studies evaluating the effect of exercise on obesity-related biomarkers of breast cancer risk were considered for inclusion. This included anthropometric measures (BMI, percentage body fat, waist circumference), inflammatory markers and adipokines [CRP, interleukin (IL)-6, tumour necrosis factor (TNF)-alpha, leptin, adiponectin] and markers of insulin resistance (insulin, glucose, insulin resistance, IGFs, IGFBPs). These biomarkers were chosen because as discussed above, they have been identified as being involved in the biological mechanisms linking PA to breast cancer development and progression. Studies which examined the effect of exercise on markers of immune function, such as natural killer cells, macrophages and neutrophils, were not included for review. Although these biomarkers are associated with long-term breast prognosis, immunosuppression in cancer survivors results as a direct effect of anti-cancer therapies and is therefore not considered an obesity-related biomarker.[31]

Search strategy

The authors adhered to the preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines when conducting this review. Studies were identified through a comprehensive electronic search using the databases PubMed, Embase, SciVerse, the Cochrane Library, AMED, and PEDro. The following search algorithm was used to identify potentially

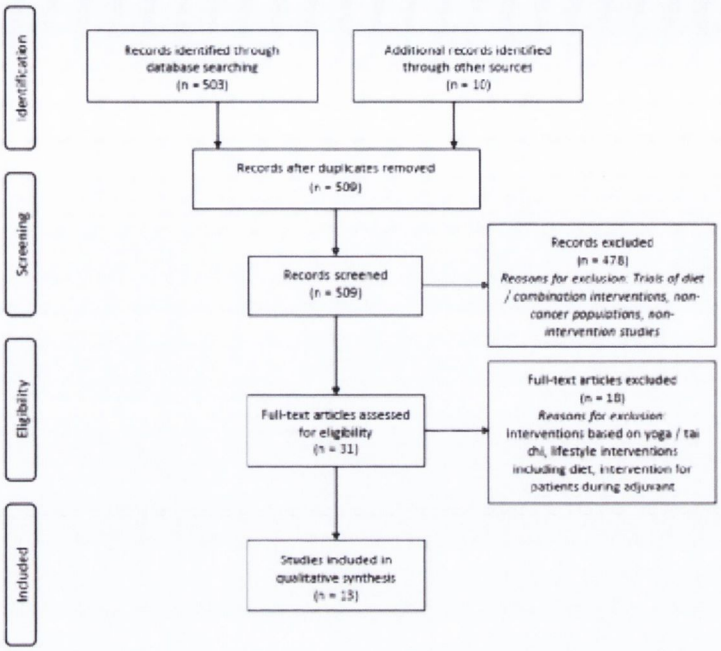


Figure 1 PRISMA diagram.

suitable articles: ['breast cancer' (Title/Abstract) OR 'breast cancer patient' (Title/Abstract) OR 'breast cancer survivor' (Title/Abstract) OR 'cancer survivor' (Title/Abstract) OR 'cancer survival' (Title/Abstract)) AND ('biomarker' (Title/Abstract) OR 'body mass index' (Title/Abstract) OR 'body fat' (Title/Abstract) OR 'waist circumference' (Title/Abstract) OR 'waist to hip ratio' (Title/Abstract) OR 'glucose' (Title/Abstract) OR 'insulin' (Title/Abstract) OR 'insulin-like growth factor' (Title/Abstract) OR 'insulin resistance' (Title/Abstract) OR 'c-reactive protein' (Title/Abstract) OR 'tumor necrosis factor' (Title/Abstract) OR 'interleukin' (Title/Abstract) OR 'adipokine' (Title/Abstract) OR 'adiponectin' (Title/Abstract) OR 'leptin' (Title/Abstract) OR 'inflammation'(Title/Abstract)) AND ('exercise training' (Title/Abstract) OR 'aerobic exercise' (Title/Abstract) OR 'aerobic training' (Title/Abstract) OR 'resistance training' (Title/Abstract) OR 'resistance exercise' (Title/Abstract) OR 'endurance training' (Title/Abstract) OR 'endurance exercise' (Title/Abstract) OR 'physical activity' (Title/Abstract) OR 'intervention' (Title/Abstract)]. Sex hormones including estrogens, androgens and sex hormone binding globulin were included in the initial search; however, as no interventions were identified, these terms were removed from the algorithm. In addition, a manual search of the reference lists of associated reviews and relevant articles was conducted. All applicable articles published in the English language up until June 2012 were considered for inclusion. Searches were carried out by one reviewer (EG) who assessed potential studies against inclusion criteria. The search strategy was repeated and verified by a second reviewer (JH).

Quality assessment

The methodological quality of RCTs included for review was assessed using the PEDro scale, a valid measure of methodological quality used for clinical trials.[32] The scale, which is based on the Delphi list, contains 11 criteria for quality assessment. Two criteria relating to blinding subjects and therapists were not considered for this review as it is impossible to blind these groups to treatment provided in this area of research. Therefore, nine of the 11 criteria were evaluated. A score >6 indicates good methodological quality and a score of 9 indicates excellent methodological quality.

Results

The search strategy identified 513 potentially suitable articles. When inclusion and exclusion criteria were applied a total of 13 articles representing nine interventions remained for inclusion, including seven RCTs[33–44] and two non-randomized trials[45,46] (Fig. 1). Three RCTs have multiple publications included for review: The Rehabilitation Exercise for Health after Breast Cancer (REHAB) trial has four,[33–36] The Yale Exercise and Survivorship (YES) study[42,43] has two and the RCT by Ligibel *et al.*[40,41] has two.

Methodological quality

Quality scores are presented in Table 1. The mean quality score for the seven RCTs was 7, with two studies adhering to all nine criteria.[33,42] The main shortcomings were follow-up assessments completed on <85% of participants, and subsequently a failure to use intention-to-treat analysis.

Study designs and participants

All seven RCTs compared an exercise group (EG) to a non-exercising control group (CG). Non-randomized trials included an EG only. Results were reported from pre- and post-treatment assessments. Breast cancer stage was reported in all trials and ranged from *in situ* cancer (stage 0) to stage IIIb. Participants had completed all prescribed adjuvant chemotherapy and/or radiotherapy. In two studies all participants were taking hormone therapy during the interventions[39,44] while in six other studies[33–37,40–43,45,46] varying percentages of participants were taking hormone therapy. Herrero *et al.*[38] did not describe endocrine therapy use. While the majority of studies included participants who were within five years of diagnosis, the range spanned 0.8 to 22.0 years post-diagnosis[45] and 0.45 to 28.5 years post-diagnosis[41] in two studies. Mean time since diagnosis or treatment was not described by two studies.[39,44]

Menopausal status was described by all studies. Six studies included postmenopausal women only[33–36,38,39,42–44,46] while in the remaining trials the majority (81.5%,[37] 92.6%,[45] 85%[40,41]) of participants were postmenopausal. Baseline BMI was reported in seven trials[33–38,40–44,46] where the majority of participants were either overweight (BMI: 25–29.4 kg/m^2) or obese (BMI: > 30 kg/m^2). Baseline PA levels were described in six studies[33–38,40–43] with three studies stating sedentary behaviour as an inclusion criterion.[38,40–43] In all other studies, participants spent the majority of time in sedentary or light intensity activity prior to study entry. One study recruited participants from the all-breast cancer survivor dragon boat team following the competitive dragon boat season. While baseline PA levels were not reported, it is plausible to assume that this cohort was more physically conditioned than the other groups reviewed.

Exercise interventions

Exercise interventions are described in detail in Table 2. Seven of the nine programmes included some element of aerobic exercise, either on its own or in combination with resistance training.[33,38,40,42,44–46] Schmitz *et al.*,[37] prescribed resistance training only. At least one element of exercise training was supervised in all programmes with the exception of that by Payne *et al.*,[39] who prescribed a home-based walking programme for older women receiving hormonal therapy. Home-based aerobic programmes (usually walking) were also prescribed by Cheema and Gaul,[45] Ligibel *et al.*[40,41] and Irwin

Table 1 Methodological quality of randomized controlled trials reviewed

	Eligibility	Random allocation	Concealed allocation	Similar at baseline	Blinding of assessors	Measures from >85%	Intention-to-treat analysis	Between group comparison	Measures of variability	Total items reported
REHAB trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Courneya[33]										
Fairey[34]										
Fairey[35]										
Fairey[36]										
Schmitz[37]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Herrero[38]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
Payne[39]	Yes	Yes	No	Not reported	No	Yes	No	Yes	Yes	5
Ligibel[40]	Yes	Yes	No	Yes	No	No	No	Yes	Yes	5
Ligibel[41]										
YES Study[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Irwin[43]										
Irwin[45]	Yes	Yes	No	Not reported	Yes	Yes	No	Yes	Yes	6
Rahnama[44]										

Table 2 Summary of exercise interventions

Authors	Design	Participants	Description of intervention	Outcomes	Adherence	Results
REHAB trial Courneya[33] Fairey[34] Fairey[35] Fairey[36]	RCT	Overall: n=53 EG: n=25, mean age 59 ± 5 years CG: n=28, mean age 58.6 ± 6 years Time post rx: 14 ± 6 months	15-week, three times weekly supervised aerobic intervention. Exercise intensity set at 70–75% VO_2max. Class duration commenced at 15 minutes (weeks 1–3), increasing by 5 minutes every 3 weeks to 35 minutes (weeks 13–15) CG received usual care	BMI %BF Insulin Glucose HOMA-IR IGFs IGFBPs CRP IL-6 TNF-alpha	EG completed 44.3/45 (98.4%) of prescribed sessions	Significant decrease in IGF-I (P=0.05), increase in IGFBP-3 (P=0.02) and decrease in the IGFI/IGFBP3 molar ratio (P=0.02). There were no other significant findings between groups; BMI (P=0.33), %BF (skinfolds) (P=0.095), insulin (P=0.94), glucose (P=0.82), HOMA-IR (P=0.25), IGF-II (P=0.10), IGFBP-1 (P=0.77), CRP (P=0.07), IL-6 (P-value NR) or TNF-alpha (P-value NR)
Schmitz[37]	RCT	Overall: n=85 EG: n=42, mean age 53.3 ± 8.7 years, CG: n=43, mean age 52.8 ± 7.6 years Time post rx: 18–24 months	6 month, twice weekly, progressive resistance programme; months 1–3 supervised and months 3–6 unsupervised Upper body exercises started with no weight or 0.5 lb and progressed as symptoms allowed. Lower limb exercises were prescribed at 8–10 repetitions of 1RM, building up to three sets before progressing. Sessions lasted 60 minutes CG served as a delayed treatment group	BMI %BF WC Glucose Insulin HOMA-IR IGFs	EG completed 92% of supervised classes and adhered to 66% of HEP	Significant decrease IGF-II (P=0.02) and %BF (DEXA) (P=0.03) and significant increase in lean body mass (P=0.008). There were no other significant findings between groups; BMI (P=0.77), WC (P=0.22), glucose (P=0.17), insulin (P=0.46), HOMA-IR (P=0.78), IGF-I (P=0.64), IGFBP-1 (P=0.47), IGFBP-2 (P=0.89), IGFBP-3 (P=0.32)
Cheema and Gauf[15]	Non-RCT	n=27, Mean age 57.7 ± 7.2 years Mean time post rx: 5.2 (range 0.8–21 years)	8-week aerobic and resistance programme. Resistance training was supervised weeks 1–2 and weeks 5–8. 8–12 repetition of 1RM to a maximum of 3 sets. Aerobic sessions were unsupervised at an intensity of 65–85% HRmax. Exercise duration progressed from 15 minutes (weeks 1–2) to 30 minutes (weeks 7–8)	%BF WC	99.1 (2.9)% to resistance training, 97.1 ± 6.5% to aerobic training	Significant decrease in %BF (skinfolds) (P <0.01) and WC (P<0.01). There was no change in body weight (P-value NR)
Herrero[38]	RCT	Overall: n=16 EG: n=8, mean age 50 ± 5 years CG: n=8, mean age 51 ± 10 years. Time post rx: EG: 36 ± 13; CG: 35 ± 12 months	8-week, three times weekly, aerobic and resistance programme; all sessions supervised. Resistance training incorporated 11 exercises at 12–15 repetition of 1RM, to a maximum of 3 sets. Aerobic training was performed for 20 minutes at 70% HRmax progressing to 30 minutes at 80% HRmax CG received usual care	BMI %BF	Mean adherence in the EG was 91.1 ± 6.9%	Significant decrease in %BF (skinfolds) between groups (P<0.05). No change in BMI (P-value NR)
Knobf[39]	Non-RCT	n=26 Mean age 51.3 ± 6.2 years Time post rx: NR	16–24 week, three times weekly, supervised progressive walking treadmill programme using a weight belt and backpack. Training commenced with 10–20 minutes walking at a self-selected intensity with a 1lb weight loading and progressed to 45 minutes at 65–75% HRmax with a 5-lb weight loading	%BF	Mean adherence 88.2 ± 6.8%	No changes in % BF (DEXA) (P=0.14), lean body mass (P=0.08) or body weight (P=0.59)

Table 2 Continued

Authors	Design	Participants	Description of intervention	Outcomes	Adherence	Results
Payne[39]	RCT	Overall: $n=20$, mean age 64.7 $\pm$ 6.3 years EG: $n=10$ CG: $n=10$ Time post rx: NR	14 week, four times weekly walking intervention, 20 minutes in duration. Intensity described as 'moderate' CG received usual care	IL-6	NR	No significant differences between groups for changes in IL-6
Ligibel[40] Ligibel[41]	RCT	Overall: $n=101$, EG: $n=51$, mean age 52 $\pm$ 9, CG: $n=50$, mean age 53 $\pm$ 9. Time post diagnosis: EG: 21.2 (range 8–223) months; CG: 28.6 (range 5.4–342 months)	16-week resistance and aerobic programme. Resistance training was supervised, twice weekly for 50 minutes. Intensity: 80% 1RM, 2–4 sets of 10 repetitions, progressing by 10% as able. Aerobic exercise was unsupervised with a target of 90 minutes/week at 55–80% HRmax. Adherence was measured using a HR monitor, pedometer and exercise logs CG received routine care	BMI %BF WC Insulin Glucose HOMA-IR Adiponectin Leptin	EG attended 73% of resistance classes and performed 114 minutes/week of aerobic exercise	No significant changes in BMI ($P=0.42$), %BF (DEXA) ($P=0.26$), WC ($P=0.06$), insulin ($P=0.07$), glucose ($P=0.47$), HOMA-IR ($P=0.09$), leptin ($P=0.76$), adiponectin ($P=0.59$) or HMWA ($P=0.22$)
YES Study Irwin[42] Irwin[43]	RCT	Overall: $n=75$ EG: $n=37$, mean age 56.5 $\pm$ 9.5 years; CG: $n=38$, mean age 55.1 $\pm$ 7.7 years Time post diagnosis: EG: 3.6 $\pm$ 2.2; CG: 3.3 $\pm$ 2.6 years	6-month aerobic intervention; supervised three times weekly and home-based twice per week. Exercise duration commenced at 15 minutes and progressed to 30-minutes from week 5 to study completion. Exercise intensity commenced at 50% HRmax and progressed to 60–80% HRmax. Adherence to the HEP was monitored using activity logs CG received usual care	BMI %BF WC Insulin IGF-I IGFBP-3	73% adherence to exercise protocol	Significant decrease in in %BF (DEXA) ($P=0.002$), IGF-I ($P=0.03$) and IGFBP-3 ($P=0.006$) There were no changes in BMI ($P=0.42$), WC ($P=0.57$) or insulin ($P=0.09$)
Rahnama[44]	RCT	Overall: $n=29$ EG: $n=14$ EG: $n=15$ Mean age: NR Time post since rx: NR	15 week resistance and aerobic intervention. Supervised resistance training twice weekly for 60 minutes; three sets of 10 repetitions of 1RM weeks 1–5 progressing to 14 repetition weeks 11–15. Supervised walking programme twice weekly at an intensity of 45% HRmax for 25 minutes week one and progressing to 65% HRmax for 45 minutes by week 11 CG received usual care	BMI WC (WHR)	NR	Significant decrease in BMI ($P=0.022$) and WHR ($P=0.001$) in the EG versus the CG

Note: RCT=randomized controlled trial; EG=exercise group; CG=control group; rx=treatment; VO_2max=maximal oxygen consumption; BMI=body mass index; %BF=percentage body fat; HOMA-IR=homeostatic model assessment index – insulin resistance; IGFs=insulin-like growth factors; IGFBPs=insulin-like growth factor binding proteins; CRP=C – Reactive Protein; IL-6=interleukin-6; TNF=tumour necrosis factor; NR=not reported; lb=pound; WC=waist circumference; DEXA=dual-energy X-ray absorptiometry; HEP=home exercise programme; RM=repetition maximum; HRmax=maximum heart rate. Data are presented as mean (standard deviation) for continuous variables and *n* (%) for categorical variables.

et al..[42,43] Adherence was monitored using a combination of heart rate (HR) monitors,[40,42] pedometers,[40] exercise logs,[39,40,42] and manual pulse.[45]

Exercise intensity increased progressively throughout each aerobic intervention to a moderate-to-vigorous aerobic intensity (80% heart rate maximum (HRmax), see Table 2 for individual programme aerobic intensity prescription and progression) with the exception of the study by Rahnama *et al.*,[44] which had an upper aerobic limit of 65% HRmax. Aerobic intensity in the walking programme by Payne *et al.*,[39] was described as 'moderate'; however, no specific intensity was described. Unsupervised home programmes required participants to exercise at an intensity equivalent to that in the supervised class[42] or to prescribed target HR zones.[40,45] Knobf *et al.*[46] included the use of weight belts and a backpack to increase bone loading during aerobic activity.[46] Resistance training progressed similarly throughout sessions, with arm lymphedema dictating progression of upper limb exercises.[37] Participants trained at either 80 or 100% one repetition maximum (1RM) over 10–14 repetitions.[37,38,40,41,44,45]

Effects of exercise on anthropometrics

Seven of the nine interventions reviewed measured the effect of exercise on anthropometric variables. A number of studies reported changes in percentage body fat. Schmitz *et al.*,[37] reported a significant decrease in percentage body fat following six months resistance training (EG mean change $-1.15 \pm 0.45\%$, CG mean change $0.23 \pm 0.44\%$, $P=0.03$) as did Irwin *et al.*[42] following six months of moderate intensity aerobic training (EG mean change -1.9%, CG mean change 1.1%, $P=0.002$). Body fat was measured using dual energy X-ray absorptiometry (DEXA) in both trials. Herrero *et al.*,[38] reported an overall decrease in mean body fat of -2.0% (95% CI, -0.3 to -3.8%, $P<0.05$) while Cheema and Gaul[45] reported a decrease of $11.7 \pm 17.0\%$ ($P<0.01$) in percentage body fat among their EG following combined aerobic and resistance training. The two latter trials used the sum of skinfolds technique. No change in body fat was reported by any other trial using a range of measurement techniques including sum of skinfolds,[33] DEXA[46] and bioimpedance analysis.[40]

Three trials of combined resistance and aerobic exercise, of various durations (8–16 weeks), reported changes in body weight and waist/hip girth. The trial by Rahnama *et al.*,[44] was the only one to report a change in body weight ($P=0.03$) or BMI ($P=0.02$). This group also reported a significant decrease in waist-to-hip (WHR) ratio (EG changed from 0.98 ± 0.07 to 0.94 ± 0.07 m, CG changed from 0.96 ± 0.03 to 0.96 ± 0.04 m, $P=0.001$). Ligibel *et al.*[40] reported a significant reduction in hip circumference (EG mean change -2.3 ± 3.3 cm, CG mean change -0.5 ± 3.3 cm, $P=0.02$) but no significant change in waist circumference (EG mean change -1.5 ± 4.6 cm, CG mean change 0.3 ± 3.8 cm, $P=0.06$). Cheema and Gaul[45] reported a decrease in waist circumference in their exercising group (mean change $-3.2 \pm 3.6\%$, $P<0.01$).

Effect of exercise on inflammation and adipokines

Three interventions examined the effect of exercise on adipokines and inflammatory markers. Fairey *et al.*[36] reported no change in serum CRP levels following 15 weeks moderate-to-vigorous intensity aerobic training (EG mean change -1.39 mg/l, CG mean change 0.10 mg/l, $P=0.07$). The same trial reported no changes in either IL-6 or TNF-alpha.[35] Similarly, Payne *et al.*[39] reported no change in IL-6 following 14 weeks of a moderate intensity walking programme. Ligibel *et al.*[41] reported no changes in either adiponectin (EG mean change -1.2 ± 3.2 μg/ml, CG mean change -1.3 ± 6.1 μg/ml, $P=0.59$), high-molecular weight adiponectin (EG mean change -1.6 ± 3.2 μg/ml, CG mean change -0.6 ± 2.1 μg/ml, $P=0.22$) or leptin (EG mean change 0.0 ± 4.0 ng/ml, CG mean change 0.5 ± 2.9 ng/ml, $P=0.76$) following 16 weeks of resistance and aerobic training.

Effect of exercise on markers of insulin resistance

Four RCTs examined the effect of exercise on markers of insulin resistance with no changes observed across any of the trials for fasting glucose,[34,37,40] fasting insulin[34,37,40,43] or insulin resistance as estimated by the homeostatic model assessment (HOMA-IR).[34,37,40] Two moderate-to-vigorous intensity aerobic interventions reported significant decreases in IGF-I (Fairey *et al.*,[34] EG mean change -4.9 ± 10.7 ng/ml, CG mean change 2.5 ± 14.8 ng/ml, $P=0.05$; and Irwin *et al.*,[43] EG mean change -7.36 ± 6.02 ng/ml, CG mean change 12.7 ± 6.39 ng/ml, $P=0.03$). In contrast, conflicting results were reported by these studies for IGFBP-3 with Fairey *et al.*[34] reporting a significant increase (EG mean change 103.4 ± 224.7 ng/ml, CG mean change -77.1 ± 313.5 ng/ml, $P=0.02$) while Irwin *et al.*[43] reported a significant decrease (EG mean change -0.19 ± 0.08 ng/ml, CG mean change 0.15 ± 0.1 ng/ml, $P=0.01$). Schmitz *et al.*[37] reported a significant decrease in IGF-II (EG mean change -26.23 ± 16.73 ng/ml, CG mean change 28.28 ± 16.31 ng/ml, $P=0.02$) following 6 months resistance training.

Discussion

This review summarizes the evidence from exercise trials examining the effect of exercise interventions on anthropometric variables and related biomarkers of cancer risk in breast cancer survivors. The review highlights the extensive gaps that exist in the literature with regards to this topic. While improvements in body composition parameters, including decreased

percentage body fat and circumferential measures, and changes in IGF-I, IGF-II and IGFBP-3 have been described by some studies, the majority failed to demonstrate significant changes.

Obesity is a well-recognized risk factor for postmenopausal breast cancer, primarily due to the secretion of a number of biological products from the adipose tissue including endogenous sex hormones, insulin, adipokines and inflammatory markers.[13] Estrogen and insulin are two highly influential factors, due to their mitogenic effects on mammary cells resulting in tumour growth and progression.[13,47] Similarly, binding of IGFs such as IGF-1 to its receptor IGFBP-3, stimulates cell proliferation and differentiation, inhibits cell apoptosis and has been associated with increased breast cancer risk.[48] Insulin resistance occurs when insulin-mediated glucose uptake is impaired, resulting in hyperglycaemia and hyperinsulinemia. Adipokines, secreted from the adipose tissue, including leptin, TNF-alpha and IL-6 are directly associated with insulin resistance while adiponectin demonstrates an inverse relationship with insulin resistance.[49] IL-6 and TNF-alpha stimulate hepatic production of CRP, resulting in a state of chronic low-grade inflammation, creating a protumour environment.[18,49]

The protective effect of PA on breast cancer outcome is hypothesized to be mediated through alterations in many of these obesity-related pathways[13,14] and therefore there is a need to investigate the effects of structured exercise interventions on these outcomes to understand the potential of PA as an adjunct to breast cancer therapy. This review identified seven RCTs and two non-randomized trials evaluating the effect of exercise on various anthropometric variables including body weight, BMI, percentage body fat and waist circumference. Significant decreases in percentage body fat were reported by three RCTs following aerobic,[42] resistance[37] and combined aerobic/resistance[38] training. Cheema and Gaul[45] also reported a decrease in percentage body fat however their results should be interpreted with caution due to the non-randomized design and use of sum of skinfolds technique, as opposed to DEXA, to estimate body fat. In general, BMI and body weight remained stable throughout the interventions with only Rahnama *et al.*[44] reporting changes.

RCTs examining the effects of moderate-to-vigorous intensity (70–80% HRmax) aerobic exercise in non-breast cancer populations have demonstrated improvements in various anthropometric variables including body weight,[50] total body fat[50,51] and abdominal fat.[50–52] Higher intensity aerobic exercise targets abdominal fat more effectively than diet alone.[52] Abdominal fat is strongly correlated with insulin resistance and therefore may be more important than total body fat in terms of breast cancer risk.[13,49,53]

The lack of change in waist circumference reported by the aerobic RCTs reviewed is surprising due to the prescribed aerobic intensity (55–80% HRmax) and the adequate programme duration (4–6 months).[40,43] One possible explanation may be excessive sedentary time. While sedentary time was not measured throughout the reviewed studies, inactivity at baseline was a requirement for three programmes[38,40–43] and all other trials stating that participants spent the majority of time inactive prior to study entry (exception: Cheema and Gaul[45]). It is well documented that breast cancer survivors as a group spend the majority of time inactive.[24,25,54] Sedentary time is associated with an increase in abdominal fat[51] and is directly related to a number of cancer-related biomarkers.[55] Ligibel *et al.*[40,41] and Irwin *et al.*[42,43] both reported increases of 11 and 129 minutes/week respectively versus baseline activity levels, however these values were self-reported and therefore do not account for inactivity. In light of the characteristic sedentary behaviour of this group, future trials should endeavour to include a more accurate measure of change in PA following intervention, such as accelerometry, which could objectively measure levels of moderate-to-vigorous intensity activity and sedentary time, and may provide some of the answers as to why breast cancer survivors do not experience changes in abdominal adiposity despite apparently appropriate exercise prescription.

There is clearly a dearth of exercise trials examining either inflammatory markers or adipokines following breast cancer, with only three RCTs identified for review.[36,39,41] No significant findings were reported for CRP, IL-6, TNF-alpha, leptin or adiponectin. As adipokines are derived almost exclusively from the adipose tissue, a reduction in body fat may be required for PA to stimulate change. Studies have reported significant decrease in leptin,[21,56] IL-6[20] and CRP[20] and a significant increase in the leptin/adiponectin ratio[56] following twelve months high intensity aerobic exercise in overweight postmenopausal women who also experienced a significant decrease in BMI, percentage body fat and central adiposity. The trials reviewed[36,41] reported no significant changes in anthropometric variables including BMI and waist circumference and may have been of insufficient duration (15–16 weeks) to have an impact on adipokines and inflammatory markers.

In contrast, exercise may improve insulin sensitivity in the absence of change in body fat in obese and previously sedentary individuals,[57,58] through improvements in glucose tolerance by upregulation of the glucose transporter (GLUT)-4 and insulin receptor

substrate-1.[59] However, for these changes to occur exercise programmes must be of high frequency (5 days/week), long duration (50–60 minutes/day) and high intensity (65–75% HR reserve). This type of exercise prescription may be inappropriate for a cancer survivor group, especially individuals in the early stages post treatment and may explain why none of the RCTs reviewed reported significant decreases in glucose, insulin or insulin resistance with either aerobic,[34,43] resistance[37] or combined aerobic/resistance[40] exercise. Furthermore, the reviewed trials reported no significant decrease in BMI or waist circumference. In overweight postmenopausal women high intensity aerobic exercise interventions have led to improvements in insulin,[21,56] insulin resistance[21,56] and insulin sensitivity[51] with associated improvements in anthropometric outcomes. While high-intensity exercise alone may improve insulin sensitivity in non-cancer populations, exercise combined with fat-loss is most effective in this regard[52,57] and should be the target for future trials in breast cancer survivors.

The IGF-axis is another potential target for exercise to improve breast cancer outcomes. Significant decreases in IGF-I were reported by two aerobic interventions[34,43] and in IGF-II following resistance training.[37] There was conflicting evidence regarding changes in IGFBP-3.[34,43] It could be expected that increasing levels of IGFBP-3 would be beneficial as this would act to control bioavailability of IGF-I, however associations between IGFBP-3 and breast cancer have been inconsistent.[48] In addition, the optimal exercise prescription required to alter these proteins has not been fully established.[56,60] The clinical significance of the findings from this review regarding the effect of exercise on the IGF-axis is unclear, however as understanding of the role of this pathway in breast cancer risk increase, they may become an important target for intervention.

Overall, trials reviewed were high quality RCTs, as shown by PEDro score (Table 1), with well-designed exercise protocols, however, the small sample sizes involved in the reviewed studies maybe have resulted in insufficient power to detect changes. Only three trials described a power analysis to calculate sample size (the REHAB trial,[33–36] the YES study,[42,43] and Ligibel *et al.*[40,41]). RCTs measuring similar variables in postmenopausal women have included between 170 and 310 women[21,50,51,56] compared to the interventions reviewed which recruited between 16 and 101 survivors. Each trial reviewed examined the effect of exercise on multiple outcomes, however statistical correction for multiple comparisons was not made, resulting in a bias towards reporting significant results. Another shortcoming across trials reviewed was the lack of long-term follow-up assessment. The importance of the reviewed interventions lies in their potential for improving long-term breast cancer prognosis and therefore an evaluation of how the benefits of exercise interventions are maintained following programme completion is crucial.

While most studies included participants within five years of diagnosis, this extended to almost thirty years in some trials.[40,41,45] It may be more clinically relevant to involve a group who are at a similar survivorship-point to control for factors such as hormone therapy use or cancer-related fatigue which may resolve as survivorship progresses. The timing of an intervention in relation to diagnosis may also be important in terms of the build-up to the moderate-to-vigorous intensity activity necessary to result in meaningful improvements in the biomarkers studied. Survivors in the acute stage post treatment may require a more gradual introduction to high intensity exercise, while long-term survivors may be able to cope with higher intensity activity from an earlier stage. There is a greater need for trials in the early phase after breast cancer treatment. Early intervention may prevent some of the weight gain, improve biomarker profiles and have a greater impact on survival than an intervention completed later into survivorship.

Conclusion

While there is evidence that exercise interventions can have a positive influence on percentage body fat, IGFs and IGFBPs in breast cancer survivors, gaps remain to fully elucidate the optimum exercise dose in terms of programme length or frequency for changes in anthropometric and related cancer biomarkers. The optimum timing of an exercise intervention in relation to breast cancer diagnosis remains to be established. Interventions occurring early in survivorship have the benefit of reducing the risk of developing long-term sedentary habits and weight gain, however, interventions at this timepoint may be confounded by treatment-related side-effects limiting the ability of survivors to exercise at the higher intensity aerobic levels needed to bring about significant change in biomarkers of breast cancer risk.

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Commentary

Exercise to improve obesity-related biomarkers in breast cancer survivors

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Invited commentary on: 'Exercise training in breast cancer survivors — a review of trials examining anthropometric and obesity-related biomarkers of breast cancer risk', Guinan E et al.

In the past 20 years, the advice around physical activity for individuals during and following breast cancer treatment has changed drastically. While recommendations for rest and recovery were once the norm, there is now evidence that physical activity during and following breast cancer treatment is safe and can improve quality of life, and many side effects of cancer treatment, such as fatigue.[1,2] There is a clear role for physical therapists to be leaders in the delivery of cancer rehabilitation programming, based on our knowledge and skills around exercise prescription for a variety of health conditions.[3]

However, physical therapists also should know that there is now consistent observational evidence that those who are physically active after a breast cancer diagnosis have decreased likelihood of breast cancer-related and all-cause mortality.[4] While these findings are promising, well-designed randomized controlled trials (RCTs) are needed to determine causality, and to identify the dose–response relationship between physical activity and breast cancer outcomes. To date, no trials have been completed that have used cancer-related or all-cause mortality as primary end points; however one trial is currently underway.[5] The potential barriers to undertaking such a trial have meant that proposed biomarkers linked to breast cancer outcomes have been used as a proxy outcome in intervention studies.[6] The review in the current issue of *Physical Therapy Reviews* by Guinan *et al*.[7] builds upon what has been reported in the literature to date, by reviewing the studies that have examined the effect of exercise on proposed biomarkers of breast cancer outcomes. A better understanding of the impact of exercise on these proposed biomarkers is crucial to designing the most effective exercise interventions to impact long-term outcomes for breast cancer survivors.

The authors performed a rigorous review, using appropriate methodology and clearly outlined where multiple endpoints were reported from the same trial. The review is focused on exercise interventions that were structured aerobic or resistance exercise only, excluding studies that included other interventions (e.g. diet or pharmaceuticals) or other exercise types (e.g. Tai Chi). However, the effects of aerobic versus resistance exercise were not specifically outlined. As the physiological effects of aerobic and resistance training may be very different, it will be important to consider the effects of these two interventions separately as more intervention trials, particularly of resistance exercise, become available. With the exception of one study, all included studies had a supervised component to the exercise program. The reported results must be interpreted with this in mind. In breast cancer survivors, greater improvements in a variety of outcomes have been reported with supervised versus purely home-based physical activity interventions. Yet despite this demonstrated benefit, there is ongoing discussion around feasibility and cost associated with provision of supervised clinical exercise programming for breast cancer survivors.

The authors correctly note several limitations in the literature to date that may affect the interpretation of their findings. First, the elements of the exercise prescription, including the prescribed exercise intensity, may be a key factor in the effects of the interventions on biomarkers. Limitations in the reporting of the specific dose of exercise prescribed and achieved in RCTs of exercise in breast cancer survivors have been identified as a potential problem in the interpretation and replication of the published exercise intervention studies.[8] Our current understanding is also limited by the duration of these interventions. The length of the interventions reviewed ranged from 8 weeks to 6 months. It is possible that more long-term exercise is needed to significantly change the biomarkers of interest.

The proposed biomarkers linking exercise and breast cancer outcomes have been reviewed by Friedenreich *et al*.[9] The authors of this review chose to focus on 'obesity' biomarkers, namely, adipokines,

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DOI 10.1179/1743288X13Y.0000000068

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inflammatory markers, and markers of insulin resistance, with the exclusion of other proposed biomarkers such as immune function or oxidative stress. Higher levels of exercise, in the absence of weight change, have been linked to improved breast cancer outcomes, suggesting that exercise may play a unique protective role in the absence of weight loss or negative energy balance.[10] Therefore, the focus on obesity-specific biomarkers in this review is a key methodological question for readers to consider, as the review excluded studies that included a dietary weight loss component, a likely key factor in weight loss and altering obesity related biomarkers. The lack of conclusive findings in this review may be due to this issue.

The authors note that the majority of participants were overweight/obese at study entry. Being overweight may put women at a higher risk of developing postmenopausal breast cancer and weight gain is common for breast cancer survivors related to reductions in physical activity during treatment and acceleration of pre-mature menopause.[11] A unique contribution of this review is the synthesis of the impact of body composition changes on biomarkers of breast cancer outcomes. However, the authors correctly report that there was limited weight loss or body composition change in the studies included. While the authors provide some suggested theories for why weight loss was not seen, such as increased sedentary behaviour outside of supervised exercise sessions, there is a wealth of evidence that exercise-alone, without concomitant reduction in caloric intake, results in limited weight loss.[12]

The question of the relative importance of physical activity versus weight loss on biomarkers of breast cancer risk was recently reported in a large four-arm RCT of aerobic exercise-alone, calorie-reduced dietary weight loss-alone, combined exercise, and dietary weight loss, compared to a usual lifestyle control group.[13] Participants were inactive, overweight, postmenopausal women, but were not breast cancer survivors. For all proposed biomarkers, including sex-hormones, insulin and inflammatory markers, modest changes were seen with exercise versus control, but the greatest changes were noted in the two weight loss groups. While a similar trial has not yet been completed in breast cancer survivors, these findings suggest that weight loss may be key to altering the specific biomarkers examined in this review.

So, what should the focus of physical therapists be when designing and delivering rehabilitation programming for women following a breast cancer diagnosis? Based on the summary of the available literature to date, more work is needed to understand the ideal prescription of exercise and weight loss interventions to alter breast cancer outcomes. In the meantime, physical therapists should encourage breast cancer survivors to engage in physical activity for symptom management, such as reduced arm function, fatigue, or reduced physical function, and also to reap the well-known benefits of aerobic and resistance exercise for overall health and well-being.

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Invited Response

Response to commentary on: 'Exercise training in breast cancer survivors: a review of trials examining anthropometric and obesity-related biomarkers of breast cancer risk'

Exercise to improve obesity-related biomarkers in breast cancer survivors

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The authors would like to thank Campbell and Neil for their commentary[1] on a recently published review by Guinan, Connolly and Hussey[2] which explores the effect of exercise training in breast cancer survivors on anthropometric and obesity-related biomakers of breast cancer risk outcomes. We welcome discussion on this topic which, due to the increasing number of breast cancer survivors, is becoming a public health issue that needs to be addressed by physical therapists with proficient skills in prescribing exercise in clinical populations. Of course, the issues addressed explore the impact of physical activity on many diseases where obesity and inactivity are risk factors, e.g. cardiovascular disease. Breast cancer survivors however, characterize a unique group for whom physical activity may impact on not only chronic disease risk factors but also breast cancer-specific outcomes including risk of recurrence and mortality. Data from our research group have described breast cancer survivors, in the first number of years following adjuvant treatment, as largely overweight or obese and/or centrally obese and physical inactive,[3,4] which led to the need to implement exercise interventions in addition to healthy weight strategies early in the cancer trajectory.

Campbell and Neil correctly point out that exercise alone, in the absence of diet modification, is not sufficient to produce meaningful, long-lasting weight loss. The end-points examined in the review by Guinan *et al.*[2] were termed 'obesity-related biomakers' and were therefore inherently related to adiposity. Campbell and Neil discuss the results of a recent four-arm randomized control trial by Foster-Schubert and colleagues,[5] comparing the effect of four different interventions: (i) aerobic exercise; (ii) weight loss (calorie restriction); (iii) exercise and weight loss (calorie restriction); and (iv) usual care control group on selected biomarkers. The results of this trial are similar to others[6–8] in suggesting that the benefits to be gained from exercise combined with weight loss through calorie restriction are superior to those stimulated by either exercise or diet modification alone.

In relation to breast cancer, both physical activity and maintenance of a healthy body weight are associated with improved survival and breast cancer-related outcomes.[9,10] A number of cohort studies have, however, demonstrated that physical activity alone is associated with improved cancer outcomes, even following adjustment for measures of obesity including waist-to-hip ratio and body mass index.[11–13] There is agreement among experts that physical activity most likely influences breast cancer control outcomes via alterations in obesity-related pathways including sex hormones, measures of inflammation, and measures of insulin-glucose metabolism.[9,14] It is important, therefore, to investigate the independent contribution that physical activity makes to these proposed biomarkers.

As discussed in the review by Guinan and colleagues,[2] high-intensity aerobic exercise is more effective in reducing abdominal visceral fat than diet alone.[6] Abdominal visceral fat is known to be highly metabolically active, responsible for the direct and indirect secretion of a number of biomarkers of breast cancer risk[14] and therefore, may be a more important target than total body fat. However, a high

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DOI 10.1179/1743288X13Y.0000000074

volume of exercise [high intensity (70–80% maximum heart rate) and duration >6 months] is suggested to stimulate these changes.[15,16] Interestingly, results from a pilot study by our research group demonstrated a decrease in waist circumference (WC) ($P<0.05$) in a group of breast cancer survivors 2–6 months post-chemotherapy who adhered to >90% of a prescribed supervised and home-based moderate intensity aerobic exercise protocol.[17,18] The decrease in WC occurred in the absence of significant change in other anthropometric measures. While there were no accompanying changes in measures of insulin resistance or inflammatory markers, these results provide a meaningful target for designing a larger study and suggest that rigorous adherence to an appropriate aerobic intervention over a short period of time may decrease WC. Where no effect is demonstrated, the lack of response may be due to ineffective exercise prescription, but also may be attributed to other factors such as non-compliance or displacement of habitual physical activity. As discussed in the review by Guinan and colleagues,[2] breast cancer survivors are a predominantly sedentary group for whom it may be difficult to change exercise behaviour through intervention. We advocate the need for supervised exercise prescription in this group and the objective monitoring of physical activity to ensure accuracy and compliance.

Insulin sensitivity may also be improved by physical activity through obesity-independent pathways, most notably through translocation of the glucose isoform 4 protein in response to activation of the 5′AMP-activated kinase pathway.[19] This occurs following both acute aerobic exercise and isometric muscle contraction. As Campbell and Neil correctly mention, Guinan and colleagues[2] do not distinguish between the effects of aerobic and strength training. Traditionally, strength training was not encouraged in breast cancer survivors due to concerns regarding the impact of this type of intervention on arm symptoms and increased risk of lymphedema; however, results from studies such as the Physical Activity and Lymphedema trial have shown the benefits and safety of correctly prescribed weight training.[20] Subsequently, only one trial reviewed by Guinan and colleagues[2] prescribed resistance training only. While a number of trials prescribed both resistance and aerobic training, there were insufficient data to distinguish between the effects of aerobic versus resistance exercise. This is a clear limitation in the current literature. In addition, the effect of other forms of exercise training, such as high intensity interval training (HIT), requires investigation. HIT is based on the principles of anaerobic exercise training[21] and therefore improvements that are gained may be independent of weight loss. The beneficial effects of HIT have been shown to be similar to, and in some incidences superior to, traditional continuous aerobic training protocols in terms of improvements in both anthropometric variables including body weight and WC and cardiometabolic parameters including inflammatory markers and insulin sensitivity.[22–24]

We look forward to the results on mortality when the current randomized controlled trial by Courneya and colleagues[25] is complete which will provide some clarity on volume of exercise required to influence cancer outcomes. In the breast cancer cohort, we are currently restricted to investigating the impact of exercise intervention on surrogate markers of breast cancer mortality. There is a need for further rigorous investigations with the ultimate aim being to determine the volume of exercise needed for optimum therapeutic responses in this cohort.

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Study I Publication: Supportive Care in Cancer

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Support Care Cancer
DOI 10.1007/s00520-013-1743-5

ORIGINAL ARTICLE

The effect of aerobic exercise on metabolic and inflammatory markers in breast cancer survivors—a pilot study

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Received: 23 May 2012 / Accepted: 4 February 2013
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Abstract
Purpose Physical activity is associated with a reduced risk of breast cancer development and recurrence. There are several hypothesised mechanisms for this including positive effects on metabolic and inflammatory biomarkers and favourable changes in anthropometric variables. This pilot study examined the effect of an 8-week aerobic exercise intervention on several of these outcomes, including body composition, the metabolic syndrome, C-reactive protein (CRP) and physical activity, in breast cancer survivors 2–6 months post-chemotherapy.
Methods Assessments were completed at baseline, at 8-weeks and 3-months post-intervention. Measures taken following a 12-h fast included body composition (bioimpedance analysis), metabolic syndrome (waist circumference, blood pressure, high-density lipoprotein cholesterol, triglycerides and fasting glucose), insulin resistance (homeostatic model assessment), CRP and physical activity (accelerometry and questionnaire). Participants were randomized to either an 8-week moderate-intensity aerobic exercise group or a usual-care control group. Analysis was completed using repeated-measures analysis of variance (ANOVA) ($p=0.05$).
Results Twenty-six breast cancer survivors participated (mean (standard deviation) age 48.1 (8.8) years, exercise group; $n=16$, control group; $n=10$). At baseline, 13 participants were overweight, 6 were obese and 19 centrally obese. Intention-to-treat analysis revealed no significant differences between the exercise and control groups in any of the outcomes measures; however, analysis of those who adhered to >90 % of the supervised exercise class showed a significant decrease in waist circumference ($p=0.05$) and a significant increase in subjectively reported "total weekly" ($p=0.005$) activity.
Conclusion While this 8-week aerobic exercise pilot intervention did not elicit significant improvements in biomarkers of breast cancer risk, there was some suggestion of improvements in waist circumference and subjectively measured physical activity in participants with >90 % adherence to the programme. A trial of longer duration and greater subject numbers is warranted.

Keywords Breast cancer survivor · Physical activity · Obesity · Insulin resistance · Inflammation · Exercise intervention

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Published online: 23 February 2013

Introduction

Breast cancer is the most commonly diagnosed female cancer worldwide and is the leading cause of female cancer-related death [1]. In recent years, the numbers of women surviving breast cancer has increased greatly, generating

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interest in the role of modifiable risk factors for breast cancer, such as obesity and physical activity, in improving breast cancer outcomes.

Physical activity can reduce breast cancer occurrence by up to 25 % in postmenopausal women engaging in the highest quartile of habitual exercise [2]. Breast cancer survivors who engage in aerobic exercise equivalent to 9 metabolic equivalent-hours (MET-h) for 2–3 h per week have a significantly lower risk of breast cancer recurrence and improved breast cancer and all-cause mortality when compared with less active women (<3 MET-h/week) [3–5]. Obesity is a well-established risk factor for postmenopausal breast cancer development [6] and recurrence [7]. Weight gain, a common side-effect of adjuvant chemotherapy and hormonal therapy [8], observed most commonly in premenopausal women [9], has also been associated with poorer breast cancer outcomes [10].

The mechanisms through which physical activity exerts its protective effect are hypothesised to be through alterations in a number of biomarkers of breast cancer risk including the insulin-glucose pathways and inflammatory markers and improvements in anthropometrics [11, 12]. The current study is the first to examine the effect of aerobic exercise on the clustering of these variables in breast cancer survivors. The metabolic syndrome [13] represents a pro-inflammatory state and encompasses many of the biomarkers associated with breast cancer risk including abdominal obesity and insulin resistance [14]. While individually, high insulin resistance and chronic low-grade inflammation characterised by high circulating C-reactive protein (CRP) are associated with poor breast cancer prognosis and increased mortality [15, 16], the co-existence of inflammatory and metabolic biomarkers may be a more crucial target for improving breast cancer outcomes.

The aim of the current study was to evaluate the effect of aerobic exercise on a clustering of anthropometric and blood biomarkers for breast cancer risk, including the metabolic syndrome and CRP in breast cancer survivors. A secondary aim was to investigate if such a programme resulted in improvements in physical activity levels as measured by accelerometry.

Materials and methods

Setting and participants

This study was designed as an ancillary study to a randomized controlled trial (RCT) (Prescribed Exercise after Chemotherapy (PEACH)) [17]. The PEACH examined the effect of an 8-week aerobic exercise intervention on physical activity, aerobic fitness and quality of life in a heterogeneous group of cancer survivors, 2–6 months post-chemotherapy. Breast cancer survivors who had consented to the PEACH trial were eligible to participate in the current study. All other inclusion and exclusion criteria were as per the PEACH trial [17]. Ethical approval was granted by the hospital Research Ethics Committee.

Protocol

Participants attended the laboratory for testing on three occasions; baseline (pre-randomisation), immediately post-intervention (8-week visit) and 3 months post-intervention (3-month visit). Participants were randomized to either an exercise group (EG) or control group (CG) following the baseline visit, as per the PEACH trial using a computer-generated random numbers list (GraphPad Software, San Diego, CA). Assessments were completed by the same researcher at every visit who was blinded to the participants' group assignment. Demographic details, medical and cancer treatment history were obtained from medical charts and through participant interview.

Exercise intervention

The intervention has been described in full previously [17]. The EG completed an 8-week, twice weekly supervised aerobic intervention and a home-exercise programme. Fitness levels were classified as "Poor", "Fair" or "Average" from pre-determined cut-off values, as per baseline fitness tests. Participants with "Poor" fitness started the intervention at an intensity range of 35–55 % heart rate reserve (HRR), participants with "Fair" fitness started at 40–60 % HRR, while those classified as "Average" commenced at 45–65 % HRR. Aerobic intensity zones were progressed by 5 % HRR every 2 weeks. Class duration increased by 3 min every 2 weeks, alternate to the increase in exercise intensity, from 21 min in week 1 to 42 min in week 8. Heart rate (HR) was monitored using polar HR monitors (Polar FT4F Heart Rate Monitor). Participants rotated between three aerobic exercise stations during the class (stationary bike, treadmill, rowing ergometer).

The intensity of the home-exercise programme progressed in the same manner as the supervised class. Participants wore HR monitors to monitor compliance. Initially, participants exercised at home on one day of the week, increasing to 5 days per week at study completion. The CG did not engage in a structured exercise programme but were offered an exercise advice session following the final assessment.

Assessments

Body composition analysis and blood pressure

Anthropometric data were collected following a 12-h fast. Standing height was measured, barefoot, to the nearest millimetre using a SECA stadiometer. Body composition,

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including body weight, was estimated using a bioimpedance analyser, the Tanita MC 180 MA Multi-Frequency Body Composition Analyzer (Tanita Corp, Tokyo, Japan). Waist circumference was measured using a flexible measuring tape, in duplicate, to the nearest millimetre, at the mid-point between the top of the iliac crest and the last rib. Resting blood pressure was measured using the auscultatory method following a 5-min rest period. Blood pressure measurements were taken on the non-surgical side, in duplicate and averaged for data entry.

Venous blood sampling

Venous blood samples were collected in the morning following a 12-h fast. Participants were asked to refrain from moderate-vigorous intensity exercise for 24-h prior to collection. Samples were taken to measure glucose, insulin, lipid profile (total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides), glycosylated haemoglobin levels (HBA1c) and CRP. Insulin resistance was calculated using the Homeostatic Model Assessment (HOMA): [(fasting glucose (mmol/L)×fasting insulin (mU/L))/22.5] [18].

Metabolic syndrome classification

The metabolic syndrome was diagnosed in the presence of any three of the following: elevated waist circumference (≥80 cm); elevated triglycerides (≥1.7 mmol/L) or drug therapy for lipid abnormalities; reduced HDL-C (<1.3 mmol/L) or drug therapy for lipid abnormalities; elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) or antihypertensive medication; elevated fasting glucose (≥100 mg/dL) or glucose-lowering medication [13].

Physical activity

Physical activity was measured objectively using the triaxial RT3 activity monitor (Stayhealthy Inc. Montrovia, California, USA). Participants wore the monitor for 7 days, during waking hours, following each assessment. The validity [19] and reliability [20] of the accelerometer have been established. The RT3 is a reliable tool for assessing moderate-to-vigorous activity in overweight and obese adults [21] and has been used previously in our laboratory to monitor activity levels in cancer patients prior to surgery [22].

Physical activity was measured subjectively using the Godin Leisure Time Exercise Questionnaire, which records the frequency of strenuous, moderate and mild exercise bouts of at least 15 min duration. The validity and reliability of the questionnaire has been established [23] and it has been used in cancer survivors [24].

Dietary intake

Participants were asked to complete an estimated dietary record (Medical Research Council, UK) on three consecutive days comprising of 2 weekdays and 1 weekend day, within 1 week of providing the blood samples at each assessment. No specific diet was prescribed. Diaries were analysed using WISP (Tinuveil Software, Llanfechell, Anglesey, UK) nutrition analysis programme.

Statistical analysis

Data was analysed using an intention-to-treat analysis with SPSS version 18.0 software (SPSS, Inc., Evanston, IL). The last-observation-carried forward procedure was used for missing variables. Secondary analysis examined if outcomes were influenced by adherence to the programme. Participants were grouped into two categories; adherence to >90 % of the exercise class or attended all three CG assessments (per-protocol analysis) or those who either dropped out or adhered to <90 % of the exercise class. Distributions were checked for normality using the K-S normality test.

Baseline characteristics were compared using independent sample *t* tests for continuous variables and Pearson chi-squared and Fisher's exact tests for categorical variables. Log transformations were applied to non-parametric variables. Changes in endpoints were examined using general linear model repeated-measures ANOVA. Mean changes in variables from baseline to 8 weeks and from baseline to 3 months are described with 95 % confidence intervals (95 % CI). The lowest detectable value for CRP was 1 mg/L and therefore results <1 mg/L were assigned a value of 1 mg/L.

One participant was prescribed Metformin following baseline assessment and was excluded from analysis of metabolic variables. Another participant with a baseline CRP value over tenfold higher than subsequent results was excluded from CRP analysis as this result most likely represented an acute inflammatory event. Non-normally distributed data was examined using the Wilcoxon test. Statistical significance was set at $p<0.05$.

Results

Participants were recruited from St. James's Hospital, Dublin, between March 2010 and January 2011. Forty-three participants were enrolled onto the PEACH trial, 32 of whom with breast cancer and 26 consented to the current study. Baseline characteristics are described in Table 1. The two groups were similar for all demographics ($p<0.05$). All

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Table 1 Baseline demographic details

Variable	Total (n=26)	Exercise group (n=16)	Control group (n=10)	p value*
Demographics				
Age (years)	48.12 (8.75)	50.05 (8.27)	45.05 (9.04)	0.16
Menopausal status[a]				
Premenopausal	18 (69.2)	9 (56.3)	9 (90)	0.09
Postmenopausal	8 (30.8)	7 (43.8)	1 (10)	
Marital status				0.76
Married	14 (53.8)	9 (56.3)	5 (50)	
Single	12 (46.2)	7 (43.7)	5 (50)	
Ethnicity				1.00
Caucasian	25 (96.2)	15 (93.8)	10 (100)	
Asian	1 (3.8)	1 (6.3)	0	
Current smoker	7 (26.9)	3 (18.8)	4 (40)	0.37
Months since diagnosis	8.62 (1.13)	8.5 (1.16)	8.8 (1.14)	0.52
Months since chemotherapy	3.74 (1.06)	3.8 (0.97)	3.63 (1.24)	0.69
Cancer stage				
I	7 (26.9)	3 (18.8)	4 (40)	0.74
II	13 (50)	10 (62.6)	3 (30)	
III	6 (23.1)	3 (18.8)	3 (30)	
Surgery				
WLE	13 (50)	9 (56.3)	4 (40)	0.69
Mastectomy	13 (50)	7 (43.8)	6 (60)	
Axillary clearance	15 (57.7)	9 (56.3)	6 (60)	
Radiotherapy	24 (92.4)	15 (93.8)	9 (90)	1.00
Hormonal therapy	20 (76.9)	11 (68.8)	9 (90)	0.35
Tamoxifen	15 (57.6)	7 (43.8)	8 (80)	0.32
Aromatase inhibitors	5 (19.2)	4 (25)	1 (10)	
Additional therapies				
Trastuzumab	5 (19.2)	3 (18.8)	2 (20)	1.00
Lapatinib	1 (3.8)	0	1 (10)	

WLE Wide local excision

Data are presented as the mean (standard deviation) for continuous variables and as frequency (percentage) for categorical variables

[a]Refers to menopausal status at diagnosis

*p values comparing the exercise and control groups at baseline

participants received anthracycline and/or taxane containing adjuvant chemotherapy. Six participants, three per group, continued to receive anti-HER2 directed therapy during the intervention period.

Two participants dropped out of the EG due to time constraints. A further six adhered to <90 % of the exercise class but completed follow-up assessments. There were no differences between those who adhered to the exercise class and those who didn't in terms of cancer stage (p=0.74), time since completion of chemotherapy (p=0.69), baseline body mass index (BMI) (p=0.98) or baseline physical activity (p>0.05 for all activity domains). Two members of the CG didn't complete the final assessment due to illness unrelated to their breast cancer.

Metabolic and inflammatory biomarkers

At baseline, the metabolic syndrome was present in nine participants (EG: n=6, CG: n=3). Nineteen participants were centrally obese (waist circumference >80 cm), and there was no difference between the two groups (p=0.60). Groups were similar for systolic and diastolic blood pressure (p=0.96 and p=0.38 respectively), with three members of each group taking antihypertensive medications. Lipid profiles were significantly worse in the exercise group for both TC (p=0.002) and LDL-C (p=0.001). Dyslipidaemia (TC >5.2 mmol/L) was present in half the overall group (EG; n=11, CG; n=2) and two participants in the EG took lipid-lowering medication. Baseline glucose levels were <100 mg/dL (88.6 (7.6) mg/dL). Five participants in the EG were hyperinsulinemic (insulin >12 mU/L) versus one in the CG (p=0.06). Consequently, insulin resistance was significantly higher among exercisers (p=0.05). There were no baseline differences in CRP (p>0.05).

Results of the intention-to-treat analysis for metabolic parameters are presented in Table 2. Examination of the accompanying confidence intervals suggest significant within-group changes in a number of parameters; however, changes were not significant when groups were compared. Per-protocol analysis showed a significant (p=0.05)

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Table 2 Changes in metabolic biomarkers

Variable		Baseline	8 weeks	3 months	Δ0–8 weeks	Δ0–3 months	*p* value*
	N	Mean (SD)	Mean (SD)	Mean (SD)	Mean (95 % CI)	Mean (95 % CI)	
WC (cm)*							
Exercise group	16	87.4 (11.9)	85.6 (12.5)	86.2 (12.2)	−1.8 (−2.7 to −0.8)	−1.2 (−2.4 to 0.1)	0.45
Control group	10	85.1 (8.9)	84.8 (10.8)	84.8 (12.3)	−0.2 (−1.3 to 0.9)	−0.3 (−1.8 to 1.3)	
SBP (mmHg)*							
Exercise group	16	124.6 (11.5)	118.5 (16.5)	117.00 (14.2)	−6.1 (−8.4 to −3.7)	−7.6 (−9.7 to −5.5)	0.53
Control group	10	116.7 (10.9)	114.4 (9.5)	111.80 (12.8)	−2.3 (−4.9 to 0.4)	−4.9 (−7.9 to −1.7)	
DBP (mmHg)*							
Exercise Group	16	78.4 (10.7)	78.8 (9.7)	76.1 (7.8)	0.4 (−0.9 to 1.7)	−2.3 (−3.9 to −0.8)	0.71
Control Group	10	75.0 (6.4)	74.6 (4.4)	74.0 (7.2)	−0.4 (−2.5 to 1.7)	−1.0 (−3.4 to 1.4)	
TC (mmol/L)							
Exercise group	15	5.8 (1.0)	5.6 (1.1)	5.6 (0.9)	−0.2 (−0.4 to −0.0)	−0.2 (−0.4 to −0.1)	0.69
Control group	10	4.8 (0.5)	4.4 (0.7)	4.3 (0.6)	−0.4 (−0.6 to −0.2)	−0.5 (−0.6 to −0.3)	
HDL-C (mmol/L)*							
Exercise group	15	1.6 (0.6)	1.5 (0.4)	1.5 (0.3)	−0.0 (−0.1 to 0.1)	−0.1 (−0.2 to 0.1)	0.96
Control group	10	1.5 (0.5)	1.5 (0.5)	1.4 (0.4)	−0.1 (−0.1 to 0.01)	−0.1 (−0.1 to −0.01)	
LDL-C (mmol/L)							
Exercise group	14	3.5 (0.9)	3.4 (0.9)	3.3 (0.9)	−0.1 (−0.3 to 0.01)	−0.2 (−0.3 to −0.01)	0.78
Control group	10	2.6 (0.5)	2.3 (0.5)	2.3 (0.9)	−0.3 (−0.4 to −0.1)	−0.3 (−0.4 to −0.1)	
TC:HDL-C ratio							
Exercise group	15	3.9 (0.9)	3.89 (1.2)	3.8 (1.0)	−0.1 (−0.2 to 0.1)	−0.2 (−0.3 to −0.01)	0.91
Control group	10	3.4 (0.8)	3.2 (0.8)	3.2 (0.8)	−0.4 (−0.3 to 0.01)	−0.2 (−0.4 to −0.01)	
TG (mmol/L)*							
Exercise Group	15	1.4 (0.7)	1.4 (0.9)	1.4 (0.6)	−0.02 (−0.2 to 0.2)	−0.02 (−0.3 to 0.1)	0.37
Control group	10	1.5 (0.8)	1.3 (0.8)	1.2 (0.7)	−0.2 (−0.2 to −0.1)	−0.3 (−0.4to −0.2)	
Fasting glucose (mg/dL)*							
Exercise group	15	88.3 (7.7)	88.9 (6.1)	90.4 (9.5)	0.6 (−0.9 to 2.2)	2.0 (−0.3 to 4.3)	0.84
Control group	10	88.9 (7.9)	88.5 (7.9)	91.1 (9.9)	−0.4 (−2.2 to 1.4)	2.2 (−0.3 to 4.7)	
Fasting insulin(mU/L)							
Exercise group	14	10.5 (4.9)	10.4 (4.6)	10.2 (4.5)	−0.1 (−1.2 to 1.1)	−0.3 (−1.6 to 1.0)	0.51
Control group	9	6.9 (2.8)	9.1 (4.5)	7.4 (2.8)	2.2 (1.1 to 3.4)	0.5 (−0.8 to 1.8)	
Insulin resistance (HOMA-IR)							
Exercise group	14	2.3 (1.1)	2.3 (1.1)	2.3 (1.0)	0.1 (−0.1 to 0.3)	0.02 (−0.3 to 0.4)	0.66
Control group	9	1.5 (0.6)	1.9 (0.9	1.7 (0.8)	0.5 (0.3 to 0.7)	0.5 (−0.8 to 1.8)	
HBA1c (mmol/mol)							
Exercise group	15	35.9 (2.3)	34.1 (2.0)	35.7 (2.0)	−1.8 (−2.5 to −1.2)	−0.3 (−0.9 to 0.3)	0.07
Control group	9	35.6 (2.9)	35.9 (3.6)	36.9 (3.9)	0.3 (−0.5 to 1.2)	1.3 (0.6 to 2.1)	

WC waist circumference; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *TC* total cholesterol; *HDL-C* high-density lipoprotein cholesterol; *LDL-C* low-density lipoprotein cholesterol; *TG* triglycerides; *HBA1c*: glycosylated haemoglobin

p for MANOVA with repeated measures comparing changes between the exercise group and the control group from baseline to 3 months post intervention (time*group effect)

*Represents features of the metabolic syndrome

decrease in waist circumference in the EG versus control subjects (EG; mean change baseline to 3 months −4.63 cm (95 % CI, −5.7 to −3.6), CG; mean change baseline to 3 months −0.30 (95 % CI, −2.3 to 1.7)).

CRP decreased by 1.53 mg/L (95 % CI, −2.39 to −0.66) at 8 weeks and by 0.65 mg/L (95 % CI, −1.66 to 0.35)) at 3 months post-intervention in the EG, while it increased by 0.38 mg/L (95 % CI, 0.03 to 0.74) at 8 weeks and decreased by 0.01 mg/L (95 % CI, −0.41 to 0.39) at 3 months in the CG; however, changes were not different between groups (p= 0.07 and p=0.69, respectively).

Body composition and dietary intake

Groups were similar at baseline for all body composition measures (p>0.05). The majority of participants were

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overweight ($n=13$) or obese ($n=6$). No changes occurred in body weight ($p=0.53$), BMI ($p=0.43$), percentage body fat ($p=0.25$) or muscle mass ($p=0.46$). There were no further changes with per-protocol analysis. Similarly, energy intake at baseline was 7.62 (1.69) MJ and did not change during the study ($p=0.37$).

Physical activity

Groups were similar at baseline for subjectively and objectively measured physical activity. Neither the Godin questionnaire nor the RT3 accelerometer showed changes across any activity domain (Table 3). Per-protocol analysis showed significant improvements in subjectively reported "total weekly" ($p=0.005$) activity but not in objectively measured data.

Analysis of objectively measured activity indicated that throughout the study, over 50 % of time was spent sedentary (baseline 52 %, 8 weeks 51 % and 3 months 50 %). Light intensity activity was high (baseline 42 %, 8 weeks 43 % and 3 months 42 %), while moderate-vigorous intensity time remained low (baseline 6 %, 8 weeks 6 % and 3 months 8 %) (Figs. 1 and 2). Data were further examined for adherence to physical activity guidelines (30 min moderate intensity activity (accumulated in ≥10 min bouts), 5 days per week [25]). At baseline, five participants were exercising to recommended activity guidelines (EG: $n=3$, CG: $n=2$), with no change post-intervention.

Discussion

This pilot study demonstrated that an 8-week aerobic exercise intervention did not improve features of the metabolic syndrome, CRP or anthropometric variables in breast cancer survivors. Sub-analysis of those with >90 % adherence to the exercise class demonstrated significant improvements in waist circumference and subjectively measured "total weekly" physical activity.

Table 3 Changes in physical activity

Activity intensity		Baseline	8 weeks	3 months	Δ0–8 weeks	Δ0–3 months	*p* value
	N	Mean (SD)	Mean (SD)	Mean (SD)	Mean (95 % CI)	Mean (95 % CI)	
Godin questionnaire							
Light METS							
Exercise group	16	4.5 (6.6)	5.4 (7.6)	7.1 (8.2)	0.9 (−0.9 to 2.8)	2.6 (0.3 to 4.9)	0.29
Control group	10	6.9 (11.0)	5.1 (8.4)	4.8 (8.0)	−1.8 (−5.3 to 1.7)	−2.1 (−6.7 to 2.5)	
Moderate METS							
Exercise group	16	14.7 (18.5)	16.1 (19.3)	16.7 (17.1)	1.4 (−0.4 to 3.2)	2.0 (−0.2 to 4.3)	0.19
Control group	10	21.3 (9.8)	14.8 (10.4)	15.0 (13.9)	−6.5 (−10.5 to −2.5)	−6.3 (−13.2 to 0.7)	
Strenuous METS							
Exercise group	16	3.9 (9.8)	17.2 (20.9)	7.3 (14.8)	13.2 (8.2 to 18.1)	3.4 (−1.4 to 8.2)	0.83
Control group	10	0.0 (0.0)	0.0 (0.0)	4.5 (14.2)	0.0 (0.0 to 0.0)	4.5 (0.0 to 9.0)	
Total weekly METS							
Exercise group	16	23.1 (19.8)	38.7 (26.9)	31.2 (21.1)	15.6 (9.5 to 21.6)	8.0 (3.3 to 12.8)	0.06
Control group	10	28.2 (11.2)	19.9 (11.3)	24.3 (11.9)	−8.3 (−11.3 to −5.3)	−3.9 (−9.5 to 1.8)	
RT3 activity monitor							
Sedentary (min/week)							
Exercise group	16	427.5 (145.4)	446.0 (127.0)	438.0 (121.6)	18.5 (−9.3 to 46.1)	10.5 (−14.4 to 35.3)	0.53
Control group	9	405.6 (146.7)	385.8 (107.9)	359.5 (149.3)	−19.8 (−68.1 to 28.4)	−46.1 (−110.8 to 18.5)	
Light intensity (min/week)							
Exercise group	16	332.6 (69.7)	318.1 (72.1)	327.2 (70.5)	−14.5 (−24.2 to −4.9)	−5.5 (−22.6 to 11.7)	0.36
Control group	9	339.7 (128.1)	346.7 (101.0)	315.7 (110.1)	6.9 (−15.0 to 28.9)	−24.1 (−58.4 to 10.3)	
Moderate intensity (min/week)							
Exercise group	16	31.8 (17.0)	30.7 (15.6)	38.4 (25.9)	−1.1 (−4.4 to 2.2)	6.75 (0.9 to 12.3)	0.61
Control group	9	38.9 (21.04	31.0 (15.6)	53.4 (53.9)	−7.9 (−12.0 to −3.7)	14.5 (−5.6 to 10.3)	
Vigorous intensity (min/week)							
Exercise group	16	24.7 (53.5)	15.7 (15.7)	15.8 (22.2)	−9.0 (−22.5 to 4.4)	−8.9 (−23.2 to 5.4)	0.49
Control group	9	9.5 (11.8)	11.2 (13.5)	19.8 (29.4)	1.7 (0.1 to 3.3)	10.3 (−0.04 to 20.6)	

p for MANOVA with repeated measures comparing changes between the exercise group and the control group from baseline to 3 months post intervention (time*group effect)

METS metabolic equivalent; *Min* minutes

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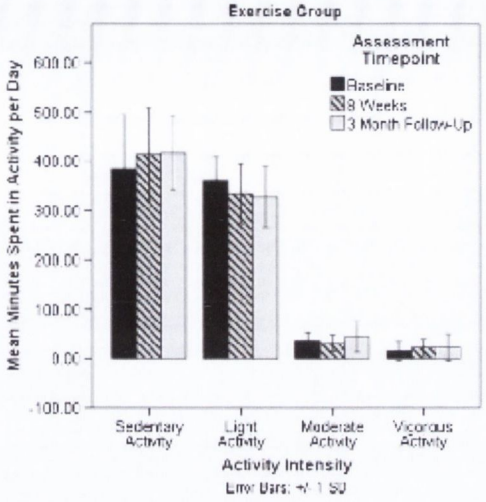


Fig. 1 Exercise group mean (SD) minutes spent in each activity domain per day

This is the first study to measure metabolic syndrome in breast cancer survivors in the acute stage post adjuvant chemotherapy. The majority of participants were overweight or obese ($n=19$) and/or centrally obese ($n=19$) at baseline and nine presented with the metabolic syndrome. The metabolic syndrome, characterised by abdominal obesity and insulin resistance [13], is identified as one of the potential

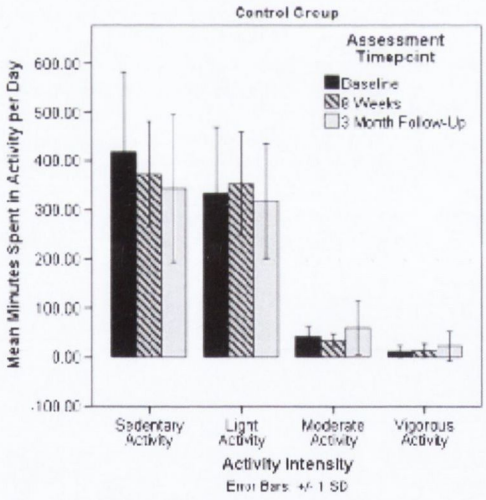


Fig. 2 Control group mean (SD) minutes spent in each activity domain per day

links between obesity and cancer [26]. The metabolic syndrome as a collective unit and its individual components have been associated with increased breast cancer risk [6, 27, 28] as well as poorer breast cancer outcomes [15, 29].

In the current study, despite marked levels of central obesity, insulin resistance and CRP values were low, characterising an obese but metabolically healthy state [30]. Visceral adipose tissue is a multi-functional endocrine organ, secreting of a number of proteins including tumor necrosis factor-α, interleukin-6, leptin, insulin-like growth factor-I (IGF-I), resulting in a pro-inflammatory, insulin-resistant environment [14]. Prior to chemotherapy, the majority of participants in this trial were premenopausal, a group at high risk of chemotherapy-related weight gain [9]. The level of obesity observed may reflect recent weight gain among this group which has yet to have an adverse impact on metabolic and inflammatory pathways. In long-term breast cancer survivors, increasing concentrations of C-peptide, leptin, IGFs and CRP have been associated with increasing BMI ($p<0.05$) [31, 32]. Thompson and colleagues [33] reported that the metabolic syndrome was present in 54.8 % of overweight/obese breast cancer survivors, 96 % of whom were centrally obese, with mean CRP levels of 5.1 mg/dL, suggestive of chronic low-grade inflammation.

Physical activity can improve breast cancer related outcomes [3–5], most likely through alterations in insulin and inflammatory pathways and improved anthropometrics [12]. While a number of interventions have examined the effect of exercise on individual components of the metabolic syndrome among breast cancer survivors [24, 34–37], this was the first study to consider the syndrome as a unit. While no changes in metabolic or inflammatory markers were observed, per-protocol analysis revealed a significant decrease in waist circumference. Previous studies have also reported reductions in waist circumference [38, 39]; however, unlike the current study, these have been limited due to non-randomized designs [38] and reporting of waist-to-hip ratio, not waist circumference [39]. Other studies in this population have reported decreases in triglycerides [24], systolic blood pressure [40, 41] and IGFs [34, 37, 42] with both aerobic and resistance training. Four RCTs have examined the effect of both aerobic and resistance exercise on markers of insulin resistance and have observed no changes in fasting glucose, fasting insulin or insulin resistance [34–37]. Only one other intervention measured CRP and reported no change [24]. In non-breast cancer populations, a number of RCTs have reported significant decreases in intra-abdominal and subcutaneous fat, insulin, insulin resistance and CRP [43–45], following year-long moderate-to-vigorous intensity aerobic interventions in overweight/obese postmenopausal women.

Whether improvements in metabolic parameters are stimulated by physical activity, without concurrent fat loss, is

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unclear. In the present study, no change in BMI or percentage body fat was observed. Generally, it appears that some fat loss is necessary for changes to occur; however, the extent to which visceral fat can be reduced is greatly influenced by incorporating high-intensity exercise into diet interventions [11]. Weight loss stimulated by diet alone reduces both fat-free mass and fat mass, having little effect on visceral fat [11]. Higher-intensity aerobic exercise specifically targets visceral fat deposits [11, 45]. The current study monitored dietary intake using food diaries and found no changes during the study period, suggesting that exercise stimulated the decrease in waist circumference observed in the per-protocol analysis.

A major strength of the current study is the use of accelerometry to objectively measure physical activity, allowing for accurate quantification of activity intensity and duration. A high percentage of objectively measured sedentary time was observed in both groups at all assessment stages (Figs. 1 and 2). This is consistent with other studies which show that breast cancer survivors spend the majority of time inactive [46]. Breast cancer patients significantly reduce activity levels upon diagnosis and rarely return to pre-morbid levels [47]. Objectively measured sedentary time is significantly associated with BMI, waist circumference, CRP, insulin and insulin resistance in postmenopausal women while moderate-to-vigorous intensity activity is inversely related to these variables [48]. These relationships were not observed in the current study. Subjectively, participants in the per-protocol analysis study reported significant increases in "total weekly" physical activity that was not reflected by increases in objectively measured physical activity. As the group remained predominantly sedentary throughout the study period, even light intensity activity may have been perceived at a higher intensity, leading to inaccurate and exaggerated reporting.

Reasons for the lack of change in the primary outcomes require consideration. The short duration of this intervention may have been insufficient to promote meaningful changes in lifestyle activity habits. The current study did not significantly reduce time spent sedentary nor did it improve adherence to physical activity guidelines, suggesting that participants compensated for exercise with prolonged rest periods. The high percentage of inactivity may reflect some side-effects of chemotherapy treatments such as cancer-related fatigue or reduced cardiorespiratory fitness, which may have a strong influence over a group in the acute stage post chemotherapy. However, all these subjects were able to participate in the exercise intervention, suggesting that they were not unduly fatigued.

The timing of the intervention may also have been unsuitable due to treatment related issues such as adjusting to hormonal therapy medication, anti-Her directed therapies during the intervention period and continuing medical appointments. Previous interventions have exercised participants during chemotherapy [41] to several years post-diagnosis [35, 38]. Courneya and Friedenreich [49] describe the 3–6-month period post-cessation of cancer treatment as the "rehabilitation period". Although the current study included participants within this period, adherence to the protocol was poor (per-protocol analysis excluded 10/26 participants), suggesting that not all breast cancer survivors appear ready for such a demanding intervention so early in their recovery.

There are a number of limitations to this intervention that warrant discussion. Firstly, this study was designed as an exploratory pilot study. An inherent limitation of a pilot study is a small sample size, such as observed in the current study, which results in issues such as reduced statistical power to detect significant change. In addition, the study was set as an ancillary study to a larger RCT, resulting in uneven group assignments and statistically significant different between groups. Finally, the short duration of the intervention may have been insufficient to elicit change in the variables measured. While these issues limit the interpretation of results and the conclusions that are drawn, the study provides rationale for developing a larger RCT to explore the questions raised by this study.

Conclusions

The results from this eight-week aerobic exercise pilot intervention did not elicit significant improvements in metabolic or inflammatory biomarkers suggested to play a role in breast cancer risk, in breast cancer survivors, 2–6 months post-chemotherapy. While results may have been limited by the small sample size, higher adherence to the exercise class did stimulate significant decreases in waist circumference and increased subjectively measured "total weekly" activity. The lack of change may be due to the short duration of the intervention resulting in a failure to change in lifestyle activity habits. The results from this pilot study would suggest that future trials with breast cancer survivors in the early stages post-treatment should include a gradual build-up in aerobic intensity to accommodate on-going treatment related issues and be of longer duration to promote long-term changes in lifestyle activity habits. A larger RCT examining this issue is warranted.

Conflict of interest Disclosures: None

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Study IIb Publication: Nutrition Journal

Guinan et al. Nutrition Journal 2013, 12:99
http://www.nutritionj.com/content/12/1/99

NUTRITION JOURNAL

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The presentation of metabolic dysfunction and the relationship with energy output in breast cancer survivors: a cross-sectional study

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Abstract

Background: Breast cancer prognosis can be adversely influenced by obesity, physical inactivity and metabolic dysfunction. Interventions aimed at improving surrogate markers of breast cancer risk such as insulin resistance may result in improved breast cancer outcomes. The design of such interventions may be improved through increased understanding of metabolic presentation in this cohort. This cross-sectional study aimed to characterise the metabolic profile of breast cancer survivors relative to abdominal obesity and insulin resistance. A secondary aim was to compare measures of energy output across these groups.

Methods: Sixty-nine women (mean (SD) age 53.43 (9.39) years) who had completed adjuvant chemotherapy and radiotherapy for breast cancer were recruited. All measures were completed during one assessment conducted 3.1 (1.0) years post diagnosis. Body composition was measured by bioimpedance analysis and waist circumference (WC). Fasting (12 hour) blood samples were drawn to measure lipid profile, glucose, insulin, glycosylated haemoglobin A1c (HBA1c) and C-reactive protein (CRP). Insulin resistance was estimated by the homeostatic model assessment index (HOMA-IR)). Energy output was evaluated by resting metabolic rate (RMR) measured by indirect calorimetry and physical activity measured by accelerometry. Characteristics were compared across four groups (1. WC <80 cm, not insulin resistant; 2. WC 80–87.9 cm, not insulin resistant; 3. WC >88 cm, not insulin resistant; 4. WC >80 cm, insulin resistant) using ANOVA ($p < 0.05$).

Results: Group 4 was characterised by significant disturbances in measures of glucose metabolism (glucose, insulin, HOMA-IR and HBA1c) and raised CRP compared to other groups. Group 4 also displayed evidence of dyslipidemia and higher body composition values compared to Groups 1 and 2. Both absolute and adjusted RMR were significantly higher in the Group 4 versus all other groups. Physical activity levels were similar for all groups.

Conclusions: The results from this study suggest that participants who were both centrally obese and insulin resistant showed evidence of dyslipidemia, low-grade inflammation and glucose dysregulation. Metabolic profiles of participants who were centrally obese only were not significantly different from lean participants. Consideration of baseline metabolic presentation may be useful when considering the therapeutic targets for future interventions in this cohort.

Keywords: Breast cancer, Insulin resistance, Metabolic syndrome, Resting metabolic rate, Physical activity, Prognosis

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Introduction

Metabolic dysfunction, including the metabolic syndrome (MetSyn) and insulin resistance, is a long-term complication of curative treatment for many cancers including breast [1], prostate [2] and testicular [2]. There is increasing evidence that metabolic disturbance, characterised by insulin resistance [3,4], altered adipokines [3] and chronic low-grade inflammation [5], is associated with increased breast cancer and all-cause mortality and a higher risk of breast cancer recurrence. Breast cancer survivors represent a unique group who endure several treatment associated alterations in lifestyle habits including weight gain [6] and reduced physical activity levels [7], along with high risk of ovarian failure in premenopausal women [8], leading to early onset menopause and consequential worsening metabolic profiles [9]. However, not all breast cancer survivors are overweight and inactive and not all overweight and obese women are metabolically unhealthy [10]. The presentation of metabolic disturbance varies greatly among obese individuals [11] and there is a need for greater understanding of the characteristics of metabolic dysfunction in breast cancer survivors in order to design targeted weight-loss and exercise interventions.

The classification of metabolically unhealthy has not been standardised due to the ever-evolving definition of the MetSyn and the ongoing debate regarding the inclusion of a measure of insulin resistance in the syndrome definition [12-14]. The current MetSyn definition includes central obesity, elevated fasting glucose, atherogenic dyslipidemia and hypertension [12]. Insulin resistance is a central component of the MetSyn and is arguably one of the most important features of metabolic dysfunction in relation to cancer due to the mitogenic effects of insulin on breast cancer cells [15] and the substantial evidence linking hyperinsulinemia and insulin resistance to cancer prognosis [3]. Equally central obesity, characterised by increased visceral fat accumulation, is considered a core component of the MetSyn and is associated with the secretion of many pro-tumour products including pro-inflammatory cytokines (interleukin (IL)-6 and tumor necrosis factor (TNF)-α), adipokines and sex hormones [16]. There is a lack of consensus regarding the cut-point for central obesity, as measured by waist circumference (WC). Generally, 80 cm is the accepted cut-point for central obesity in women while ≥88 cm is associated with substantially increased disease risk [12]. While most individuals with the MetSyn are also insulin resistant [13], the relationship between insulin resistance and atherogenic dyslipidemia and hypertension is unclear, particularly due to the inclusion of drug therapies for lipid abnormalities and hypertension in the most recent MetSyn definition. In breast cancer survivors, it may be useful to examine metabolic dysfunction in terms of insulin resistance and visceral obesity as these measures may be potentially more predictive of cancer-specific outcome.

Long-term obesity is essentially due to an imbalance between energy intake and energy output. Resting metabolic rate (RMR) is the largest component of energy expenditure [17] and has been shown to be altered in the presence of metabolic abnormalities [18]. Equally habitual physical activity, which represents up to 15% of total energy expenditure, is a key factor in the development and management of the MetSyn [14] and may positively influence breast cancer prognosis [19]. The aim of the current study was to characterise the metabolic profiles of breast cancer relative to worsening central obesity and insulin resistance. A secondary aim was to compare energy output across these groups and to examine associations between energy expenditure and metabolic parameters.

Methods

Study design and participants

The study was designed as a cross-sectional study. A convenience sample of breast cancer survivors were recruited from oncology clinics at St. James's Hospital, Dublin Ireland from May 2011 to June 2012. Participants were eligible for the study if they had completed all adjuvant breast cancer treatment including at least one of the following: chemotherapy, radiotherapy and anti Her-2 directed biological therapy. Those continuing to take adjuvant hormonal therapy were eligible to participate. Evidence of active or recurrent disease, co-morbidities including type II diabetes mellitus (T2DM) or age >70 years were considered exclusion criteria. Ethical approval was granted by the hospital research ethics committee and all participants provided written, informed consent prior to measurements.

Data collection

Body composition, including body weight, percentage body fat and fat free mass (FFM), was estimated by bioimpedance analysis using the Tanita MC 180 MA Multi-Frequency Body Composition Analyzer (Tanita Corp, Tokyo, Japan). Standing height was measured barefoot to the nearest millimetre using a SECA stadiometer. WC was measured using a flexible measuring tape, in duplicate, to the nearest millimetre, at the midpoint between the top of the iliac crest and the last rib [20]. Blood pressure measurements were taken on the non-surgical side in duplicate using the auscultatory method. Fasting (12 hour) venous blood samples were drawn to measure glucose, insulin, lipid profile (total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG)), (glycosylated haemoglobin A1c (HBA1c)) and C–Reactive Protein (CRP). Insulin

Resistance was calculated using the Homeostatic Model Assessment Index (HOMA-IR): [(fasting glucose ($mmol.L^{-1}$) × fasting insulin ($mU.L^{-1}$)/22.5] [21]. Insulin resistance was defined as the 75th percentile of HOMA-IR of participants studied (HOMA-IR = 2.45) [22]. The MetSyn was diagnosed in the presence of any three of the following: elevated WC (≥80 cm); elevated TG (≥1.7 $mmol.L^{-1}$) or drug therapy for lipid abnormalities; reduced HDL-C (<1.3 $mmol.L^{-1}$) or drug therapy for lipid abnormalities; elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) or antihypertensive medication; elevated fasting glucose (≥5.6 $mmol.L^{-1}$) or glucose-lowering medication [12].

Insulin was measured by electrochemiluminescence immunoassay (Elecsys Insulin Assay, Roche Dianostics GMBH). Enzymatic, colorimetric assays (Roche/Hitachi **cobas c** systems) were used to measure fasting glucose, TC, HDL-C and TG. LDL was calculated using the Friedewald equation. High performance liquid chromatography (Arkray/Adams A1c HA-8160 Analyser System) was used to measure HBA1c and CRP was measured by particle enhanced immunoturbidimetric assay (Roche/Hitachi **cobas c** systems). Laboratory analyses were carried out at the national biochemistry reference laboratory at St. James's Hospital, Dublin.

Energy output was measured by RMR and habitual physical activity. RMR and respiratory quotient (RQ) were measured by indirect calorimetry using the COSMED Metabolic Quart according to the guidelines of Compher and colleagues [23]. Measurements were completed with the participant in the supine position following a 10–20 minute rest period. Respiratory gas exchange was measured continuously for 20 minutes, excluding the first five minutes of data, using a canopy collection device. Data was obtained from at least 5 minutes of a stable measurement (coefficient of variation <10% (variation in oxygen consumption (VO2) ≤10%; variation in carbon dioxide production (VCO2) ≤10%). RMR was expressed in absolute values ($kJ.day^{-1}$) and as RMR adjusted for FFM ($kJ.day^{-1}.kg^{-1}$) [24]. Physical activity was measured objectively using the RT3 activity monitor (Stayhealthy Inc Montrovia, CA, USA). The RT3 is a valid [25], reliable [26] tool and was used to quantify percentage time spent in each domain of activity and to monitor adherence to physical activity guidelines (≥30 minutes of moderate intensity activity, accumulated in ≥10 minute bouts, five days per week [27]). Activity intensity was defined using validated cut-points [25] and sedentary behaviour was defined as an activity count ≤100 [28]. Habitual activity patterns in the preceding year were measured subjectively using the Minnesota Leisure Time Physical Activity Questionnaire (MLTPAQ). The MLTPAQ is a valid [29] interview-administered questionnaire designed to measure the frequency of leisure-time and recreational activities in the preceding year and combines this information with intensity scores to measure physical activity in terms of activity metabolic index (AMI) and expressed as metabolic equivalent (MET)-minutes per day ($MET\text{-}min.day^{-1}$).

Data was analysed using SPSS version 18.0 software (SPSS, Inc, Evanstron, IL). Distributions were checked for normality using the K-S test and log-transformations were applied to non-normally distributed data. Data are presented as mean ± standard deviation. Participants were classed into four subgroups: Group 1: healthy WC (<80 cm) and not insulin resistant; Group 2: elevated WC (WC 80–87.9 cm) and were not insulin resistant; Group 3: substantially increased waist circumference (WC >88 cm) and not insulin resistant; and Group 4: both centrally obese and insulin resistant. With the exception of one participant who had a waist circumference of 82.4 cm, all women in Group 4 had a WC >88 cm. Anthropometric, metabolic and energy output variables were compared between the four groups using analysis of variance (ANOVA). Significance was set at $p < 0.05$. Post hoc analysis was completed using Tukey's HSD method when a significant group effect was observed. Kruskal-Wallis non-parametric ANOVA was used to compare distributions between non-parametric data (BMI, glucose, HBA1c and CRP) and post hoc analysis was completed using Mann–Whitney U test for comparison between pairs of group Corrections were made for multiple comparisons using the bonferroni correction ($p < 0.01$). Correlations between energy output and metabolic variables were examined using Pearson Product Moment Correlation Coefficients (PPMCC) for normally distributed data and Spearman's rho for non-normally distributed data. The lowest detectable value for CRP was 1 $mg.L^{-1}$ and therefore results <1 $mg.L^{-1}$ were assigned a value of 1 $mg.L^{-1}$. Values >15 $mg.L^{-1}$ were excluded these most likely represented an acute inflammatory event [30].

Results

Sixty nine participants (mean (SD) age 53.43 (9.39)) entered the study. The mean time since diagnosis for the overall group was 3.1 (1.0) years. Participant demographics and treatment details are shown in Table 1. Groups were similar for all demographics ($p > 0.05$). The majority of participants were treated with adjuvant chemotherapy using standard anthracycline and taxane based regimens. Almost 80% of the group were taking adjuvant hormonal therapy.

Anthropometric and metabolic parameters are shown in Table 2. Women in Group 3 and Group 4 demonstrated significantly higher anthropometric measures, characterised by significantly greater body weight ($p < 0.001$ vs. Group 1 and $p < 0.002$ vs. Group 2), BMI ($p < 0.001$ for both), WC ($p < 0.001$ for both) and percentage body fat ($p < 0.001$ for

Table 1 Participant demographics

Characteristic	Group 1 (n = 19)	Group 2 (n = 16)	Group 3 (n = 16)	Group 4 (n = 18)
Participant demographics				
Age (years)	52.04 (11.7)	50.27 (8.48)	55.65 (9.49)	55.59 (6.69)
Time since diagnosis (years)	3.39 (0.90)	2.69 (0.92)	3.19 (0.85)	3.14 (1.22)
Menopausal status*				
Premenopausal	11 (58%)	11 (69%)	8 (50%)	8 (44%)
Postmenopausal	8 (42%)	5 (31%)	8 (50%)	10 (56%)
Marital status				
Married	16 (84%)	10 (63%)	11 (69%)	11 (61%)
Single	3 (16%)	6 (37%)	5 (31%)	5 (39%)
Smoking history				
Current smoker	1 (5%)	9 (56%)	2 (13%)	6 (33%)
Cancer details				
Cancer stage				
I	6 (32%)	4 (25%)	5 (31%)	4 (22%)
II	9 (47%)	9 (56%)	8 (50%)	10 (56%)
III	4 (21%)	3 (19%)	3 (19%)	4 (22%)
Estrogen receptor positive	14 (74%)	14 (88%)	14 (88%)	14 (78%)
Surgery				
Wide local excision	9 (47%)	5 (31%)	10 (63%)	7 (39%)
Mastectomy	10 (53%)	11 (69%)	6 (38%)	11 (61%)
Axillary clearance	7 (37%)	9 (38%)	4 (25%)	10 (56%)
Chemotherapy	17 (90)	14 (88%)	13 (81%)	16 (89%)
Radiotherapy	15 (79)	11 (69%)	14 (88%)	16 (89%)
Hormone therapy				
Tamoxifen	9 (47%)	7 (44%)	12 (75%)	7 (39%)
Aromatase inhibitor	5 (26%)	6 (38%)	2 (13%)	7 (39%)
Biological therapy				
Herceptin	3 (16%)	2 (13%)	1 (6%)	2 (11%)

Data are presented as mean (standard deviation) for continuous variables and as frequency (percentage) for categorical variables.
*Refers to menopausal status at diagnosis.

both) when compared to Group 1 and Group 2. FFM was significantly higher in both Group 3 ($p = 0.002$) and Group 4 ($p = 0.001$) compared to Group 1. Metabolic profiles were significantly worse in Group 4 than other groups characterised by significantly lower HDL-C (Group 4 vs. Group 1 $p = 0.02$; vs. Group 2 $p = 0.008$), elevated TG (Group 4 vs. Group 1 $p < 0.001$; vs. Group 2 $p = 0.009$), measures of insulin-glucose metabolism (fasting glucose, fasting insulin, HOMA-IR and HBA1c, $p < 0.001$ vs. all groups) and raised CRP (Group 4 vs. Group 1 $p < 0.001$; vs. Group 2 $p = 0.005$; vs. Group 3 $p = 0.01$). Metabolic profiles did not vary between non-insulin-resistant groups.

Energy output variables across the four groups are presented in Table 3. Absolute RMR ($kJ.day^{-1}$) was significantly higher in Group 4 compared to all other groups (vs. Group 1 $p < 0.001$, vs. Group 2 $p = 0.005$ and vs. Group 3 $p = 0.05$). Results remained significant when RMR was adjusted for FFM ($kJ.day^{-1}.kg^{-1}$) (Group 4 vs. Group 1 $p < 0.001$; vs. Group 2 $p = 0.005$; vs. Group 3 $p = 0.05$). Adjusted RMR was significantly correlated with a number of metabolic features including WC ($r = 0.32$; $p < 0.01$), HOMA-IR ($r = 0.48$; $p < 0.001$), CRP ($rho = 0.31$; $p = 0.02$), HDL-C ($r = -0.31$; $p = 0.02$), TG ($r = 0.34$; $p = 0.009$). Adjusted RMR was not correlated with either measure of glucose metabolism (glucose or HBA1c) or blood pressure. Neither objective nor subjective habitual activity varied between groups. Regardless of whether measured by objective or subjective methods, physical activity did not display any correlations with metabolic parameters.

Table 2 Comparison of anthropometric and metabolic variables across groups

Characteristic	Group 1 (n = 19)	Group 2 (n = 16)	Group 3 (n = 16)	Group 4 (n = 18)
Age (years)	52.16 (11.69)	50.37 (8.52)	55.56 (9.42)	55.61 (6.77)
Anthropometry				
Body weight (kg)	59.73 (6.76)	66.22 (5.68)	79.55 (12.58)[a, b]	79.61 (13.85)[a, b]
BMI (kg.m^{-2})	23.09 (21.7-24.6)	24.86 (23.5-26.6)[a]	30.21 (27.5-32.0)[a, b]	30.84 (26.0-36.3)[a, b]
BMI categories				
Healthy weight (18.5-24.9 kg.m^{-2})	17 (90%)	8 (50%)	0	1 (6%)
Overweight (25–29.9 kg.m^{-2})	2 (10%)	8 (50%)	10 (62%)	8 (44%)
Obese (> 30 kg.m^{-2})	0	0	6 (38%)	9 (50%)
Waist circumference (cm)	74.05 (4.65)	83.20 (2.54)[a]	95. 18 (6.56)[a, b]	97.45 (10.57)[a, b]
Percentage body fat (%)	31.15 (3.69)	33.41 (3.08)	40.37 (3.04)[a, b]	40.19 (5.21)[a, b]
Fat free mass (kg)	40.978 (3.59)	44.08 (4.19)	47.22 (5.77)[a]	47.12 (5.37)[a]
Blood pressure				
Systolic blood pressure (mmHg)	114.74 (15.57)	117.00 (9.39)	119.09 (9.98)	125.92 (13.49)
Diastolic blood pressure (mmHg)	77.29 (9.96)	75.69 (4.79)	78.50 (8.73)	80.56 (7.91)
Hypertensive (BP >130/85 mmHg)	4 (21%)	2 (13%)	5 (31%)	9 (50%)
Anti-hypertensive medication	2 (10%)	2 (13%)	4 (25%)	6 (33%)
Lipid profile				
TC (mmol.L^{-1})	5.24 (0.98)	5. 33 (1.09)	4.61 (0.53)	5.33 (0.93)
Dyslipidemia (TC > 5.2 mmol.L^{-1})	9 (47)	9 (56)	3 (19)	9 (50)
HDLC (mmol.L^{-1})	1.83 (0.41)	1.89 (0.51)	1.62 (0.36)	1.40 (0.41)[a, b]
LDLC (mmol.L^{-1})	2.98 (0.78)	3. 13 (1.32)	2.38 (0.67)	3.11 (0.89)
TG (mmol.L^{-1})	0.92 (0.68-1.09)	1.07 (0.7-1.4)	1. 16 (0.8-1.6)	1.46 (1.0-1.8)[a, b]
Cholesterol medications	0	1 (6%)	3 (19%)	0
Glucose metabolism				
Fasting glucose (mg.dL^{-1})	4. 72 (4.3-5.0)	4.81 (4.7-5.0)	4.86 (4.6-5.2)	5.32 (4.8-5.5)[a, b, c]
Fasting insulin (mU.L^{-1})	6. 73 (5.5-6.9)	7.30 (5.7-9.8)	8. 38 (7.3-9.6)	14.49 (11.6-19.4)[a, b, c]
Hyperinsulinemia (>12 mU.L^{-1})	0	0	1 (6%)	14 (78%)
Insulin resistance (HOMA-IR)	1. 42 (1.1-1.8)	1.61 (1.2-2. 1)	1. 81 (1.4-2.1)	3.43 (2.5-4.2)[a, b, c]
HBA1c (mmol.mol^{-1})	35.21 (33.0-38.0)	35.25 (33.5-37.0)	35. 75 (34.0-37.0)	38.39 (33.5-41.0)[a, b]
Glucose medications	0	0	0	0
Inflammatory marker				
CRP (mg.L^{-1})	1. 53 (1.0-1.8)	1.89 (1.0-2. 2)	2. 09 (1.1-2.4)	4.98 (1.4-7.0)[a, b, c]
Metabolic syndrome	0	3 (19%)	5 (31%)	12 (67%)

Data are displayed as mean (± standard deviation) for normally distributed variables and median (inter-quartile range) for non-normally distributed variables and as frequency (percentage) for categorical variables. Abbreviations: *kg* kilogram, *BMI* body mass index, *TC* total cholesterol, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *TG* triglycerides, *HOMA-IR* homeostatic model assessment index, *HBA1c* glycosylated haemoglobin A1c, *CRP* C - reactive protein.
a = significantly different from Group 1; b = significantly different from Group 2; c = significantly different from Group 3.

Discussion

Results demonstrate that breast cancer survivors, who are both centrally obese and insulin resistant, are characterised by greater metabolic dysfunction in terms of dyslipidemia, glucose dysmetabolism, raised CRP and a higher prevalence of the MetSyn compared to women who are centrally obese in the absence of insulin resistance. This altered metabolic profile was accompanied by higher absolute and adjusted RMR levels but was not associated with differing habitual physical activity levels. These results are consistent with others which have demonstrated deteriorations in lipid-lipoprotein profile, inflammatory status and measures of glucose-insulin homeostasis when central obesity exists concurrently with insulin resistance [31,32]. In these studies, participants who were centrally obese and not insulin resistant were characterised by metabolic profiles that were similar to lean controls.

Table 3 Comparison of energy output variables across groups

Characteristic	Group 1 (n = 19)	Group 2 (n = 16)	Group 3 (n = 16)	Group 4 (n = 18)
Resting metabolic rate				
RMR (kJ.day^{-1})	4884.59 (619.37)	5232.79 (438.65)	5484.26 (625.03)	6190.93 (959.43)$^{a, b, c}$
Adjusted RMR (kJ.day^{-1}.kg^{-1})	111.7 (12.5)	112.9 (7.6)	110.5 (11.7)	122.3 (10.7)$^{a, b, c}$
RQ (VCO2/VO2)	0.77 (0.74-0.82)	0.75 (0.72-0.77)	0.76 (0.72-0.83)	0.79 (0.76-0.85)
Physical activity				
RT3 activity monitor				
Sedentary (min.day^{-1})	374.73 (86.55)	414.06 (104.19)	456.38 (98.89)	412.88 (103.94)
Light intensity (min.day^{-1})	390.19 (87.51)	346.31 (55.74)	346.91 (85.76)	380.26 (61.28)
Moderate intensity (min.day^{-1})	56.46 (18.0-81.4)	47.40 (17.8-76.7)	34.91 (20.1-48.6)	45.48 (28.8-54.5)
Vigorous intensity (min.day^{-1})	25.22 (3.0-37.2)	20.37 (2.1-46.1)	8.94 (0.7-9.9)	11.54 (0.4-28.8)
Minnesota LTPAQ				
Light AMI (MET-h.week^{-1})	0	0	0	0
Moderate AMI(MET-h.week^{-1})	14.0 (13.1)	16.7 (18.8)	12.3 (9.5)	13.7 (9.0)
Vigorous AMI (MET-h.week^{-1})	2.8 (6.4)	1.0 (2.9)	2.0 (7.6)	0.4 (6.9)
Total AMI (MET-h.week^{-1})	24.4 (17.3)	20.1 (21.3)	16.3 (15.6)	15.1 (18.8)
Adherence to PA guidelines	6 (32%)	5 (31%)	3 (19%)	3 (17%)

Data are presented as mean (± standard deviation) for normally distributed variables and as median (inter-quartile range) for non-normally distributed variables and as frequency (percentage) for categorical variables. *Abbreviations: RMR* resting metabolic rate, *RQ* respiratory quotient, *VCO2* carbon dioxide produced, *VO2* oxygen consumed, *LTPAQ* leisure time physical activity questionnaire, *AMI* activity metabolic index, *PA* physical activity.
a = significantly different from Group 1; b = significantly different from Group 2; c = significantly different from Group 3.

In the present study inflammatory status was measured by CRP, an acute-phase reactant secreted from the liver in response to pro-inflammatory cytokines (TNF-α and IL-6). Pro-inflammatory cytokines are secreted from the visceral adipose tissue in response to infiltration by macrophages to expanding adipose tissue and act on the liver to stimulate gluconeogenesis, resulting in increased production of hepatic glucose and consequently increased pancreatic secretion of insulin leading to the development of insulin resistance [33]. CRP levels >3 mg.L^{-1} are indicative of chronic low-grade inflammation [14]. Therefore in the current study, CRP values suggestive of low-grade inflammation (4.98 (3.46) mg.L^{-1}) were observed in those who were insulin resistant. These values are comparable to those reported by Thomson and colleagues [1] who described a mean high sensitivity CRP of 5.1 (5.3) mg.L^{-1} in an overweight cohort of breast cancer survivors. Interestingly, in the present study mean CRP values did not exceed the 3 mg.L^{-1} cut-point in any of the non-insulin resistant groups. Among breast cancer survivors, significant associations have been documented between acute inflammatory markers (CRP and serum amyloid A (SAA)) and a number of anthropometric and lifestyle related prognostic indicators including BMI, increasing waist circumference and decreasing physical activity levels [34] in addition to all-cause mortality following breast cancer [5].

Chronic inflammation may also adversely influence lipid-lipoprotein profiles resulting in dyslipidemia [33]. Consequently, in the current study HDL-C was significantly lower and TG significantly higher in the insulin resistant group compared to all other groups. There is a lack of consensus regarding the presentation of dyslipidemia in obese, insulin resistant adults. Nieves and colleagues [31] reported in insulin resistant, non-obese individuals, that the presentation of dyslipidemia could be explained by differing levels of visceral fat accumulation. In contrast, Piché and colleagues [32] suggested that variations in the presentation of dyslipidemia in centrally obese adults were driven by insulin resistance. In the current study, only those who were insulin resistant showed evidence of dyslipidemia, however causality cannot be inferred.

It should be acknowledged that the HOMA-IR scores observed in this study (mean 2.09 (range: 0.47 – 6.36) were lower than observed in similar cohorts for example the HEAL study which reported mean HOMA-IR scores of 2.55 (range: 0.25 – 40.16) [3]. The HEAL study is a multicentre, multiethnic trial based in the United States of America. To the authors' knowledge, the current study is the first to examine metabolic characteristics in an Irish cohort of breast cancer survivors. One of the limitations of this cohort is a lack of diversity variables such as BMI scores. The mean BMI of participants in the current study was 27.02 (range 19.7-39.9) kg.m^{-2} compared to 27.3 (range 16.2 – 53.3) kg.m^{-2} in those involved in HEAL [3]. While the mean values are comparable, the range and maximum values were lower in the current study. As obesity is the predominant underlying cause of insulin resistance [35], the lower HOMA-

IR scores observed in the current study may be attributed to lower range of BMI values. The prevalence of obesity in Ireland is increasing steadily [36], albeit at a slower rate than observed in North America [37]. Nonetheless, the metabolic and physiological health consequences of obesity in Ireland are becoming increasingly evident and there is a need for intervention to prevent further decline.

A relationship between physical activity and metabolic markers was not observed in the current study. This is in contrast other studies in breast cancer survivors who reported correlations between physical activity and several metabolic variables including fasting insulin [28], HOMA-IR [28], CRP [34], leptin [38], IGF-I [38] and IGFBP-3 [38]. Furthermore habitual physical activity levels did not vary between groups. Sedentary behaviour was prevalent across each of these groups representing 50% (Range: 44% in Group 1 to 54% in Group 3) of waking hours. In contrast, moderate and vigorous intensity activity accounted for only 7% of waking hours (Range: 5% in Group 3 to 10% in Group 1) with less than one-third of any group achieving recommended physical activity guidelines. It could be suggested that the high percentage of sedentariness made it difficult to identify differences between equally sedentary groups in this small sample. These results, like others [7,28], represent the extent of the problem of inactivity among breast cancer survivors and may also represent the problem of inactivity at population level. Recent reports suggest that 31% of adults globally are inactive (not achieving recommended physical activity guidelines), with inactivity levels highest in Europe and America and greatest amongst women [39]. Excess sedentary behaviour is particularly concerning among breast cancer survivors however due to the association between physical inactivity and prognosis. Physical activity undertaken following breast cancer is associated with up to a 35% reduction in all-cause mortality [19,40] while inactivity has been linked to a four-fold increase in mortality risk [41].

RMR comprises the largest component of energy expenditure and therefore is an essential determinant of energy balance. Mean RMR levels (1297.53 (203.13) $jK.day^{-1}$ (equivalent to 1297.53 (203.13) $kcal.day^{-1}$ in the current study were comparable to those reported previously in a similar cohort (1300 (183.9) $kcal.day^{-1}$) [1]. In addition, both absolute and adjusted RMR were significantly higher in the insulin resistant group compared to all others and demonstrated moderate-to-weak correlations with a number of metabolic variables. These results are consistent with others which report that adjusted RMR is typically increased in individuals with T2DM relative to healthy counterparts [42,43]. Weyer and colleagues [18] suggested that increases in RMR occur early in the development of T2DM in conjunction with the development of progressive metabolic abnormalities including an increase in gluconeogenesis and increased hepatic glucose productions. In contrast, there is a lack of consensus as to whether RMR is increased or decreased in individuals with clinically defined MetSyn compared to metabolically healthy counterparts [44,45]. Despite the exclusion of individuals with T2DM from the current study, results are consistent with the development of underlying glucose dysregulation. In contrast, non-insulin resistant groups with lower RMR values may be at risk of continued weight gain [46].

The aim of the current study was to identify known modifiable prognostic risk factors that may respond favourably to intervention to improve breast cancer survival. This evaluation did not compare findings to a matched control group however it is highly likely that the presented metabolic characteristics are comparable to population norms. Population statistics suggest that "normal" is characterised by obesity [37], inactivity [39] and sedentariness [47]; factors which are all associated with reduced breast cancer outcome and will contribute to metabolic decline. The challenge therefore with rehabilitation in the cancer context is the need for cancer survivors to adopt health promoting lifestyle behaviours which may be different from pre-diagnosis levels. Rehabilitation which focuses on a return to "normal" function or baseline levels is no longer adequate. Therefore it is suggested that metabolic screening to identify key modifiable risk factors and inform exercise prescription in this cohort may be more valuable than comparison to a matched control group.

Conclusions

In recent years there has been increasing evidence of a relationship between increasing levels of obesity, and metabolic dysfunction, with poorer breast cancer prognosis [3-5,48], highlighting the importance of accurately assessing metabolic disturbance among breast cancer survivors. A greater understanding of the presentation of metabolic dysfunction will inform the design of targeted, outcome-specific weight-loss and physical activity interventions aimed at improving biomarkers of breast cancer risk. In the present study we defined the MetSyn according to the most recent consensus statement [12], and then compared metabolic profiles across groups based on increasing levels of central obesity and the presence or absence of insulin resistance. Results identify that the insulin resistant group displayed alterations in both measures of insulin-glucose homeostasis and CRP, two significant predictors of breast cancer outcome [3,5]. In addition, results show that increasing central obesity in the absence of insulin resistance was not associated with a greater deterioration in metabolic profile when compared to lean controls, suggesting that the

assessment of insulin resistance is crucial in the assessment of metabolic dysfunction for identifying potentially prognostic characteristics. While physical activity was not associated with differing levels of metabolic dysfunction, the high prevalence of sedentary time and low adherence to physical activity guidelines is concerning. Elevated RMR values in the insulin resistant group however are consistent with others which have shown that RMR is increased in the presence of serious metabolic dysfunction and glucose dysregulation. In breast cancer survivors, a comprehensive assessment of metabolic dysfunction is required to identify profiles that may potentially have greater prognostic significance and may inform the design of future targeted exercise interventions.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
All authors (EG, EC, MJK and JH) developed the idea for this study. Measurements and data analysis was completed by EG. EC and MJK provided medical advice regarding interpretation of the data. EG was responsible for drafting the manuscript with contributions from JH. All authors approved the final version of the manuscript.

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Received: 16 January 2013 **Accepted:** 5 July 2013
Published: 15 July 2013

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doi:10.1186/1475-2891-12-99
Cite this article as: Guinan *et al*.: **The presentation of metabolic dysfunction and the relationship with energy output in breast cancer survivors: a cross-sectional study.** *Nutrition Journal* 2013 **12**:99.

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STUDY PROTOCOL Open Access

'Pragmatic randomized controlled trial of individually prescribed exercise versus usual care in a heterogeneous cancer survivor population': A feasibility study PEACH Trial: Prescribed exercise after chemotherapy

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Abstract

Background: Many cancer survivors suffer a range of physical and psychological symptoms which may persist for months or years after cessation of treatment. Despite the known benefits of exercise and its potential to address many of the adverse effects of treatment, the role of exercise as well as optimum duration, frequency, and intensity in this population has yet to be fully elucidated. Many cancer rehabilitation programmes presented in the literature are very long and have tight eligibility criteria which make them non-applicable to the majority of cancer survivors. This paper presents the protocol of a novel 8-week intervention which aims to increase fitness, and address other physical symptoms in a heterogeneous cancer survivor population.

Methods/design: The aim is to recruit 64 cancer survivors 2-6 months after completion of chemotherapy, usually adjuvant, with curative intent. Subjects will be recruited through oncology clinics in a single institution and randomised to usual care or an exercise intervention. The exercise intervention consists of two specifically tailored supervised moderate intensity aerobic exercise sessions weekly over 8-weeks. All participants will be assessed at baseline (0 weeks), at the end of the intervention (8 weeks), and at 3-month follow-up. The primary outcome measure is fitness, and secondary patient-related outcome measures include fatigue, quality of life, and morphological outcomes. A further secondary outcome is process evaluation including adherence to and compliance with the exercise program.

Discussion: This study will provide valuable information about the physical outcomes of this 8-week supervised aerobic programme. Additionally, process information and economic evaluation will inform the feasibility of implementing this program in a heterogeneous population post cessation of chemotherapy.

Trial Registration: NCT01030887

Background

The benefits of exercise in the general population are well established [1,2]. The current physical activity recommendation for adults aged between 18-65 years to promote and maintain health is to accumulate at least 30 minutes of moderately intense physical activity on at least five days of the week. Sedentary behaviour, such as time spent sitting is positively associated with coronary heart disease risk factors, obesity, and development of the metabolic syndrome [3,4]. More recently, the link between sedentary behaviour and the development of certain cancer types has been reported.

Newer evidence indicates that increased physical activity after a cancer diagnosis may reduce the risk of cancer recurrence and mortality [5-7]. Cancer survivors are at risk of developing new primary tumours as well as secondary tumours and chronic diseases such as cardiovas-

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cular disease, osteoporosis, and diabetes [8]. This increased risk across conditions may be genetic or treatment-related but may also reflect the fact that common life-style factors, including a sedentary lifestyle, increase the risk for more than one disease [8].

Physical activity is also advocated during and after the treatment for cancer. However, the adverse effects of treatment which frequently impact on physical functioning and quality of life, may persist even years after treatment [9-11], and must be taken into account. Many treatments for cancer are toxic, increasing the risk for a number of medical problems and late treatment effects such as neuropathy [12] and cardiovascular disease [12-14]. Cardiopulmonary capacity may also be compromised in cancer survivors because of side effects of therapy regimens such as weight gain and inactivity secondary to treatment. The reduction in cardiopulmonary capacity may lead to decreases in quality of life [15,16]. A downward trajectory in aerobic fitness is generally observed, possibly caused by chemotherapy and associated side-effects such as anaemia, tachycardia, dehydration, and cardiac dysfunction [17,18].

Other cancer survivors experience somatic symptoms which may also persist for years after treatment such as chronic fatigue [19,20], weight gain [19], loss of muscle strength [21,22] and difficulty sleeping [20]. Physical and functional well-being are essential dimensions for overall quality of life [23], and poor physical functioning may explain some of the psychological distress experienced by cancer survivors [21,22].

The rationale for physical activity interventions following cancer diagnosis includes minimizing biological processes associated with tumour growth [24], enhancing behavioural changes to try to minimise lifestyle risk factors for recurrence of cancer [25], and improving psychosocial factors during and after cancer [26]. The main physiological outcomes of physical activity after cancer are improved fitness and physical functioning [27,28], reduced fatigue [29], and modestly decreased weight and body fat [30].

Even though there is strong evidence for the benefits of physical activity aftercancer-treatment, the majority of cancer survivors do not meet public health guidelines for levels of physical activity necessary for health-related benefits [31-34]. Clearly, there is a need to promote physical activity, but the optimal intervention modality, intensity, training and duration are still unknown.

Many programmes in cancer rehabilitation are mainly based on psychotherapy or social support. Such therapies however do not usually deal with the physical problems encountered by many patients, such as fatigue, loss of functional capacity and weight gain [35]. Many cancer rehabilitation programs and/or trials which include a physical rehabilitation are lengthy in duration, extremely intensive [36] and have tight eligibility criteria. They would be expensive to translate into general clinical practice or to apply to the general cancer survivor population.

We have therefore devised a RCT to evaluate the effectiveness and feasibility of an 8-week intervention to improve fitness and other secondary outcomes.

Methods/Design

Study design

This will be a single-blind 2 arm pragmatic randomised controlled trial of individually prescribed exercise in a class setting versus usual care.

Primary aims

Outcome evaluation

To examine the effects of a supervised exercise program commenced within 2-6 months after completion of chemotherapy and/or radiotherapy with curative intent on cardio-respiratory fitness, and on quality-of-life, fatigue and morphological outcomes.

Process Evaluation

As this is a feasibility study, an additional aim is to determine the acceptability of the programme, as well as adherence and compliance with the prescribed duration and intensity during supervised exercise sessions.

Patient Recruitment

Participants will be sourced from the institutional cancer database, by invitation from study personnel in cancer clinics and directly from the oncology service in St. James's Hospital, Dublin, Ireland. Study personnel will provide further information to these patients and assess them for eligibility. Ethical approval has been approved from the institutional Research Ethics Committee and informed consent will be gained from each participant prior to study inclusion.

Aerobic fitness will be measured using the Modified Bruce treadmill test and those with aerobic fitness levels average or below age- and gender norms [37] and meeting other inclusion criteria will be invited to participate in the study. Subjects scoring average or below for age and gender cut-off levels according to the Modified Bruce Protocol, will be randomized to the exercise intervention or usual care.

Inclusion criteria

(i) Diagnosis of solid tumour and completion of adjuvant chemotherapy or radiotherapy with curative intent within the preceding 2-6 months. Patients who have received neoadjuvant chemotherapy or chemoradiotherapy followed by surgery will also be eligible. Patients continuing onto adjuvant hormone therapy and anti-Her2 directed therapy are eligible

(ii) Ability to understand English

(iii) Willing to be randomised

(iv) Medical clearance to exercise

(v) Age 21-69

(vi) Fitness level average, fair or poor according to certain pre-determined cut-off points for age and gender[37]

(vii) Willing and able to attend supervised exercise sessions twice weekly for a period of 8 weeks, with an intention of achieving > 90% attendance

(viii) LVEF > 50% and not < 20% worse than baseline in applicable patients

Exclusion criteria

(i) Evidence of active cancer

(ii) Chronic medical and orthopaedic conditions that would preclude exercise (eg uncontrolled congestive heart failure or angina, recent MI, breathing difficulties requiring oxygen use or hospitalization)

(iii) On beta-blocker medication

(iii) Prior history of another cancer in previous 5 years (exception: non-melanoma skin cancer and non-invasive cancer of the cervix)

(iv) Confirmed pregnancy

(v) Dementia or psychiatric illness that would preclude ability to participate in study

(vi) Incomplete haematological recovery after chemotherapy (WCC < 3, Hb < 10 or Platelets < 100)

(vii) BMI > 35

(viii) LVEF post chemotherapy < 50% or > 20% deterioration of baseline compared to LVEF before systemic treatment. LVEF criteria are applicable in patients who have received systemic therapy (eg anthracycles, Her-2 antagonists etc) deemed in normal clinical practice to have a potential effect LVEF and in whom the LVEF will have been measured before systemic treatment and at end of chemotherapy

Assessment

Post randomization follow-up will be at baseline (week 0), end programme (8 weeks) and 3 month follow-up.

Baseline Characteristics

Cancer grade, stage, surgical management, treatment regimen (chemotherapy, radiation therapy, hormonal therapy) and previous medical history will be recorded by accessing medical charts. Socio-demographic variables recorded will include age, gender, ethnicity, employment status, smoking, and alcohol habits accessed from medical charts and/or subjective interview.

Body Composition

Anthropometric parameters will be measured at baseline, 8 weeks and at 3 months. Body weight will be measured to the nearest gram (g) using a standardised digital scales. Standing height will be measured, without shoes, to the nearest millimetre (mm) using stadiometer. BMI will be calculated by dividing weight in kilograms by height in metres squared.

Lean body mass will be evaluated using bioimpedence (Tanita). Waist Circumference will be measured as per the protocol outlined in the ACSM Resource Manual [38].

Cardiovascular Parameters

Resting heart rate will be measured after a five minute rest period in a seated position. Heart rate reserve will be calculated by subtracting the resting heart rate from peak heart rate during exercise. Oxygenation saturation will be monitored using a finger pulse oximeter.

Blood pressure (BP) will be measured using the auscultatory method in accordance with the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines.

Outcome Measures

Primary Outcome measure: Fitness Physical fitness will be measured by the Modified Bruce Protocol. A submaximal test was chosen over a maximal test for this population because of safety and motivational concerns [39]. Verbal encouragement during the exercise test will be standardised.

Secondary outcomes Quality of life We will use the FACT-G scale (general) (and the physical functional measure of the SF-36. Many uncontrollable factors influence QOL during and after chemotherapy and a global measure of cancer-specific QOL may be too broad to detect the likely narrower effects of exercise training, therefore a more appropriate and realistic primary end-point in exercise trials may be the functional component of QOL [40]. A statistically significant increase of greater than 4.0 points on the FACT scale represents a clinically meaningful improvement in quality of life from exercise [41].

The Fact-G (version 4) is a 27-item questionnaire divided into 4 primary QOL domains: physical well-being, social/family well-being, emotional wellbeing, and functional well-being and an overall quality of life level is also yielded. The FACT-G takes about 5 minutes to complete and has been written at the 6th grade level. This questionnaire was initially developed by Cella et al. 1993 and has been validated in a mixed cancer population [42]. Patients rate all items using a 5-point rating scale ranging from "not at all" to "very much". Strong concurrent validity is reported by strong Pearson correlations with the Functional Living Index - Cancer (0.79) and the patient-completed version of the QL index (0.74). Using the global rating of change (GRC) scale as an anchor, Cella et al proposed that a clinically meaningful change corresponds to a total FACT-G raw score in the range of 5-7 points [43]. A 2008 review by Victorson et al., reported the average reliability of the FACT-G to be 0.88 with the reliability of subsets ranging from 0.71-0.83.

The SF-36v2 is a widely used generic measure of health status. Psychometric properties of the SF-36 have been well established [44]. Thirty five of the 36 items are grouped into eight scales that address health constructs considered to be important to most health care situations: physical functioning, role limitations (physical problems), bodily pain, general health, vitality, social

functioning, role limitations (emotional problems), and mental health We will use the Physical Health measure only of the SF-36 for the purposes of this study.

Current activity level We will use the modified version of the Godin Leisure Time Exercise Questionnaire which has been shown to be a reliable and valid self-report measure of physical activity [45]. The questionnaire contains three questions that assess the average frequency and duration of mild, moderate, and strenuous exercise during free time in a typical week Godin et al. reported the test-retest reliability coefficient of the Godin questionnaire to be 0.64 and the concurrent validity to range from 0.38 to 0.54 over three validity criteria [45].

Accelerometry will be used to monitor 7 days of activity at Week 0, Week 8 (immediately post intervention) & 3 months post intervention. We will use the RT3 accelerometer (Stayhealthy Inc.) which has been shown to be reliable [46] and valid [47]. The RT3 accelerometer measures activity in three dimensions. With the RT3 worn on the hip, the vectors are as follows: vertical (x), antero-posterior (y), and medio-lateral (z) and generates a summary variable-vector magnitude.

Cancer-related fatigue We will use the 13-item Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACT-Fatigue) of the Functional Assessment of Chronic Illness Therapy measurement system which has been developed specifically for the cancer population [42,48]). The reliability of the FACT-fatigue scale has been reported to be 0.84 and it has been shown to have good validity with other measures of fatigue, a significant negative relationship with vigor and with social desirability [49].

Satisfaction Self-administered questionnaire on completion of programme will be administered. Participants will also be asked to highlight what they liked about the programme, what they didn't like, and suggestions for change.

Demographics to be recorded Self-reported socio-demographic variables will include age, gender, ethnicity, employment status, smoking & alcohol habits. Medical information will include co-morbidities and disease vari-

Table 1: Progression of the intensity & duration of the exercise class

Intensity	Poor	Fair	Average
Week 1	35-55% HRR 21 mins aerobic	40-60% HRR 21 mins aerobic	45-65% HRR 21 mins aerobic
Week 2	35-55% HRR 24 mins aerobic	40-60% HRR 24 mins aerobic	45-65% HRR 24 mins aerobic
Week 3	40-60% HRR 24 mins aerobic	45-65% HRR 24 mins aerobic	50-70% HRR 24 mins aerobic
Week 4	40-60% HRR 30 mins aerobic	45-65% HRR 30 mins aerobic	50-70% HRR 30 mins aerobic
Week 5	45-60% HRR 30 mins aerobic	50-65% HRR 30 mins aerobic	55-70% HRR 30 mins aerobic
Week 6	45-60% HRR 36 mins aerobic	50-65% HRR 36 mins aerobic	55-70% HRR 36 mins aerobic
Week 7	50-60% HRR 36 mins aerobic	55-70% HRR 36 mins aerobic	65-75% HRR 36 mins aerobic
Week 8	50-60% HRR 42 minutes aerobic	55-70% HRR 42 minutes aerobic	65-75% aerobic 42 minutes aerobic

ables such as cancer grade, stage and regimen (chemotherapy, radiation therapy, hormonal therapy) will be collected from medical charts.

Additional details to be recorded Protocol deviations, modifications made to any of the exercises will be recoded. Safety is paramount and any adverse events will be reported. We are aiming for a withdrawal and drop-out rate of < 10%. Protocol deviation such as switching or contamination, subjects dropping-out or adhering non-perfectly will also be recorded. The following details on compliance and adherence will also be recorded; compliance (X% of exercise sessions attended and successfully completed), adherence: we are aiming for adherence to exercise intervention (attendance or completion of exercise session) of > 70%.

Exercise Training Interventions

The class will be supervised by a physiotherapist and a research assistant. There will be a maximum of 10 participants in each class, giving a ratio of at most 1:5 instructor: patient ratio.

The warm-up will consist of performing the mode of exercise prescribed for the work phase at a low intensity to allow the cardiopulmonary system to adapt to the new demand and to allow the temperature of the muscles to increase. Warm-up will be 7-10 minutes duration but slightly longer at the, initial stage of training.

Exercise intervention

The class will take 1 hour in total, with an aerobic component of 20–40 minutes increasing on a weekly basis (Table 1). The type of exercise will be continuous, rhythmic exercise using large muscle groups. There will be 3 aerobic stations: including treadmills, cycle ergometer, and rowing machine or stepper or other aerobic exercise such as marching on the spot deemed suitable by the class instructor.

The class frequency will be twice per week and as well as exercise in the home environment, starting with at least 1 other day (alternating) exercise building up to 3 other days per week. Exercise in the home environment can be carried out in multiple sessions (but no less than 10 minutes each time). A polar watch will be worn during these exercise sessions to monitor intensity.

Statistical analysis

Randomization will be by a computer-generated random numbers list (GraphPad Software, San Diego, CA) with intention-to-treat as the primary analysis and per protocol as the secondary analysis.

Assuming a difference of 5 mL/kg/min^{-1}, with a SD of 6.5, and a 5% significance (two-sided) and 80% power, 28 participants would be required per group. However, the goal would be to accrue 32 subjects to allow for a 15% drop out rate and subgroup analyses. One year will be allowed for accrual of participants. The drop-out rate is calculated to include patients who are unfortunately diagnosed within 3 months of the final assessment as having a relapse of their cancer. As occult return of cancer could have a negative impact on fitness and capacity to exercise, these patients' data will be excluded from the primary outcome measure but included in the process analysis. The same will be done for the data of any participant on anti-Her2 therapy in whom an LVEF assessment during the study or within 3 months of the end of the study has a drop in LVEF to < 50% or by > 20% compared to baseline, as, similarly, occult ongoing myocardial toxicity could have a negative impact on fitness.

We will provide descriptive data and 95% CIs for all possible comparisons. For our primary analysis, we will use the intent-to-treat principle and for the secondary analysis, per-protocol analysis. In sensitivity analyses (intent-to-treat), the impact of missing values will be studied by using a range of imputed change scores for missing values, and by analysing those subjects who provide complete data. Repeated measured of analysis (ANOVA) will be used across more than two time points for continuous data. Mixed-model analysis will be used to model each outcome measure at three (or two) time points and compare the differences across groups over time for non-continuous data. We will use t-tests between 2 groups when data are normally distributed and the Mann-Whitney U test will be used when data are non-normally distributed. The Chi-squared test will be used for categorical data. Tests for interaction will be carried out for the effect of gender and type of cancer.

Discussion

This study will assess the effect of a novel 8-week exercise programme in cancer survivors 2-6 months post cessation of adjuvant therapy. No intervention studies to date have explored a relatively short individually prescribed exercise intervention in a heterogeneous cancer population in terms of physiological and process outcomes. This study will provide valuable insights into the effect and feasibility of this type of programme and if successful would be clinically transferable to a broad range of cancer settings.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JW, DOD and JH developed the idea for this study. JW was responsible for drafting the manuscript with contributions from DOD, JH and EG. EG will assess all subjects at the time-points outlined in the manuscript, and JW will implement the protocol and collect the data. All authors read and approved the final manuscript.

Acknowledgements

This research is funded by a Health Research Board (Ireland). JW was awarded a Health Research Board Fellowship for the Therapy Professions in 2008 (grant no. CTPF/2008/12). We also acknowledge the contribution of Dr. Kathleen Bennett for her statistical advice in this study.

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Received: 30 December 2009 Accepted: 15 February 2010
Published: 15 February 2010

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Pre-publication history
The pre-publication history for this paper can be accessed here:
http://www.biomedcentral.com/1471-2407/10/42/prepub

doi: 10.1186/1471-2407-10-42
Cite this article as: Walsh *et al.*, 'Pragmatic randomized controlled trial of individually prescribed exercise versus usual care in a heterogeneous cancer survivor population': A feasibility study PEACH Trial: Prescribed exercise after chemotherapy *BMC Cancer* 2010, **10**:42

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STUDY PROTOCOL Open Access

A prospective investigation of predictive and modifiable risk factors for breast cancer in unaffected *BRCA1* and *BRCA2* gene carriers

Emer M Guinan[1*], Juliette Hussey[1], Sarah A McGarrigle[2], Laura A Healy[3], Jacintha N O'Sullivan[2], Kathleen Bennett[4] and Elizabeth M Connolly[5]

Abstract

Background: Breast cancer is the most common female cancer worldwide. The lifetime risk of a woman being diagnosed with breast cancer is approximately 12.5%. For women who carry the deleterious mutation in either of the *BRCA* genes, *BRCA1* or *BRCA2*, the risk of developing breast or ovarian cancer is significantly increased. In recent years there has been increased penetrance of *BRCA1* and *BRCA2* associated breast cancer, prompting investigation into the role of modifiable risk factors in this group. Previous investigations into this topic have relied on participants recalling lifetime weight changes and subjective methods of recording physical activity. The influence of obesity-related biomarkers, which may explain the link between obesity, physical activity and breast cancer risk, has not been investigated prospectively in this group. This paper describes the design of a prospective cohort study investigating the role of predictive and modifiable risk factors for breast cancer in unaffected *BRCA1* and *BRCA2* gene mutation carriers.

Methods/design: Participants will be recruited from breast cancer family risk clinics and genetics clinics. Lifestyle risk factors that will be investigated will include body composition, metabolic syndrome and its components, physical activity and dietary intake. PBMC telomere length will be measured as a potential predictor of breast cancer occurrence. Measurements will be completed on entry to the study and repeated at two years and five years. Participants will also be followed annually by questionnaire to track changes in risk factor status and to record cancer occurrence. Data will be analysed using multiple regression models. The study has an accrual target of 352 participants.

Discussion: The results from this study will provide valuable information regarding the role of modifiable lifestyle risk factors for breast cancer in women with a deleterious mutation in the *BRCA* gene. Additionally, the study will attempt to identify potential blood biomarkers which may be predictive of breast cancer occurrence.

Keywords: *BRCA1*, *BRCA2*, Breast cancer, Metabolic syndrome, Physical activity, Body composition, Dietary intake, Telomere length

Background

Breast cancer is the most common female malignancy worldwide. The lifetime risk of a woman being diagnosed with breast cancer approximately 12.5% [1]. While most breast cancers are sporadic in nature, is approximately 5-10% are attributed to genetics, arising from autosomal dominant mutations in specific cancer genes, the strongest of which are the two breast cancer susceptibility genes, *BRCA1* or *BRCA2*. Women who carry these mutations have up to an 80% risk of developing breast and up to a 60% risk of ovarian cancer [2-4]. In recent years, there has been increased penetrance of *BRCA1/2* mutations, which is most likely mediated by lifestyle or environmental influences [2,5,6], prompting investigation into the potential of reducing risk through lifestyle modification in this group. Understanding how modifiable and lifestyle risk factors effect cancer risk, specifically in *BRCA* mutation carriers, may have important implications for cancer prevention in this high risk group.

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The associations between obesity, physical inactivity and certain components of dietary intake such as alcohol consumption and sporadic breast cancer risk are well established [7-10]. Obesity may increase breast cancer risk through a number of different mechanisms including insulin resistance, the metabolic syndrome, increased production of sex hormones, insulin growth-like factors, chronic low-grade inflammation and alterations in adipokines[9,11-15]. These biological pathways, in turn, are the hypothesised targets through which physical activity may exert its protective effects over breast cancer development [16,17]. However, knowledge regarding the role of these lifestyle factors in *BRCA1/2* mutation carriers is limited.

A number of case-control studies have investigated the association between adult weight change and breast cancer risk in *BRCA* gene mutation carriers through self-reported recall of lifetime weight changes [2,18-20]. Healthy weight during adult life, particularly from menarche to 21 years, has been associated with decreased breast cancer risk [18,20] while weight loss between 18 and 30 years of age has been associated 34% reduction in breast cancer risk, particular among *BRCA1* mutation carriers [18]. Consistent with sporadic breast cancer, menopausal status is a potentially modifying factor in the relationship between obesity and breast cancer risk in *BRCA* mutation carriers, however results are conflicting. A study by Kotsopoulos and colleagues [18], reporting increased breast cancer risk with adult weight gain, regardless of menopausal status, while Manders *et al.*, [19] reported an association with postmenopausal breast cancer only. However, in these studies, body weight has been self-reported, rather than objectively measured, leading to potential inaccuracies in results. The association between physical activity and *BRCA* mutation-associated breast cancer is unclear with two studies reporting a protective effect [2,21] and one showing no association [20]. However, as with the anthropometric variables, measurement methods were limited and relied on self-reported recall.

In addition, it has been suggested that measuring telomere length may help predict risk of occurrence of certain types of cancer [22-24] including *BRCA* mutation-associated breast cancer [25,26]. There is some evidence to suggest that exercise may affect telomere length. For example, Puterman *et al*, showed that increased perceived stress was associated with increased odds of having short telomeres but only in non-exercising women [27]. Non-exercising women with a history of childhood abuse had shorter telomeres than those with no history of abuse; however, in women who exercised regularly no link between childhood abuse and telomere length was found [28]. Together these findings suggest that telomere shortening may be modifiable by physical activity.

Reproductive factors including parity and breastfeeding practices have been associated with risk reduction in *BRCA* mutation carriers similar to that of the general population [29,30], suggesting that modifiable risk factors can attenuate risk in this group. However, our understanding of the potential for risk reduction for the majority of modifiable of risk factors in this high risk group remains unknown. Studies investigating women with a strong family history of breast cancer have shown that these women are no more likely to engage in healthy lifestyle habits than women in the general population [31,32] making lifestyle interventions a potentially important target. The Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) is currently examining the role of various genetic modifiers of cancer risk in *BRCA* mutation carriers. Within CIMBA, and as part of the Epidemiological Study of Familial Breast Cancer (EMBRACE) study and others, the influence of lifestyle factors on breast cancer occurrence will be measured subjectively using a lifestyle questionnaire (http://cgge.medschl.cam.ac.uk/embrace/). However these associations have not been investigated using validated and objective measures of lifestyle parameters.

We plan to prospectively and objectively examine the association between modifiable (body composition, metabolic syndrome, physical activity and dietary intake) and potentially predictive (telomere length) risk factors for breast cancer and breast cancer occurrence in unaffected *BRCA1* and *BRCA2* gene carriers. This study will also investigate the hypothesised link between physical activity and telomere length in a cohort of unaffected *BRCA*-mutation carriers. Various correlations between telomere length and physical activity, lifestyle factors and breast cancer occurrence will be examined.

Methods / design

Study design

This study is designed as a prospective cohort study aiming to evaluate the role of modifiable and predictive risk factors for breast cancer in women who have been genetically tested and identified as carriers of a deleterious mutation in either one of the *BRCA* genes, *BRCA1* or *BRCA2*.

Objectives

1. To determine information on metabolic syndrome, body composition, physical activity, diet, markers of telomere length and hormone measurements from women who are unaffected *BRCA1/2* mutation carriers.
2. To assess the associations between the following with body composition, physical activity and dietary intake in unaffected *BRCA1/2* mutation carriers:

- Insulin resistance
- Leptin
- Adiponectin
- Inflammatory markers
- Telomere length

3. To prospectively examine the relationship between the metabolic syndrome, body composition, physical activity, diet, telomere length, and hormone measurements with breast cancer occurrence among *BRCA1/2* mutation carriers.

Participant recruitment

A convenience sample of *BRCA* gene mutation carriers will be recruited from St. James's Hospital, Dublin and the National Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin. Potentially suitable participants, who have previously undergone genetic testing and have been identified as carriers of either the *BRCA1* or *BRCA2* mutation, will be identified at Breast Cancer Family Risk Clinic and Cancer Genetics clinics, by medical teams and specialised breast cancer and medical nurses. At the St. James's Hospital site, potentially suitable participants will be provided with information leaflets about the study during routine medical consultations, and if interested in gaining further information, will be directed to speak to a member of the research team who will attend the clinic. At the National Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin potentially suitable participants will be provided with information leaflets detailing the study during medical appointments and invited to contact the research team by email or by telephone if interested in gaining further information. Study personnel will provide further information to interested participants and assess for eligibility. Ethical approval has been granted by the SJH/AMNCH Joint Hospital Research Ethics Committee, in accordance with the Helsinki declaration, and written informed consent will be obtained from all participants.

Participants who meet the following criteria will be eligible to participate:

i. Women who have been genetically tested and identified as carriers of the deleterious mutation in either one of the *BRCA* genes, *BRCA1/2*and who do not have a history or either breast or ovarian cancer.
ii. Aged 18 years or above
iii. Able to understand English.
iv. Willing to travel to the study site for measurements.

Participants will be excluded for the following reasons:

i. History of cancer or evidence of active disease (exception: non-melanoma skin cancer).
ii. Confirmed pregnancy or history of childbirth in the preceding 6 months. Women who become pregnant during the study period will complete follow-up active assessments at least 6 months after giving birth.
iii. Any medical co-morbidity that would preclude the ability to participate in the study
iv. Dependence on a mobility assistive device.
v. Participants, who at the local investigator's discretion are not thought appropriate e.g. very upset and emotional regarding finding of *BRCA* gene mutation, family, work or transport issues that would make participation difficult.

Assessments

Participants will complete three active assessments during the study (baseline/entry to the study, two-years, and five-years) during which all measurements outlined below will be completed. Information on disease occurrence, risk reducing procedures and current lifestyle habits will be gathered yearly for 10 years using posted questionnaires. The flow of data collection throughout the study is shown in Figure 1. F1

Baseline characteristics

Demographic details will be gathered from medical charts and through patient interview. Details on past medical history, breast cancer risk factors (family history of breast cancer, oral contraceptive use, age at first birth, menopausal status, parity), and socio-demographic variables including smoking history, alcohol habits, employment status and marital status will be collected.

Body composition

Anthropometric data will be collected following a 12 hour fast. Standing height will be measured, without shoes, to the nearest millimetre using SECA stadiometer. Body composition will be estimated using a bioimpedance analyser, the Tanita MC 180 MA Multi-Frequency Body Composition Analyzer (Tanita Corp, Tokyo, Japan). Data output from the Tanita will be recorded and will include body weight, body mass index (BMI), percentage body fat, muscle mass and fat free mass. Waist circumference was measured using a flexible measuring tape, in duplicate, to the nearest millimetre, at the mid-point between the top of the iliac crest and the last rib [33]. Lifetime weight changes will be assessed at the initial assessment by asking participants to recall their birth weight, weight at menarche, weight at age 18, 21, 30 and 40 respectively.

Blood pressure

Resting blood pressure will be measured using the auscultatory method in accordance with the Joint National

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Figure 1 Flow of data collection throughout the study. Active assessments will be completed at baseline, two years and five years. Annual questionnaires will be sent by post to participants following enrolment to monitor change in lifestyle risk factors being measured.

Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines [34]. Measurements will be taken in duplicate and the mean taken for data entry.

Venous sampling

Metabolic profile

Venous blood samples will be collected in the morning following a 12-hour fast. Participants will be asked to refrain from moderate-vigorous intensity exercise for 24 hours prior to collection. Samples will be taken to measure glucose, insulin, lipid profile (total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG)), glycosylated haemoglobin levels (HBA1c), C - reactive protein (CRP), leptin, total adiponectin and sex hormone binding globulin. Insulin resistance will be estimated using the Homeostatic Model Assessment: [(Fasting glucose ($mmol.L^{-1}$) x fasting insulin ($mU.L^{-1}$))/22.5] [35].

Many biomarkers of carcinogenesis must be collected and stored prior to cancer occurrences, to ensure an unequivocal link between biomarker exposure and tumorgenesis [36]. Previous studies examining lifestyle factors in this group have adopted a case-control design and therefore have not facilitated this type of analysis. In the current prospective study, serum and plasma samples

will be collected and stored in a biological bank at -80°C for future analysis of associations between carcinogenesis and biological markers of obesity, physical activity and diet.

Telomere length

Peripheral blood mononuclear cells (PBMCs) will be isolated from venous blood by density centrifugation using Ficoll-Paque™ Plus (GE Healthcare, Uppsala, Sweden). Genomic DNA will be extracted from PBMCs by standard procedures. Telomere length will be measured in extracted genomic DNA by quantative PCR (qPCR) using a method adapted from the one originally described by Cawthon [37]. Briefly, two PCRs will be performed for each sample: one to amplify the telomeric DNA and a second to amplify a single-copy control gene (36B4, acidic ribosomal phosphoprotein PO). This provides an internal control to normalize the starting amount of DNA. A five-point standard curve (2-fold serial dilutions from 10 to 0.625 ng of DNA) will be included on all plates to allow the transformation of Ct (cycle threshold) into nanograms of DNA. All samples will be run in triplicate and the median will be used for subsequent calculations. A relative measurement of the telomere length of each sample will be calculated by dividing the amount of telomeric DNA by the amount of control-gene DNA.Two control samples will be run in each experiment to allow for normalization between experiments and periodical reproducibility experiments will be performed to guarantee correct measurements.

Genomic DNA samples (50 ng) will be amplified in a total reaction volume of 20 μl containing 2X Quantifast™ SYBR green PCR master mix (Qiagen Inc., CA, USA), 1 μl of forward and reverse primer (Metabion, Germany) and 7 μl of DNase free water. For the telomere amplification PCR, 300 nM of each primer primer (tel1b: CGGTTTGTT TGGGTTTGGGTTTGGGTTTGGGTTTGGGTT; tel2b: GGCTTGCCTTACCCTTACCCTTACCCTTACCCT TACCCT) will be used. The thermal cycling profile for the telomere amplification will be 30 cycles of amplification at 95°C for 15 s and at 56°C for 60s. For the control gene amplification, 300nM of forward primer (36B4u: CAGCAAGTGGGAAGGTGTAATCC) and 500nM (36B4d: CCCATTCTATCATCAACGGGTACAA) of reverse primer will be used. The thermal cycling profile in this instance will be 35 cycles of amplification at 95°C for 15 s and at 56°C for 20s and 72°C for 20 s. Both PCR reactions will require an initial denaturation step at 95°C for 15 min. Threshold cycle (Ct) values for each sample will be converted into nanograms of DNA using standard curves.Ct values from the telomere assay will be normalized to the single gene reference. The telomere length (x) from each sample will be calculated as the telomere to single copy gene ratio (T/S ratio) and will be based on the calculation of the ΔC_T [C_T(telomere)/C_T (single gene)]. Telomere length (expressed as a relative T/S ratio) will be normalized to the average T/S ratio of the reference sample $\left[\frac{2^{-(\Delta CT \cdot \Delta CT)}}{xy}\right] = 2^{-\Delta\Delta C}$.

Metabolic syndrome classification

The metabolic syndrome will be diagnosed in the presence of any three of the following: elevated waist circumference (≥80 cm); elevated TG (≥1.7 mmol.L^{-1}) or drug therapy for lipid abnormalities; reduced HDL-C (<1.3 mmol.L^{-1}) or drug therapy for lipid abnormalities; elevated blood pressure (systolic ≥130 mm Hg and/or diastolic ≥85 mmHg) or antihypertensive medication; elevated fasting glucose (≥100 mg.dL^{-1}) or glucose-lowering medication [38].

Physical activity

Current physical activity levels will be objectively measured using the RT3 activity monitor (Stayhealthy Inc. Montrovia, California, USA). The RT3 activity monitor is a small, lightweight, battery operated device, designed to measure accelerations along three orthogonal planes (triaxial accelerometer). Participants will wear the monitor for seven days, during waking hours, following each active assessment (baseline, two-years and five-years). Participants will be provided with the monitor following completion of each assessment and will be given detailed written and verbal instruction on its use. Participants will also be provided with a stamped addressed envelope to return the monitor to the centre after one week (battery life of the monitor = 21 days). The validity [39] and reliability [40] of the accelerometer have been established. The output from the RT3 activity monitor will provide objective quantification of sedentary, light, moderate and vigorous intensity activity, while also facilitating analysis for adherence to activity guidelines.

Physical activity during the preceding 12 months will be estimated using two quantitative history questionnaires, The Minnesota Leisure-Time Physical Activity Questionnaire (MLTPAQ) and the Tecumseh Occupational Physical Activity Questionnaire (TOPAQ). The MLTPAQ is an interview administered questionnaire, measuring leisure-time physical activities [41] while the TOPAQ can be either self-administered or interview based and focuses on occupation-related activities of a maximum of three jobs [42]. Both questionnaires measure frequency of activity during the preceding year in terms of months and time per occasion, and combine this information with intensity scores to measure physical activity in terms of metabolic-equivalent minutes per day (MET-min/day) [41,43]. The MET-score can be derived from the Compendium of Physical Activities [44], and values can be updated accordingly during the study period. The questionnaires will be interview-administered at each of the three active

assessment points (baseline, two-years and five-years). The validity of both questionnaires have been well established in a range of populations [41,42,45,46], with one study reporting significant correlations between cardiorespiratory fitness and both leisure-time activity and household activity in 375 middle-aged women [47]. Both the MLTPAQ and the TOPAQ will be completed during each of the three active assessments, through interview, according standardised interview guidelines [41].

Finally, the Godin Leisure-Time Exercise Questionnaire will be incorporated into the annual questionnaire. Participants will be required to complete this questionnaire independently, but will be informed to contact study personnel should issues arise. The Godin is a simple, self-administered, four-item questionnaire that is designed to measure an individual's leisure-time activity during a typical week to provide a global impression of an individual's activity status [48]. The validity and reliability of the questionnaire have been established [46,48] and the questionnaire has been widely used in cancer research [49,50].

Dietary intake

Dietary intake will be assessed using two different methods, in this prospective cohort study on modifiable risk factors for *BRCA1* and *BRCA2* associated breast cancer, "current" intake will be assessed using food diaries and "habitual" or usual intake assessed by a food frequency questionnaire (FFQ).

Participants will be asked to complete an open-ended estimated 3 day food diary following each of the three active assessments. Participants will be provided with the diary at the end of each assessment and receive detailed verbal and written instructions detailing how it should be completed. The diet-diary booklet contains clear instructions of how to complete the food diary, as well as a detailed good and poor example of food intake. The instructions indicate that the respondent should record the food brand, portion size, cooking methods and includes a prompt for the name and daily dose of any vitamin, mineral or food supplements taken each day. General questions, for example, on the type of milk, spreadable fat usually consumed, and salt use will be asked as part of a general food habits questionnaire. Participants will be given a prepaid envelope to return the completed diary. The energy intake: calculated BMR ratio [51] was used as a measure of the degree of energy underreporting with each dietary method.

The FFQ used in this prospective study is a self-administered Willett FFQ adapted from the European Prospective Investigation of Cancer (EPIC) study [36] and was used in the Irish Survey of Lifestyle, Attitudes and Nutrition (SLÁN) 2007 [52]. This FFQ has previously been validated for use in an Irish adult population [53]. The FFQ consists of a checklist of 149 food and beverage items divided into the following main food groups consumed in Ireland; bread and savoury biscuits; cereals; potatoes, rice and pasta; dairy products and fats, meat fish and poultry; fruit; vegetables; sweets and snacks; soups, sauces and spreads and lastly drinks. Participants will be asked to report how often each food item was consumed during the previous year using common units or portion size for each food, e.g. one egg or one slice of bread will be specified. The nine frequency responses range from 'never or less than once per month' to 'six or more times per day'. Calculations for nutrient intake can be estimated via computerized software programs that multiply the reported frequency of each food by the amount of nutrient in a serving of that food. The FFQ will be incorporated into the annual questionnaire and completed by participants independently at home. Participants will be encouraged to contact study personnel if issues arise.

Annual questionnaire

Information on cancer occurrence and potential confounding factors affecting breast cancer risk will be gathered using questionnaires which will be completed on an annual basis after participants have enrolled. The questionnaire aims to track changes in modifiable lifestyle risk factors (weight, smoking, alcohol use, physical activity and diet), risk reducing procedures (prophylactic surgery), reproductive factors (childbirth, breastfeeding, use of oral contraceptive pill or hormonal replacement therapy) or cancer occurrence.

Statistical analysis

Sample size calculation: There is some evidence to suggest an association between BMI and breast cancer incidence in *BRCA* mutation carriers [19-21] and even stronger evidence to suggest an association with sporadic breast cancer [7]. Therefore BMI was the chosen outcome on which the power analysis is based. Assuming a difference of in BMI of 15 $kg.m^{-1}$ between cases and controls, with a relative risk of 2.08, 80% power and two-sided 5% significance level 141 participants would be required per group. However, a minimum sample size of 352 was calculated to allow for a 25% drop out rate due to the long-term nature of this study.

Data will be analysed using the SPSS package for Windows. Baseline descriptive statistics will be presented as means (standard deviations) for normally distributed continuous data, medians (inter quartile range, IQR) for non-normal data and as frequency (percentage) for categorical variables. Distributions will be checked for normality using the K-S test and non-normal data will be transformed using appropriate transformations. Differences in means of continuous variables (waist circumference, blood pressure (systolic and diastolic), lipids (TC, HDL-C, LDL-C and TG), glucose, insulin,

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HBA1c, CRP, leptin, adiponectin, BMI, fat free mass, percentage body fat, muscle mass, percentage time in each domain of physical activity, energy intake, telomere length) will be compared across categories (BMI sub-groups, presence or absence of metabolic syndrome, adherence to physical activity guidelines) using independent sample t-tests or ANOVA as appropriate for normally distributed variables and the Mann Whitney U test (or Kruskal-Wallis test) for non-normally distributed data. Chi-squared analysis will be used to compare categorical variables across the above stated groups.

Pearson or Spearmans correlation analysis will be conducted between body composition (BMI, waist circumference, percentage body fat), physical activity and dietary intake and the following variables: insulin resistance, leptin, adiponectin, inflammatory markers and telomere length for normally and non-normally distributed data respectively. Variables found to be associated at $p<0.10$ will be examined further using separate multiple regression analyses with body composition, physical activity and dietary intake as the dependent variables.

Cox proportional hazards regression models will be used to compute adjusted hazard ratios of time to breast cancer (event) with 95% confidence intervals. Data will be censored at the last available follow-up where the breast cancer status was recorded. Continuous variables will be categorised into known cut-points based on previous research (BMI will be categorised as <18.5 kg.m^{-2}, 18.5-24.9 kg.m^{-2}, 25-29.5 kg.m^{-2}, 30-34.9 kg.m^{-2}, 35-39.9 kg.m^{-2}, >40 kg.m^{-2}; waist circumference will be categorised as <80 cm, 80-87.9 cm, >88 cm; physical activity will be categorised as adherence to physical activity guidelines (30 minutes moderate intensity activity, 5 days per week) and non-adherence to activity guidelines). Quartile cut-offs will be established for markers without pre-determined categories. Metabolic syndrome variables (waist circumference, blood pressure, HDL-C, TG and glucose) will be standardized to z-score variables with mean=0, SD=1 and a composite z-score will be computed for the presence/absence of the metabolic syndrome. Confounding variables that will be considered in the analysis include: prophylactic surgery, hormone therapy use, parity, age at menarche, breastfeeding history, age at first birth, oral contraceptive use, smoking and age. All analyses will be stratified according to menopausal status.

Due the repeated nature of the data a multilevel regression model will be performed to examine the relationship between changes over time in outcome measures, such as body composition, physical activity and dietary intake, and the metabolic syndrome while controlling for other confounding variables. Significance at $p<0.05$ will be assumed and SPSS will be used for statistical analysis.

Data collection

Participant recruitment will be co-ordinated by EG and SMcG. Data will be collected by EG and processed by EG, SMcG and LH. Standardized testing and data processing protocols have been developed to ensure long-term valid data collection methods. Long-term management of the data collection and processing will be directed by L.C. and JH (principle investigators). All measurements and data processing will be completed at the Trinity Centre for Health Sciences, St. James's Hospital, Dublin, Ireland.

Discussion

The results of this prospective cohort study will provide valuable information regarding the risk reducing potential of modifiable risk factors for breast cancer in unaffected *BRCA1* and *BRCA2* gene carriers. To date, no study has prospectively examined lifestyle risk factors in this group, nor have the biological mechanisms linking obesity, physical inactivity and to breast cancer risk been investigated. This study will provide information regarding whether modifiable factors including body composition, the metabolic syndrome, physical activity and dietary intake can modulate breast cancer risk in *BRCA* mutation carriers, whether risk of breast cancer occurrence can be predicted in these individuals by PBMC telomere length and whether telomere length in these individuals is associated with various physical activity and lifestyle factors.

Abbreviations

BMI: Body mass index; PCR: Polymerase chain reaction; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TG: Triglycerides; HBA1c: Glycosylated haemoglobin; CRP: C - reactive protein; cm: Centimetre; mmol.L^{-1}: Millimoles per litre; mmHG: Millimetres mercury; mg.dl^{-1}: Milligrams per decilitre; MLTPAQ: Minnesota leisure time physical activity questionnaire; TOPAQ: Tecumseh occupational physical activity questionnaire; MET-min/day: Metabolic equivalent minutes per day; Kg.m^{-2}: Kilograms per metre squared; FFQ: Food frequency questionnaire; BMR: Basal metabolic rate.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

EG, JH, JOS and EC developed the idea for this study. EG was responsible for drafting the manuscript with contributions from SMcG and LH. EG is responsible for measurement and analysis of body composition, physical activity and metabolic syndrome outcomes. SMcG is responsible for DNA processing and analysis and for measurement of DNA telomere length. LH is responsible for assessment and analysis of dietary outcomes. KB provided statistical advice and contributed to the study design. All authors approved the final version of the manuscript.

Acknowledgements

Recruitment for this study has commenced. The authors would like to acknowledge Mr. Terence Boyle and the breast surgery team, the Breast Care Specialist Nurses, Dr. David Gallagher and the Genetics Nurses St. James's Hospital, Dublin and Professor Andrew Green and the genetics team at National Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin for their assistance with recruitment to date.

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Received: 15 October 2012 **Accepted:** 12 March 2013
Published: 21 March 2013

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doi:10.1186/1471-2407-13-138
Cite this article as: Guinan *et al.*: A prospective investigation of predictive and modifiable risk factors for breast cancer in unaffected *BRCA1* and *BRCA2* gene carriers. *BMC Cancer* 2013, 13:138.

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Appendix III: Participant Information Leaflets and Consent Forms

Study I Participant Information Leaflet and Consent Form





PARTICIPANT INFORMATION LEAFLET

TITLE: Effects of an Individually Prescribed Exercise Programme verses Usual Care on the Cardiovascular Risk Profile in a Population of Breast Cancer Survivors

Introduction

Weight gain can occur after chemotherapy treatment for breast cancer. This weight gain can have a negative effect on health and can increase the risk of future heart disease or type II diabetes. This study aims to investigate if body composition and cardiovascular risk can be improved by completing an exercise programme after chemotherapy. This study involves the same assessments and exercise interventions as the Prescribed Exercise after Chemotherapy Trial (PEACH trial), which you have already agreed to participate in. The only extra requirements of this study are a blood sample and completion of a food diary at the three assessment time points outlined below.

Who is being asked to participate?

Women who have completed their treatment for breast cancer and have agreed to participate in the PEACH trial will be invited to participate. Should you choose not to participate in this study, your participation in the PEACH trial will remain unaffected.

I have more questions, who will I ask?

For more information or answers to your questions about the study, your participation in the study, and your rights from Emer Guinan (Study Investigator & Physiotherapist) who can be telephoned at (01) 896 3613 (9am to 5pm Monday to Friday).

CONSENT FORM

TITLE: Effects of an Individually Prescribed Exercise Programme verses Usual Care on the Cardiovascular Risk Profile in a Population of Breast Cancer Survivors

This study and this consent form have been explained to me. The investigator has answered all my questions to my satisfaction.

I believe I understand what will happen if I agree to be part of this study. I will carry out all assessments related to the PEACH study including a fitness test, activity monitoring and completion of questionnaires. In addition, I will provide a blood sample and complete a food diary as part of this ancillary exploratory study.

I understand my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care being affected. I agree to allow the investigator in this study to access my medical chart in order to record information relating to the type of illness I have, the treatment/procedures I received and other medical conditions that might be relevant to the study.

I consent to the publication of data from this study and understand that my identity will remain confidential. I agree to the use of data collected in this study to be used in future studies without the need for giving consent again.

I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights

PARTICIPANT'S NAME:_____

PARTICIPANT'S SIGNATURE:_____

Date:_____

Date on which the participant was first furnished with this form:_____

Statement of investigator's responsibility

I have explained the nature, purpose, procedures, benefits, risks of or alternatives to this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's Signature:_____

Date:_____

Study II Participant Information Leaflet and Consent Form

PARTICIPANT INFORMATION LEAFLET

"THE METABOLIC RISK PROFILE OF BREAST CANCER SURVIVORS"

What is this study about?

In the last number of years, the numbers of women surviving breast cancer has increased greatly. However, emerging research indicates that physical activity and fitness levels can decrease considerably at diagnosis. Unfortunately many women do not return to their past physical activity levels after their treatment is complete. In addition, women may find that they experience weight gain during their treatment which they subsequently find difficult to lose. This combination may put breast cancer survivors at increased risk of developing heart disease and type II diabetes in the future. This study aims to evaluate a group of breast cancer survivors, up to 5 years following diagnosis, for a range of risk factors related to heart disease.

Who is being asked to participate?

Women who were diagnosed with breast cancer and subsequently treated with chemotherapy and/or hormonal therapy at St. James's Hospital in the last 5 years are being offered the opportunity to participate in this study. Your oncologist is happy for the research team to contact you and has provided medical approval for you to complete the assessments involved in this study. All assessments are free of charge.

What do I have to do?

You would be required to attend the Trinity Centre for Health Sciences, which is located on the grounds of St. James's hospital, for one appointment during which your assessment will take place. The assessment will last approximately an hour and a half.

What assessments are involved?

1. Body Composition



You will be asked to stand on a machine called a body composition analyser. This machine will calculate your body mass index, which is an equation used to estimate the ideal weight for your height. In addition, the machine will provide details on your percentage body fat, your muscle mass and your total body water. The machine is painless and takes 30 seconds to complete the measurements.

In addition, we will measure your waist circumference. This will measure the amount of weight you store on your stomach which may have important implications for your health.

2. Blood Sampling

Blood samples will be taken which will measure your cholesterol, fats, glucose, insulin, hormones and inflammatory markers. You will be asked to attend you appointment fasting so that these samples can be measured accurately.

3. Physical Activity

We will measure your physical activity in two ways. Firstly, the researcher will go through a questionnaire with you during your appointment. This questionnaire will ask you about your physical activity patterns in the past year.



In addition, you will be given an activity monitor to wear when you leave the centre. This monitor, call the RT3 accelerometer, is the same size as a bleep machine. You will be asked to wear it on the band of your trousers for one week. You will be provided with a stamped addressed envelope to post the monitor back to the study investigator.

4. Resting Metabolic Rate

Your resting metabolic rate refers to the amount of energy expenditure you use at rest. To measure it you will be asked to lie still for 20 minutes on a bed. During this time resting energy data will be collected by measuring the air you breathe in and out. You will feel very comfortable and relaxed during this assessment.

5. Aerobic Fitness

Your fitness will be tested by asking you to complete an exercise test on a treadmill. You will be given time to get familiar with walking on the treadmill before starting. The test will last 10-15 minutes. Your heart rate and blood pressure will be measured before the test starts and will be monitored throughout. You are free to stop the test at any time and the study investigator will be beside the treadmill for the duration of the test.

What are the benefits to me?

You will receive feedback regarding all the assessments completed during the study from a chartered physiotherapist with a particular interest in cancer research. In addition, you will be invited to ask any questions you may have regarding physical activity and exercise guidelines.

What are the risks?

We do not anticipate adverse effects during the assessments. Occasionally, people can feel dizzy or breathless when doing an exercise test. However, because the exercise test is carefully graded, the risks of this happening are minimal. You will be required to complete a medical screening questionnaire prior to participation to assess suitability.The assessment will be conducted by a qualified physiotherapist with experience in all of the assessments outlined above. If any concerns are expressed, you will have the opportunity to be followed up by referral to the Physiotherapy Department or appropriate medical team for review. The practitioners involved in this study have current medical indemnity cover.

Will my information be confidential?

Your identity and data will remain confidential. Your name will not be published and will not be disclosed to anyone outside of the hospital.

Compensation

The postgraduate research student who is conducting the assessment is a chartered physiotherapist and is covered by the Trinity College Dublin insurance scheme. Nothing in this document restricts or curtails your rights.

What if I change my mind?

If you volunteer to participate in this study, you may stop at any time. If you decide not to participate, or if you stop, you will not be penalised and will not give up any benefits which you had before entering the study.

Stopping the study

Your doctor or the investigator in this study may stop your participation at any time without your consent.

Permission

This study has received Hospital Research Ethics committee approval.

I have more questions, who will I ask?

For more information or answers to your questions about the study, your participation in the study, and your rights from Emer Guinan (Study Investigator & Physiotherapist) who can be telephoned at (01) 896 3613 (9am to 5pm Monday to Friday).

CONSENT FORM

"THE METABOLIC RISK PROFILE OF BREAST CANCER SURVIVORS"

This study and this consent form have been explained to me. The investigator has answered all my questions to my satisfaction.

I believe I understand what will happen if I agree to be part of this study. I will attend the Trinity Centre for Health Sciences at St. James's Hospital for one appointment. During this appointment I will carry out all assessments related to the study including measurement of body composition, a fitness test, measurement of resting metabolic rate and completion of questionnaires. In addition, I will provide a fasting blood sample. I am happy to take home an activity monitor which I will wear for one week. I will post these items back to the study investigator in the stamped addressed envelope provided to me.

I understand my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care being affected. I agree to allow the investigator in this study to access my medical chart in order to record information that might be relevant to the study. I consent to the publication of data from this study and understand that my identity will remain confidential. I agree to the use of data collected in this study to be used in future studies without the need for giving consent again.

I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights

PARTICIPANT'S NAME:_____

PARTICIPANT'S SIGNATURE:_____

Date:_____

Date on which the participant was first furnished with this form:_____

Statement of investigator's responsibility

I have explained the nature, purpose, procedures, benefits, risks of or alternatives to this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's Signature:_____

Date:_____

Study III Participant Information Leaflet and Consent Form



PARTICIPANT INFORMATION LEAFLET



A PROSPECTIVE INVESTIGATION OF PREDICTIVE AND MODIFIABLE RISK FACTORS FOR BREAST CANCER IN UNAFFECTED *BRCA1* AND *BRCA2* GENE CARRIERS

What is this study about?

Women who inherit the deleterious mutation in either of the two breast cancer risk related genes, *BRCA1* or *BRCA2*, have an increased lifetime risk of developing breast cancer. Currently, management of this group involves having regular screening for breast cancer using MRI, mammography and ultrasound, taking medication or undergoing surgical procedures such as prophylactic oophorectomy or mastectomy.

Despite the knowledge that breast cancer risk in the general population is increased in women who are obese and/or physically inactive, very little is known about the role these lifestyle factors have to play in *BRCA* gene carriers. This study aims to measure a number of lifestyle-related risk factors for breast cancer among a population of *BRCA* gene carriers who have not been affected by breast cancer. We will follow-up this group over the next 10 years to see if lifestyle factors play a role in modifying breast cancer risk. In addition, various biomarkers will be measured in blood from this population of *BRCA* gene carriers at 6 month intervals over this time period to see if these biomarkers can help predict breast cancer risk in these individuals.

Who is being asked to participate?

Women have been genetically tested and identified as carriers of either one of the *BRCA* genes, *BRCA1* or *BRCA2* are being invited to participate in this study.

What do I have to do?

You would be required to attend the Trinity Centre for Health Sciences, which is located on the grounds of St. James's hospital, for three appointments lasting approximately 1 hour. The first appointment would take place in the coming months. The second appoint would take place in two years' time and the third one in five years' time. You will also be asked to complete a questionnaire every year for the next 10 years. The questionnaire will be sent to you by post and you will be provided with a stamped addressed envelope to post it back.

What assessments are involved?

The following assessments will be completed during your three visits to the Trinity Centre for Health Sciences at St. James's hospital. In addition to the assessments outlined below, you will be asked some questions about your medical history and your social background.

1. Body Composition



You will be asked to stand on a machine called a body composition analyser. This machine will calculate your body mass index, which is an equation used to estimate the ideal weight for your height. In addition, it will provide details on your percentage body fat, muscle mass and total body water. It only takes 30 seconds to complete the measurements.

In addition, we will measure your waist circumference. This will measure the amount of weight you store around the centre which may have important implications for your health.

2. Blood Sampling

Blood samples will be taken which will measure your cholesterol, fats, glucose, insulin, hormones and inflammatory markers. In addition, white blood cells will be isolated from your blood sample and DNA and RNA will be extracted from these cells for analysis. You will be asked to attend you appointment fasting so that these samples can be measured accurately.

3. Blood pressure

Your blood pressure will be measured twice during your visit after you have been resting for at least 5 minutes.

4. Physical Activity

We will measure your physical activity in two ways. Firstly, the researcher will go through two questionnaires with you during your appointment. This questionnaire will ask you about your physical activity patterns in the past year.



You will also be given an activity monitor to wear when you leave the centre. This monitor, call the RT3 accelerometer, is the same size as a bleep machine. You will be asked to wear it on the band of your trousers for one week. You will be provided with a stamped addressed envelope to post the monitor back to the study investigator.

5. Food Diary

You will be asked to record everything you eat and drink over three days in a food diary that you will be given following you assessment.

6. Yearly Questionnaire

You will receive a short questionnaire by post once per year over the study period (10 years). The questionnaire contains 10 questions about your health status and any changes that may have occurred during the year. One of the questions will ask about a diagnosis of cancer and permission to contact your GP. Any information provided by your GP is confidential and only available to the research team. If there is a diagnosis of cancer further assessments will not be required as part of this research.

What are the benefits to me?

You will receive feedback regarding all the assessments completed during the study from a chartered physiotherapist. In addition, you will be invited to ask any questions you may have regarding physical activity and exercise guidelines.

What are the risks?

We do not anticipate adverse effects during the assessments. The assessment will be conducted by a qualified physiotherapist with experience in all of the assessments outlined above. If any concerns are expressed, you will have the opportunity to be followed up by referral to the Physiotherapy Department or appropriate medical team for review. The practitioners involved in this study have current medical indemnity cover.The blood sample will be taken using a needle and syringe. It is possible that you may experience some minor discomfort such as pain or bruising at the site where the needle is placed into the vein. Other symptoms you may experience are light-headedness and in rare cases fainting or infection.

Will my information be confidential?

Your identity and data will remain confidential. Your name will not be published and will not be disclosed to anyone outside of the hospital.

Compensation

The postgraduate research student who is conducting the assessment is a chartered physiotherapist and is covered by the Trinity College Dublin insurance scheme. Nothing in this document restricts or curtails your rights.

What if I change my mind?

If you volunteer to participate in this study you may stop at any time. If you decide not to participate or if you stop you will not be penalised and will not give up any benefits which you had before entering the study. If you withdraw from the study, unless you request otherwise, any data which has been collected up until that time may still be used for the purposes of this research but you will not be approached again to provide additional data.

Stopping the study

Your doctor or the investigator in this study may stop your participation at any time without your consent.

Permission

This study has received Hospital Research Ethics committee approval.

I have more questions, who will I ask?

For more information or answers to your questions about the study, your participation in the study, and your rights, contact Emer Guinan (Lead Investigator) who can be telephoned at (01) 896 3613 (9am to 5pm Monday to Friday).

CONSENT FORM

A PROSPECTIVE INVESTIGATION OF PREDICTIVE AND MODIFIABLE RISK FACTORS FOR BREAST CANCER IN UNAFFECTED *BRCA1* AND *BRCA2* GENE CARRIERS

I agree to take part in this study. I have read the information leaflet about the study and I have had the opportunity to ask any questions that I wished to ask. I understand the assessments and procedures involved and I consent to the recording of the information I will provide, on the understanding that it is strictly confidential and will only be used for the purposes of research. I agree to allow the investigators in this study to access my medical chart in order to record information that might be relevant to the study. I understand that I may be contacted in the future to provide additional consent for the research team to contact my GP if they require additional medical information.

I understand my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care being affected. I consent to the publication of data from this study and understand that my identity will remain confidential. I agree that data and blood samples including extracted DNA and RNA collected in this study may be used in future studies without the need for giving consent again.

I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights

PARTICIPANT'S NAME:_____

PARTICIPANT'S SIGNATURE:_____

Date:_____

Statement of investigator's responsibility

I have explained the nature, purpose, procedures, benefits, risks of or alternatives to this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Investigator's Signature:_____

Date:_____

Appendix IV: Testing Protocol

Study I Testing Protocol

PEACH Trial Testing Protocol

- All assessments to be completed by a blind assessor (Emer Guinan).
- All assessments to be completed at all three assessments (pre-intervention (baseline), post-intervention (8-week) and at 3 months post intervention (3-months).
- Following the baseline assessment all participants to be contacted by the exercise class co-ordinator (Julie Broderick) to be informed of group assignment.
- Following the final (3-month) assessment, participants from the control group will receive an exercise advice session from the exercise class co-ordinator.

The following testing procedure will be adhered to:

1. Welcome participant. Explain the procedure. Ensure all consent forms (PEACH trial and ancillary study) are signed.

2. Measure height using the stadiometer with no shoes.

3. Ask participant to void their bladder if they have not done so in the last 30 minutes prior to measuring body composition on the Tanta BIA as per protocol.

4. When the participant is sitting comfortably take blood samples as per protocol. If patient has a history of difficulty taking blood samples they will be brought to the outpatient phlebotomy department at St. James's Hospital for blood samples. This will be completed prior to BIA analysis.

5. Participant will continue to rest in a seated position during which time the following questionnaires will be completed: background demographics, Godin questionnaire, FACT-G, FACT-F, SF-36.

6. Check resting heart rate on polar heart rate monitor and measure at the radial artery.

7. Following 5 minutes of quiet sitting measure blood pressure twice on the non-surgical side as per protocol.

8. Ask the participant to stand and then measure waist circumference twice as per protocol.

9. Offer the participant some water and explain the Modified Bruce testing Protocol.

10. Complete the Modified Bruce Protocol on the treadmill to estimate aerobic fitness as per protocol. Following the cool-down ask participant to carefully step down from the treadmill. Leave the Polar heart rate monitor in place to monitor heart rate.

11. Provide the participant with the RT3 activity monitor and explain its use. Provide the participant with the 3-day food diary and explain its use. Answer any participant questions. Participants will be allowed to leave the test centre when heart rate has returned to within 10% of resting measures.

12. Participants will be contacted one week following the assessment to remind them to return the RT3 activity monitor and food diary to the test centre by post in the stamped addressed envelope provided.

Study II Testing Protocol

Study II Complete Testing Protocol

13. Welcome participant. Explain the procedure. Ensure the consent for is signed and that the PARQ is complete.

14. Measure height using the stadiometer as per protocol.

15. Ask participant to void their bladder if they have not done so in the last 30 minutes prior to measuring body composition on the Tanta BIA as per protocol.

16. Put polar heart rate monitor on participant.

17. Ask participant to lie supine on plinth. When they are comfortable take blood samples as per protocol. If patient has a history of difficulty taking blood samples they will be brought to the outpatient phlebotomy department at St. James's Hospital for blood samples. This will be completed prior to BIA analysis.

18. Participant will continue to rest supine on the plinth for at least 7 minutes. During this time the assessor collects background demographics and completes the Minnesota Leisure Time Physical Activity Questionnaire.

19. When the participant has been resting for the required amount of time (7-20 minutes) resting metabolic rate will be measured as per protocol.

20. Following RMR measurement, remove the canopy from the participants head and shoulders but ask them to remain in a supine position.

21. Check resting heart rate on polar heart rate monitor and measure at the radial artery.

22. Ask the participant to sit up slowly and to transfer to sitting in a supported seat. Following 5 minutes rest measure resting blood pressure twice on the non-surgical side as per protocol.

23. Ask the participant to stand and then measure waist circumference twice as per protocol.

24. Offer the participant some water and explain the Modified Bruce testing Protocol.

25. Complete the Modified Bruce Protocol on the treadmill to estimate aerobic fitness as per protocol. Following the cool-down ask participant to carefully step down from the treadmill. Leave the Polar heart rate monitor in place to monitor heart rate.

26. Provide the participant with the RT3 activity monitor and explain its use. Answer any participant questions about the assessment and explain results. Participants will be allowed to leave the test centre when heart rate has returned to within 10% of resting measures.

27. Participants will be contacted one week following the assessment to remind them to return the RT3 activity monitor by post in the stamped addressed envelope provided.

28. Upon return of the monitor to the test centre anthropometric, blood results, physical activity data, RMR and aerobic fitness results will be compiled and posted to the participant. Abnormal values will be highlighted and the participant will be advised to attend their GP for medical follow-up.

Study II Testing Protocol

BRCA Study Testing Protocol

1. Welcome participant. Explain the procedure. Ensure the consent form is signed.

2. Measure height using the stadiometer as per protocol.

3. Ask participant to void their bladder if they have not done so in the last 30 minutes prior to measuring body composition on the Tanta BIA as per protocol.

4. When the participant is sitting comfortably take blood samples as per protocol. If patient has a history of difficulty taking blood samples they will be brought to the outpatient phlebotomy department at St. James's Hospital for blood samples. This will be completed prior to BIA analysis.

5. Participant will continue to rest in a seated position during which time the following questionnaires will be completed: background demographics, Minnesota questionnaire and the Tecumseh questionnaire.

6. Following 5 minutes of quiet sitting measure blood pressure twice as per protocol.

7. Ask the participant to stand and then measure waist circumference twice as per protocol.

8. Provide the participant with the RT3 activity monitor and explain its use. Answer any participant questions about the assessment and explain results.

9. Participants will be contacted one week following the assessment to remind them to return the RT3 activity monitor by post in the stamped addressed envelope provided.

10. Upon return of the monitor to the test centre anthropometric, blood results and physical activity data will be compiled and posted to the participant. Abnormal values will be highlighted and the participant will be advised to attend their GP for medical follow-up.

Appendix V: RT3 Activity Monitor Participant Information Leaflet

RT3 ACTIVITY MONITOR

Thank you for agreeing to wear the RT3 activity monitor. You are required to wear your activity monitor for one week (7 days). The information collected will help us to calculate how active you are in an average week. If you have any questions during the week please do not hesitate to contact Emer on 01-8963613.

How to start your activity monitor

1. Remove the sello-tape and the see-through clip.

2. Press the big button on the front surface of the monitor once to start. You may hear a small beep when you press this to indicate that it has been switched on. Otherwise look at the screen on the top surface of the monitor. When the monitor is active the dots between the numbers will flash.

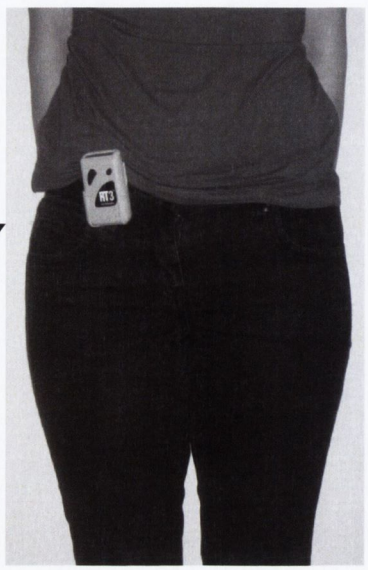
3. Clip the RT3 activity monitor onto your trousers or skirt at your right hip on the front of your body. Buttons should face outwards.

4. The RT3 activity monitor is now working. You are not required to press the buttons again during the week. Do not worry if you press one of the buttons accidentally. This will not affect the recording of your activity data.



Press the big button once to start the activity monitor.

Wear the monitor throughout the day on the front of your right hip.



Filling in your activity diary

1. You are asked to record the time you put your activity monitor on in the morning and the time you take it off when going to bed at night.

2. You should also record any other times during the day that you remove your activity monitor and when you put it on again. Reasons to remove your monitor include:
    a. Going for a shower / bath
    b. Going for a swim
    c. Going for a sleep in bed during the day (wear your monitor if taking a rest on the couch)

3. Please record what activities you complete when not wearing your monitor.

- Start wearing your monitor first thing in the morning when you get up, even if you choose not to get dressed into your day clothes at that point (eg if you wear your dressing gown in the morning-clip the monitor onto your dressing gown belt) .

- Wear your monitor until you go to bed at night. A good tip is to place your monitor on your locker when you go to bed so you see it first thing in the morning.

- At the end of the week you will be contacted by a member of the research team. Please return the activity monitor and diary to us in the stamped addressed envelope provided.

Please remember not to change your activities-our aim is to get an idea of your 'normal' activity patterns over the monitoring period.

Thank you very much for recording your physical activity

Appendix VI: Godin Leisure Time Exercise Questionnaire

Godin Leisure-Time Exercise Questionnaire

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

	Times Per Week
a) **STRENUOUS EXERCISE** **(HEART BEATS RAPIDLY)** (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	_____
MODERATE EXERCISE **(NOT EXHAUSTING)** (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____
b) **MILD EXERCISE** **(MINIMAL EFFORT)** (e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)	_____

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

OFTEN	SOMETIMES	NEVER/RARELY
1. |_|	2. |_|	3. |_|

Appendix VII: Minnesota Leisure Time Physical Activity Questionnaire

MINNESOTA LEISURE TIME PHYSICAL ACTIVITY QUESTIONNAIRE

Subject ID: _____ Date: _____

Listed below are a series of Leisure Time Activities. Related activities are grouped under general headings. Please read the list and check "YES" in column 3 for those activities which you have performed in the last 12 months and "NO" in column 2 for those you have not. Do not complete any of the other columns.

To be completed by participant		Did you perform this activity?		Do not write in this space	Month of activity												Ave no of times per month			Time per occasion			
Activity (1)		No	Yes		J	F	M	A	M	J	J	A	S	O	N	D				Hrs		Min	
SECTION A: Walking and Miscellaneous																							
010	Walking for pleasure																						
020	Walking to work																						
030	Using stairs when elevator is available																						
040	Cross Country Hiking																						
050	Back Packing																						
060	Mountain Climbing																						
115	Bicycling to work and/or for pleasure																						
125	Dancing – Ballroom, Square and/or Disco																						
135	Dancing – Aerobic or Ballet																						
140	Horseback Riding																						
SECTION B: Conditioning Exercise																							
150	Home Exercise																						
160	Health Club Exercise																						
180	Jog/Walk Combination																						
200	Running																						
210	Weight Lifting																						
SECTION C: Water Activities																							
220	Water Skiing																						
235	Sailing in Competition																						
250	Canoeing or Rowing for Pleasure																						
260	Canoeing or Rowing in Competition																						
270	Canoeing on a Camping Trip																						
280	Swimming (at least 50 ft) in a Pool																						
295	Swimming at the beach																						
310	Scuba Diving																						
320	Snorkelling																						

SECTION D: WINTER ACTIVITIES																								
340	Snow skiing, downhill																							
350	Snow skiing uphill																							
360	Ice (or Roller) Skating																							
370	Sledding or Tobogganing																							
SECTION E: Sports																								
390	Bowling																							
400	Volley ball																							
410	Table tennis																							
420	Tennis singles																							
430	Tennis Doubles																							
440	Softball																							
450	Badminton																							
460	Paddle Ball																							
470	Racket Ball																							
480	Basketball: Non-Game																							
490	Basketball: Game play																							
500	Basketball: Officiating																							
510	Touch Football																							
520	Handball																							
530	Squash																							
540	Soccer																							
	GOLF																							
070	Pulling a power cart																							
080	Walking, pulling clubs on cart																							
090	Walking and carrying clubs																							
SECTION F: Lawn and Garden Activities																								
550	Mowing Lawn with riding lawnmower																							
560	Mowing lawn walking behind power mower																							
570	Mowing lawn pushing hand mower																							
580	Weeding and cultivating garden																							
590	Spading, Digging, Filling in Garden																							
600	Raking Lawn																							
610	Snow shovelling by hand																							
SECTION G: Home Repair Activities																								
620	Carpentry in workplace																							

630	Painting inside of house, includes paper hanging																								
640	Carpentry outside																								
650	Painting outside of house																								
SECTION H: Fishing and Hunting																									
660	Fishing from river bank																								
670	Fishing in stream with wading boots																								
680	Hunting pheasants or grouse																								
690	Hunting rabbits, prairie chickens squirrels or racoons																								
710	Hunting large game: deer, elk, bear.																								
SECTION I: Other Activities																									

Minnesota Questionnaire Scoring Protocol

Energy expenditure resulting from physical activity is calculated as a product of activity intensity code (*I*) and duration of activity participation over the past year (*D*). Intensity codes correspond to MET values for each activity from the Compendium of Physical Activities (Ainsworth et al., 2011, Taylor et al., 1978). Duration of activity is calculated as a product of months spent in activity (*M*), the frequency of activity (*F*) and the time spent per occasion (*T*). The resultant Activity Metabolic Index (*AMI*) provides an estimate of kilocalories expended over time. In this thesis AMI was expressed as MET-h.week^{-1} ((AMI /60 (minutes.hour^{-1}))/52 (weeks.year^{-1})).

Activity Metabolic Index = Intensity code x Duration of time in exercise

$$AMI = I \times (M \times F \times T)$$

Light AMI was calculated by summing total AMI for all activities with intensity codes 2.0 and 2.5.[1] Moderate AMI was calculated by summing activities with the intensity codes 3.0, 3.5, 4.0, 4.5, 5.0 and 5.5 and heavy AMI is calculated by summing all of the activities with intensity codes ≥ 6.0.

[1] In the original scoring protocol by Taylor et al., (1978) light intensity was defined as MET values 2.0 to 4.0. More recent publications define light intensity as ≤3.0 METS and moderate intensity as 3.0-6.0 METS (Garber et al., 2011), thus the original scoring protocol was amended to define light intensity activity as ≤3.0 METS.

Appendix VIII: The Tecumseh Occupational Physical Activity Questionnaire

Tecumseh Occupational Physical Activity Questionnaire

SECTION A: WORK HISTORY

Please fill in the following information about jobs you have held in the past 12 months. Jobs include both full-time and part-time. You may have a single job or hold two or more jobs at once. If you change responsibility with the same employer, consider it to be a change of jobs if a substantial change occurs in physical effort or tasks demanding physical activity. For Example, changing from bookkeeping to construction work within the same company would be a "change of job". If you have held more than 3 jobs in the past 12 months, please answer for the 3 jobs which required the most physical effort.

1. Have you been employed at a job for pay in the past 12 months? 1. Yes ___-->GO TO QUESTION 2

   2. No___--> YOU ARE DONE WITH THIS QUESTIONNAIRE

2. For how many months were you employed in the past 12 months: _____ months

3. How many weeks were you on vacation (not working in any job)? _____weeks

WORK HISTORY FOR THE PAST 12 MONTHS

	JOB 1	JOB 2	JOB 3
4. Occupation :	_____	_____	_____
5. Name of Business:	_____	_____	_____
6. How many hours/weeks do/did you usually work?	_____	_____	_____

SECTION B: TRANSPORTATION TO AND FROM WORK

7. Check the months you worked each job. Then check the months you used each kind of transportation to and from each of your jobs.

	JOB 1												JOB 2												JOB 3											
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Months worked each job:																																				
Mode of Transport	JOB 1												JOB 2												JOB 3											
Car, Bus, Tram																																				
Bicycle																																				
Walk																																				

8. What is the approximate round trip distance that you walked or bicycled to and from each of your jobs in miles? (If you never walked or bicycled, enter "0" for distance. Do not include walking or bicycling on the job.)

	JOB 1	JOB 2	JOB 3
Distance walked:	_____ miles	_____ miles	_____ miles
Distance bicycled:	_____ miles	_____ miles	_____ miles

9. In months that you walked to work, how many times per month did you usually do this?

	JOB 1	JOB 2	JOB 3
Average times per month walked to work:	_____	_____	_____

10. In months that you bicycled to work, how many times per month did you usually do this?

	JOB 1	JOB 2	JOB 3
Average times per month walked to work:	_____	_____	_____

SECTION C: PHYSICAL ACTIVITY AT WORK

We are interested in the amount of activity that people do in different occupations. Then about the job-related activity you mostly did in a work week during the time you worked in the past 12 months. First, read each of the following categories and mark "YES" for the ones you usually did and "NO" for the ones you did not do. Then, go back through the list and record the number of hours per week you spend on each activity.

	JOB 1 HRS/WK	JOB 2 HRS/WK	JOB 3 HRS/WK
11. Sitting – Light work * desk work * using handtools *light assembly or repair * driving car or truck (if you carry or move heavy objects, respond to items 19-23 also)	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No
12. Sitting - Moderate work *working heavy levers *riding mower or forklift *crane operation	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No
13. Standing – Light work *bartender / lab tech work *store clerk behind a counter *standing talking with co-worker or customer / filing paper *assembling light machine parts at own pace *using handtools / car wash attender	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No

14. Standing – Light-Mod work
*light welding/stocking shelves
*assembling or repairing heavy machine parts
*packing or unpacking small objects
*sanding, scrubbing, polishing floor with power equipment

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

15. Standing – Moderate work
*pulling on wires/twisting cables
*assembling or work with light machine pars at fast rate on assembly line
*lifting up to 50 lbs every live mine or so for a few seconds at a time
*cranking up dollies/hitching trailers
*operating large levers, jacks
*jerking on ropes, cables, etc., such as repairing houses

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

16. Standing – Mod-Heavy work
*masonary/painting
*paper hanging
*lifting more than 50 lbs every five mins or so for a few secs at a time

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

17. Walking at work, not carrying anything heavier than briefcase
*between buildings/in hallways
*roving store clerk

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

18. Walking carrying something
*trays, dishes
*gas station mechanic work, changing tyres, wrecker work, etc.

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

19. Standing or walking, carrying objects about 25 lbs

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

20. Standing or walking carrying objects about 50 lbs

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

21. Standing or walking, carrying objects about 75 lbs

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

22. Standing or walking, carrying objects about 100 lbs

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

1.___ Yes-->_____ 2.___ No

23. Moving, pushing heavy objects, 75 lbs or more *desks, file cabinets, heavy stock, furniture *moving van work	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No
24. Carpentry	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No
25. Using heavy power tools such as pneumatic tools (drills, jackhammers, tampers)	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No
26. Using heavy power tools (not power tools) such as shovel, pick, funnel bar, spade	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No
27. Other activities (specify):_	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No	1.___ Yes-->_____ 2.___ No
28. Total the number of hours for each job. This should equal the totals in Questions 6	_____	_____	_____

SECTION D: WALKING UP AND DOWN STAIRS OR LADDERS

	JOB 1	JOB 2	JOB 3
29. Give the number of flights of stairs or steps per day. Use 10 stairs per flight, and count up and down as one flight.	_____	_____	_____

Tecumseh Questionnaire Scoring Protocol

Energy expended due to physical activity related to work was calculated as a product of activity intensity (METs) by hours per week in activity. Intensity codes correspond to MET values for each activity from the Compendium of Physical Activities (Ainsworth et al, 2011, Ainsworth et al., 1993). Yearly activity was corrected for weeks spent on holiday (weeks worked per year / 52 weeks per year). The resultant activity unit.week^{-1} (AU.week^{-1}) provided an estimate of energy expended per week of work in that activity. In this thesis AU.week^{-1} was expressed in MET-h.week^{-1}

AU.Week^{-1} = (MET Intensity)*(Hours.week^{-1} in activity)*(weeks worked per year/52)

Total sedentary AU.week^{-1} was calculated by summing total AU.week^{-1} for all activity with intensity codes ≤1.5 METs. Total light AU.week^{-1} was calculated by summing total AU.week^{-1} for all activities with intensity codes 1.6 to 2.9. Total moderate AU.week^{-1} was calculated by summing total AU.week^{-1} for all activity with intensity codes 3.0 to 5.9 and total heavy AU.week^{-1} was calculated by summing total AU.week^{-1} for all activities with intensity codes ≥6.0.

Appendix IX: Standard Lab Procedure for Serum Aliquoting

Laboratory procedure for sample handling and storage

Venous samples

Venous samples will be collected into Two x 6mL serum and 1 x 2mL EDTA vacutainers and processed in the laboratory in the Trinity Centre. Processing is as follows:

1. A lab-coat, disposable gloves and safety glasses must be worn.
2. Samples from one subject is dealt with at any one time.
3. At least 30 minutes is allowed to elapse between the time at which the sample was collected and the time at which the sample is processed.
4. The two vacutainers are placed in the centrifuge and the centrifuge is balanced. The vacutainers are spun in the centrifuge for **15 minutes at 3,000 rpm at 4°C.**
5. In the meantime, the 'Sample Collection and Storage Log' sheet is completed. This is used to log all volunteers' samples for that particular day.
6. Six microtubes are prepared. The microtube labels will have been pre-printed and will contain the following information:
   - Subject ID number eg E001
   - Study name ie E. Guinan PEACH
   - Today's date
   - 'Serum' (6 x microtubes)

7. When the centrifuge has stopped spinning, remove the samples. Aliquot serum from the 2 x 6mL serum vacutainers equally into the 6 microtubes which are labeled with 'serum' and plasma from the 1 x 2mL EDTA into 2 microtubes. Close each microtube with lid. Dispose of the vacutainers into cinbin.
8. Store the microtubes in the appropriate box in the -80ºC freezer and record the box number on the Sample Collection and Storage Log.
9. Once all samples have been processed for that day, replace centrifuge lid, tidy away all equipment used and disinfect the laboratory bench.

Appendix X: Instructions for Completing the Food Diary



Instructions for completing the food diary



Thank you for agreeing to keep a food diary. The information collected is a very valuable part of this study. If you have any questions as you fill in the food diary, please do not hesitate to contact Emer Guinan on 01 8963613 or email at emguinan@tcd.ie

1. You are being asked to record everything you eat and drink over 3 days. The study investigator will tell you which 3 days to choose.

2. We ask that you record when you eat/drink (i.e. approximate time), a description of the item (including brand name), how you prepared it (fried, roasted, grilled, boiled, steamed etc) and the portion size. There is space for all of this information in the diary.

3. There are some useful examples on pages 2-5.

4. It is very important that you do not change what you normally eat and drink just because you are recording it as part of the study. Please continue to eat and drink as you ordinarily do.

5. Please record everything which you eat and drink at the time that you eat and drink the items. You can carry the diary in your handbag or pocket. Please do not do it from memory at the end of the day.

6. Please ensure that you record everything that you may eat or drink in the night (including water, alcohol) and also snacks that you might have eaten/drunk between meals.
7. Please record as much information as you can about the food or drink i.e. brand name, portion size, how you cooked the food (grilled, fried, toasted etc), anything you added to the food such as sauces etc. Feel free to include labels from foods.

8. Portion size can be difficult to measure! There is no need to weigh the food/drink but we do ask that you take a look at the photos on pages 6-9. For example, if you eat a bowl of cornflakes for breakfast and the portion size you ate is similar to bowl B on page 9, then write 'portion 12B' in the column called 'Amount' which is appropriate for that day.

9. Have a look at pages 10-13 for further information which will help you to describe how you prepared a food and what portion you ate.

10. When you have finished recording all food and drinks consumed for 3 days, please turn to pages 34-35 to complete.

11. Please include the recipe or ingredients of any made-up dishes/drinks, take-away or restaurant items that you have consumed; there is space for this at the end of each day. Feel free to continue on a separate sheet if necessary.

12. Please return the food diary to the investigators in the stamped addresses envelope provided.

Thank you very much for recording your dietary intake.

Appendix XI: Physical Activity Readiness Questionnaire

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

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

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

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

YES	NO		
☐	☐	1.	**Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2.	**Do you feel pain in your chest when you do physical activity?**
☐	☐	3.	**In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4.	**Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5.	**Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6.	**Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7.	**Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

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

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

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

→ **DELAY BECOMING MUCH MORE ACTIVE:**

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

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

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

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

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

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

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

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

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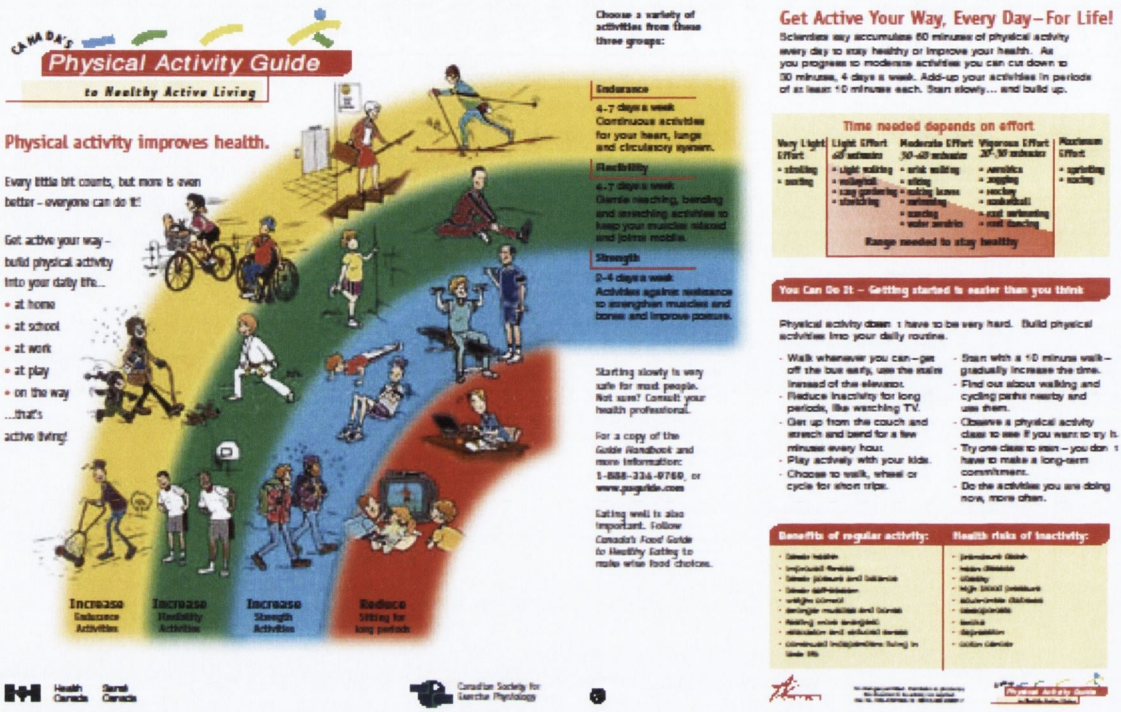
Supported by: Health Canada Santé Canada

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PAR-Q & YOU

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)



Source: Canada's Physical Activity Guide to Healthy Active Living, Health Canada, 1998 http://www.hc-sc.gc.ca/hppb/paguide/pdf/guideEng.pdf

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FITNESS AND HEALTH PROFESSIONALS MAY BE INTERESTED IN THE INFORMATION BELOW:

The following companion forms are available for doctors' use by contacting the Canadian Society for Exercise Physiology (address below):

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

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

References:

Arraix, G.A., Wigle, D.T., Mao, Y. (1992). Risk Assessment of Physical Activity and Physical Fitness in the Canada Health Survey Follow-Up Study. **J. Clin. Epidemiol.** 45:4 419-428.

Mottola, M., Wolfe, L.A. (1994). Active Living and Pregnancy. In: A. Quinney, L. Gauvin, T. Wall (eds.), **Toward Active Living: Proceedings of the International Conference on Physical Activity, Fitness and Health**. Champaign, IL: Human Kinetics.

PAR-Q Validation Report, British Columbia Ministry of Health, 1978.

Thomas, S., Reading, J., Shephard, R.J. (1992). Revision of the Physical Activity Readiness Questionnaire (PAR-Q). **Can. J. Spt. Sci.** 17:4 338-345.

For more information, please contact the:

Canadian Society for Exercise Physiology
202-185 Somerset Street West
Ottawa, ON K2P 0J2
Tel. 1-877-651-3755 • FAX (613) 234-3565
Online: www.csep.ca

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

Disponible en français sous le titre «Questionnaire sur l'aptitude à l'activité physique - Q-AAP (revisé 2002)».

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Supported by: Health Canada Santé Canada

Appendix XII: BORG Rating of Perceived Exertion

Exertion	RPE
No exertion at all	6
Extremely light	7
	8
Very light	9
	10
Light	11
	12
Somewhat hard	13
	14
Hard (heavy)	15
	16
Very hard	17
	18
Extremely hard	19
Maximal exertion	20

Appendix XIII: Fitness Reference Values

Gender	Age	Poor	Fair	Average	Good	Excellent
Men	≤29	≤24.9	25-33.9	34-43.9	44-52.9	≥53
	30-39	≤22.9	23-30.9	31-41.9	42-49.9	≥50
	40-49	≤19.9	20-26.9	27-38.9	39-44.9	≥45
	50-59	≤17.9	18-24.9	25-37.9	38-42.9	≥43
	60-69	≤15.9	16-22.9	23-35.9	36-40.9	≥41
Women	≤29	≤23.9	24-30.9	31-38.9	39-48.9	≥49
	30-39	≤19.9	20-27.9	28-36.9	37-44.9	≥45
	40-49	≤16.9	17-24.9	25-34.9	35-41.9	≥42
	50-59	≤14.9	15-21.9	22-33.9	34-39.9	≥40
	60-69	≤12.9	13-20.9	21-32.9	33-36.9	≥37

Aerobic fitness classifications are based on relative VO2max ($mL.kg.^{-1}.min^{-1}$). Taken from *"Katch, V., McArdle, W., Katch, F. "Training the Anaerobic and Aerobic Energy Systems" Chapter 13, page 426 in "Essentials of Exercise Physiology", Fourth Edition."*

Appendix XIV: PEACH Trial Home Exercise Programme

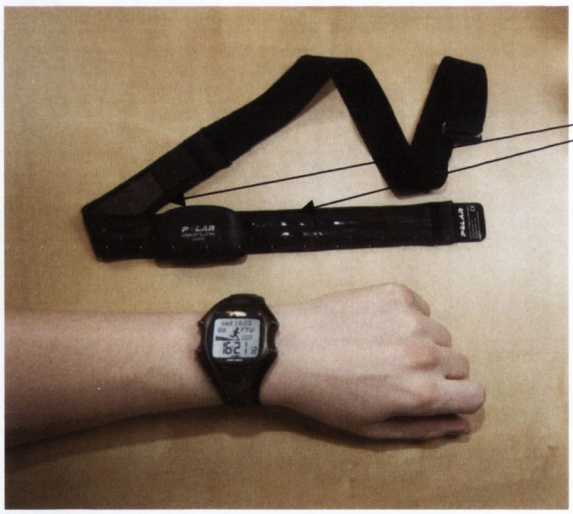
PEACH Trial - WEEK 1 Goal

Walk for at twenty minutes at a brisk pace at least 1 other day of the week

Please record your walking or any other type of exercise you carry out over the next week:

Day of the week	Activity (eg walking)	Time (in activity)	Borg Scale
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Use your polar monitor to record your exercise sessions:



1. Wet these two parts of the chest strap, and position with the plastic part and the word POLAR facing outwards



Position of chest strap



2. Press this button one to pick up your heart rate

3. Once your heart rate is displayed, press this button again at the start of your exercise session

4. Press this button twice at the end of your session

Also use the Borg scale to rate your exercise session

0	REST
1	REALLY EASY
2	**EASY**
3	**MODERATE**
4	SORT OF HARD
5	HARD
6	
7	REALLY HARD
8	
9	REALLY REALLY HARD
10	MAXIMAL EXERTION

PEACH Trial - WEEK 2

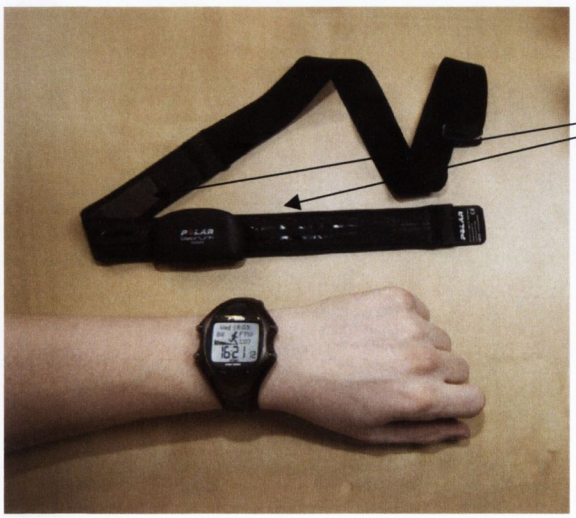
Name	
Date	

Week 2 Goal: Walk for at twenty minutes at a brisk pace at least 2 other days of the week

Please record your walking or any other type of exercise you carry out over the next week:

Day of the week	Activity (eg walking)	Time (in activity)	Borg Scale
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Use your polar monitor to record your exercise sessions:



2. Wet these two parts of the chest strap, and position with the plastic part and the word POLAR facing outwards



Position of chest strap



2. Press this button one to pick up your heart rate

3. Once your heart rate is displayed, press this button again at the start of your exercise session

4. Press this button twice at the end of your session

Also use the Borg scale to rate your exercise session

0	REST
1	REALLY EASY
2	**EASY**
3	**MODERATE**
4	SORT OF HARD
5	HARD
6	
7	REALLY HARD
8	
9	REALLY REALLY HARD
10	MAXIMAL EXERTION

PEACH Trial - WEEK 3

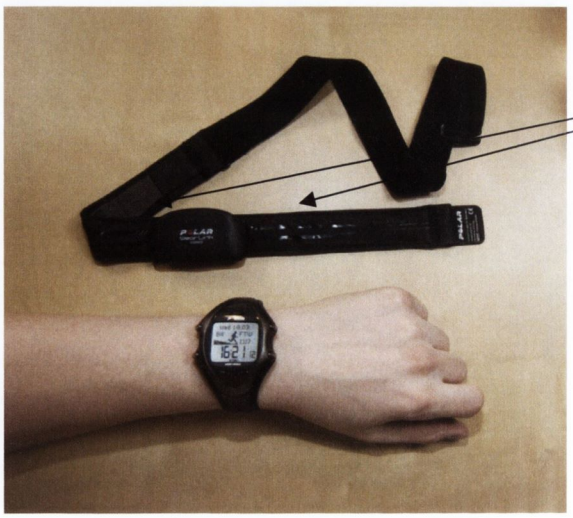
Name	
Date	

Week 3 Goal: Walk for at twenty minutes at a brisk pace at least 3 other days of the week

Please record your walking or any other type of exercise you carry out over the next week:

Day of the week	**Activity (eg walking)**	**Time (in activity)**	**Borg Scale**
Monday	Class		
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Use your polar monitor to record your exercise sessions:



3. Wet these two parts of the chest strap, and position with the plastic part and the word POLAR facing outwards



Position of chest strap



2. Press this button one to pick up your heart rate

3. Once your heart rate is displayed, press this button again at the start of your exercise session

4. Press this button twice at the end of your session

Also use the Borg scale to rate your exercise session

0	REST
1	REALLY EASY
2	**EASY**
3	**MODERATE**
4	SORT OF HARD
5	HARD
6	
7	REALLY HARD
8	
9	REALLY REALLY HARD
10	MAXIMAL EXERTION

PEACH Trial - WEEK 4

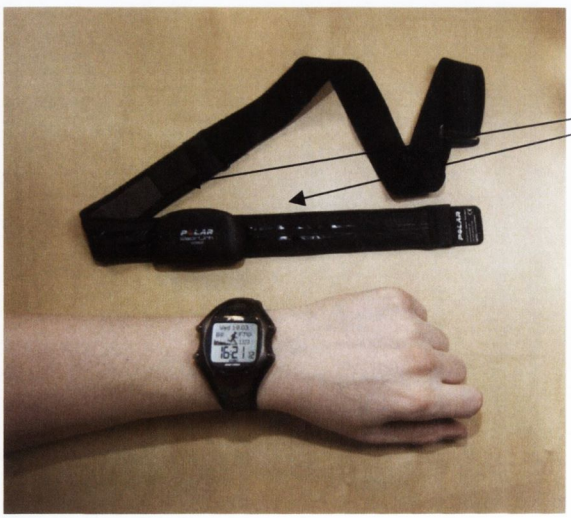
Name	
Date	

Week 4 Goal: Walk for at thirty minutes at a brisk pace at least 3 other days of the week

Please record your walking or any other type of exercise you carry out over the next week:

Day of the week	Activity (eg walking)	Time (in activity)	Borg Scale
Wednesday	Class		
Thursday			
Friday			
Saturday			
Sunday			
Monday			
Tuesday			

Use your polar monitor to record your exercise sessions:



4. Wet these two parts of the chest strap, and position with the plastic part and the word POLAR facing outwards



Position of chest strap



2. Press this button one to pick up your heart rate

3. Once your heart rate is displayed, press this button again at the start of your exercise session

4. Press this button twice at the end of your session

Also use the Borg scale to rate your exercise session

0	REST
1	REALLY EASY
2	**EASY**
3	**MODERATE**
4	SORT OF HARD
5	HARD
6	
7	REALLY HARD
8	
9	REALLY REALLY HARD
10	MAXIMAL EXERTION

PEACH Trial - WEEK 5

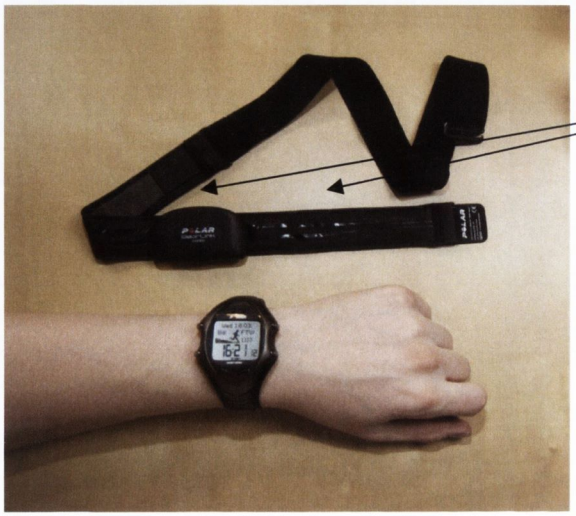
Name	
Date	

Week 5 Goal: Walk for 30-40 minutes at a brisk pace at least 3 other days of the week

Please record your walking or any other type of exercise you carry out over the next week:

Day of the week	Activity (eg walking)	Time (in activity)	Borg Scale
Wednesday	Class		
Thursday			
Friday			
Saturday			
Sunday			
Monday			
Tuesday			

Use your polar monitor to record your exercise sessions:



5. Wet these two parts of the chest strap, and position with the plastic part and the word POLAR facing outwards



Position of chest strap



2. Press this button one to pick up your heart rate

3. Once your heart rate is displayed, press this button again at the start of your exercise session

4. Press this button twice at the end of your session

Also use the Borg scale to rate your exercise session

0	REST
1	REALLY EASY
2	**EASY**
3	**MODERATE**
4	SORT OF HARD
5	HARD
6	
7	REALLY HARD
8	
9	REALLY REALLY HARD
10	MAXIMAL EXERTION

PEACH Trial - WEEK 6

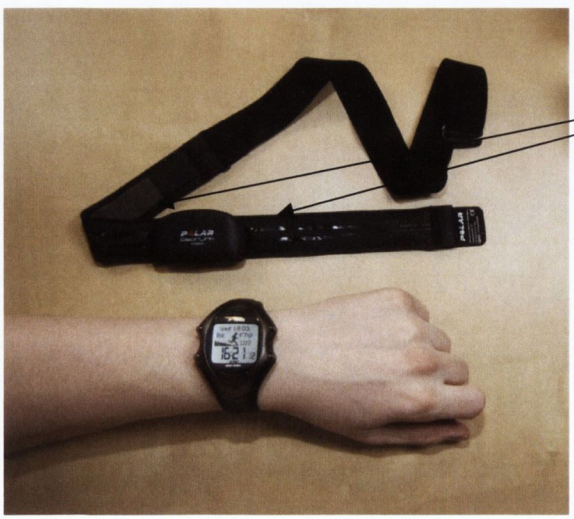
Name	
Date	

Week 6 Goal: Walk for at least 45 minutes at a brisk pace at least 3 other days of the week

Please record your walking or any other type of exercise you carry out over the next week:

Day of the week	Activity (eg walking)	Time (in activity)	Borg Scale
Wednesday	Class		
Thursday			
Friday			
Saturday			
Sunday			
Monday			
Tuesday			

Use your polar monitor to record your exercise sessions:



6. Wet these two parts of the chest strap, and position with the plastic part and the word POLAR facing outwards



Position of chest strap



2. Press this button one to pick up your heart rate

3. Once your heart rate is displayed, press this button again at the start of your exercise session

4. Press this button twice at the end of your session

Also use the Borg scale to rate your exercise session

0	REST
1	REALLY EASY
2	**EASY**
3	**MODERATE**
4	SORT OF HARD
5	HARD
6	
7	REALLY HARD
8	
9	REALLY REALLY HARD
10	MAXIMAL EXERTION

PEACH Trial - WEEK 7

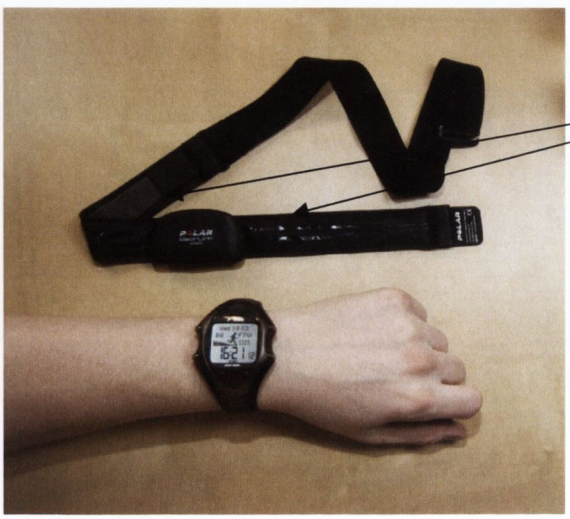
Name	
Date	

Week 7 Goal: Walk for at least 45 minutes at a brisk pace at least 3-5 other days of the week

Please record your walking or any other type of exercise you carry out over the next week:

Day of the week	Activity (eg walking)	Time (in activity)	Borg Scale
Wednesday	Class		
Thursday			
Friday			
Saturday			
Sunday			
Monday			
Tuesday			

Use your polar monitor to record your exercise sessions:



7. Wet these two parts of the chest strap, and position with the plastic part and the word POLAR facing outwards



Position of chest strap



2. Press this button one to pick up your heart rate

3. Once your heart rate is displayed, press this button again at the start of your exercise session

4. Press this button twice at the end of your session

Also use the Borg scale to rate your exercise session

0	REST
1	REALLY EASY
2	**EASY**
3	**MODERATE**
4	SORT OF HARD
5	HARD
6	
7	REALLY HARD
8	
9	REALLY REALLY HARD
10	MAXIMAL EXERTION

PEACH Trial - WEEK 8

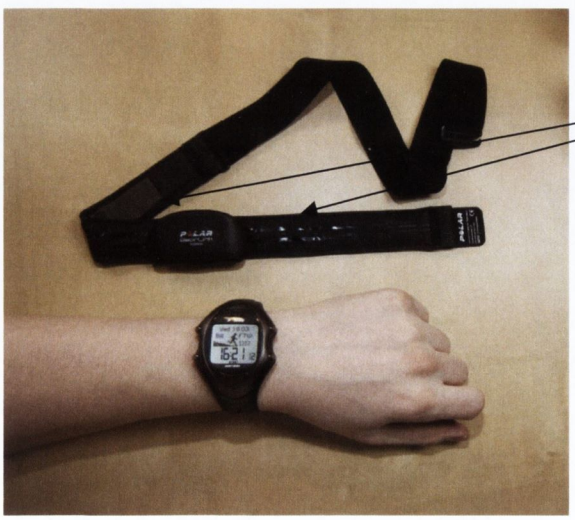
Name	
Date	

Week 8 Goal: Walk for at least 45 minutes at a brisk pace at least 3-5 other days of the week

Please record your walking or any other type of exercise you carry out over the next week:

Day of the week	Activity (eg walking)	Time (in activity)	Borg Scale
Wednesday	Class		
Thursday			
Friday			
Saturday			
Sunday			
Monday			
Tuesday			

Use your polar monitor to record your exercise sessions:



8. Wet these two parts of the chest strap, and position with the plastic part and the word POLAR facing outwards



Position of chest strap



2. Press this button one to pick up your heart rate

3. Once your heart rate is displayed, press this button again at the start of your exercise session

4. Press this button twice at the end of your session

Also use the Borg scale to rate your exercise session

0	REST
1	REALLY EASY
2	**EASY**
3	**MODERATE**
4	SORT OF HARD
5	HARD
6	
7	REALLY HARD
8	
9	REALLY REALLY HARD
10	MAXIMAL EXERTION