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PHYSICAL ACTIVITY THROUGH THE CANCER TRAJECTORY

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April 2012

Declaration

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Summary

With earlier diagnosis and newer targeted treatments for cancer, the numbers expected to survive this diagnosis continue to increase. Therefore, the longer term health and well-being of cancer survivors is garnering increased attention. Physical activity is of importance throughout the cancer trajectory.

Assessment of physical activity using Performance Status scores is an integral component of assessment at the point of cancer diagnosis. Physical activity is important to help alleviate the side-effects of cancer treatment and decrease the risk of developing secondary diseases of inactivity such as cardiovascular disease and diabetes mellitus in cancer survivors. Physical activity may even be associated with a decreased risk of the occurrence and recurrence of several cancers.

Physical activity within cancer populations has generally been measured using self-reported methods which lack accuracy, and it is difficult to quantify volume and intensity of activity. Objective methods of measuring physical activity such as accelerometers are a more robust method of measuring this construct. Little is known about the objective physical activity levels of cancer survivors. The overall aim of this thesis was to investigate the objective physical activity levels of cancer survivors at diagnosis and during the first year after cessation of chemotherapy.

The first study in this thesis assessed physical activity levels of 100 patients at the point of cancer diagnosis and compared levels to the Eastern Co-operative Oncology Group Performance Status scale (ECOG PS). Fatigue was also measured to help explain the relationship between these variables. Results indicated that ECOG PS ranked patients appropriately, and there was a significant relationship between time spent resting and performance status assigned ($p=0.04$), and a significant difference between activity levels of performance status 0 compared to PS 2-3 ($p=0.01$). However, physical activity levels were lower than verbal descriptors of the scale, and participants spent a mean (SD) of 8.1 (2.1) hours at rest per day. Fatigue levels were reported to be high, even among patients assigned a "good" performance status and the Global fatigue score was significantly related to assigned performance status ($p<0.001$). Thus, a complex picture was built up of patients at diagnosis generally displaying low objective physical activity levels, higher levels of self-report physical activity, high levels of fatigue, and almost universally assigned a 'good' performance status. The results of this study raised questions about the effect of sedentarism on 'fitness' for therapy and treatment tolerability and naturally led to questions about whether the low physical activity levels observed at diagnosis were observed throughout the cancer trajectory.

Following on from this, the second study in this thesis assessed physical activity levels over the first year at time points of 6 weeks, 6 months and 1 year after cessation of chemotherapy. As pre-diagnosis levels of activity are difficult to measure accurately, the approach taken was to use a matched non cancer comparison group. Results showed a low level of physical activity in the cancer cohort which did not increase during the time course of this study as expected. However, physical activity levels were no different to the matched control group, presumably reflecting low pre-diagnosis levels of physical activity, and low societal physical levels of physical activity. Body mass index was high in

the cancer cohort and increased over the time course of the study ($p=0.005$). By the 1 year time point, only 12% displayed a normal body mass index, while the comparable value for the control group was 56%. The physical functioning ($p=0.04$) subset of the quality-of-life measure decreased during the time-course of this study while the cognitive function ($p=0.049$) subset improved. Despite the latter positive effects, the lack of an increase in PA levels and the increased BMI levels throughout the time course of the study highlighted the need to explore interventions to target these variables.

In the third study of this thesis, an 8 week supervised exercise intervention was implemented in a heterogeneous cancer survivor population 2-6 months after cessation of adjuvant chemotherapy, and compared to a usual care control group. The study design was a pragmatic randomised controlled trial and was termed the 'PEACH' trial (Prescribed Exercise after Chemotherapy). Results indicated that while the programme was positively received, primary analysis revealed no change in study parameters. However, there were changes in self-reported physical activity ($p=0.001$), and physical well-being ($p<0.001$) in those who adhered well to the programme. This study highlighted the challenges of achieving change in fitness and physical activity behaviour, even with the implementation of an intervention.

This thesis highlighted low PA levels through the cancer trajectory from diagnosis into survivorship, and the challenges of reversing this behaviour which clearly merits further attention.

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This is for my brother.

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LIST OF PUBLICATIONS FROM THE WORK IN THIS THESIS

Published paper

Walsh, J. M., Hussey, J., Guinan E. O' Donnell D. 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

Citation

Broderick, J. M., Hussey, J. H., O' Donnell, D. M. Rapid Response: British Medical Journal (BMJ), 13.03.12 http://www.bmj.com/content/344/bmj.e70/rr/573145 on: Physical activity for cancer survivors: meta-analysis of randomised controlled trials

Conference Proceedings

1. J. M. Walsh, J.Hussey, M. J. Kennedy, D. M. O' Donnell; Objective physical activity and quality of life in breast and colon cancer patients after completion of adjuvant chemotherapy, *Journal of Clinical Oncology* 29: 2011 (suppl; abstr e19609)

2. J. M. Walsh, J. M. Hussey, M. J. Kennedy, and D. M. O'Donnell. A comparison of ECOG PS assigned and objectively measured physical activity, *Journal of Clinical Oncology* 28: 2010 (suppl; abstr e19526)

3. J. Walsh, J. Hussey, and D. O'Donnell A pilot study comparing objective physical activity to the physical component of the Eastern Cooperative Oncology Group (ECOG) performance status scale, *Journal of Clinical Oncology*, 2009 27, (suppl; abstr e20501)

LIST OF ABBREVIATIONS

APMHR	Age Predicted Maximum Heart Rate
BFI	Brief Fatigue Inventory
BMI	Body Mass Index
CCT	Controlled clinical trial
CONSORT	Consolidated Standards of Reporting Trials
CI	Confidence Interval
CT	Computed Tomography
CV	Coefficient of Variance
DXA	Dual energy X-ray absorptiometry
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group Score
EE	Energy Expenditure
FFM	Fat-free mass
GLM	General linear model
HDC	High dose chemotherapy
MHR	Maximum Heart Rate
HR	Heart Rate
HRQOL	Health-related Quality of Life
HRR	Heart Rate Reserve
ICC	Intra-class Correlation Coefficient
KPS	Karnofsky Performance Score
METs	Metabolic Equivalent
PA	Physical Activity
PBST	Peripheral blood stem-cell transplantation
QOL	Quality-of-life
RCT	Randomised Controlled Trial

SEER	Surveillance, Epidemiology, and End Results
VM	Vector Magnitude

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Chapter 1

1.1 Introduction

Cancer is the term used for over 100 diseases where 'abnormal cells divide without control and can invade nearby tissues' and which can spread to other parts of the body through the blood and lymph systems (National Cancer Institute). The most up-to-date global cancer estimates from the GLOBOCAN project report 12.7 million new cancer cases worldwide and 7.7 million cancer deaths annually (Ferlay et al., 2010). Each year in Ireland, there are an average of 29,745 new cancer cases (National Cancer Registry in Ireland (2007-2009)).

Thus, cancer is highly prevalent and its management presents challenges for many health professionals. The overall figures for invasive cancers in the years 2007 – 2009 in Ireland (apart from non-melanoma skin cancer, NMSC) were prostate (2748 cases), breast (2692 cases; 2672 in females), colorectal (2270 cases) and lung cancer (1910 cases) (National Cancer Registry in Ireland (2007-2009)). Fortunately, survival from cancer continues to improve due to earlier detection and newer targeted treatments (Lynch, 2010), and indeed in many cases the disease is now considered in terms of its chronicity. The 5-year survival in Ireland of all main cancers combined (except NMSC) from 1994-1997 was 40.1% and the latest statistics show an increase to 59.2% (National Cancer Registry in Ireland 2007-2009 data). The 5-year survival varies between individual cancer types; for example this was reported to be 85.4% for all breast cancer combined and 58.2% for all colon cancer combined (National Cancer Registry in Ireland 2007-2009).

Such improving survival statistics have naturally increased the numbers of cancer survivors (Pekmezi and Demark-Wahnefried, 2011) who in turn need long term management (Pinto and Trunzo, 2005). Data from Surveillance, Epidemiology, and End Results (SEER) registries in the US estimated that 13.7 million Americans with a history of cancer were alive on January 1, 2012, and by January 1, 2022, that number will

increase to nearly 18 million (Siegel et al., 2012). This increase in cancer survivor numbers has led to a new area of 'survivorship' research which is directed toward their long-term health and well-being of this growing population.

A cancer survivor is defined as "any individual that has been diagnosed with cancer, from the time of discovery and for the balance of life" (http://www.canceradvocacy.org (accessed 04.07.11)). Courneya and Frienenreich, prominent authors in this field, define 'survivorship' as the time period after initial treatment, and ending with recurrence or death (Courneya and Friedenreich, 2001). The goal of treatment is to "cure" the cancer, or prolong survival in patients with advanced disease, whilst preserving the highest possible quality of life throughout. Survivors, even those who are disease free, must content with the short and long term effects of the cancer treatment, as well as psychological difficulties such as the fear of recurrence (Siegel et al., 2012). There is a suggestion that cancer survivors often make positive lifestyle changes after diagnosis (Demark-Wahnefried et al., 2000), but this is not always borne out in the cancer literature.

Indeed, the transition from cancer patient undergoing active treatment to 'cancer survivor' returning to life after cancer can be difficult due to on-going health problems from the cancer and its treatment. To ease this difficulty, the implementation of survivorship care plans has been recommended. These are individualised documents, which contain concise information about the patient's diagnosis and treatment, describe possible late effects of treatment and other challenges commonly faced by survivors, and recommend ongoing care and resources available (Salz et al., 2012). Despite the potential usefulness of survivorship care plans, there are many barriers to their implementation such as time, resources and institutional commitment. In a recently conducted study, it was found that less than a half (43%) of National Cancer Institute designated centres provided survivorship care plans for patients (Salz et al., 2012).

Patients are increasingly diagnosed at older ages. In common with the rest of the population, obesity and poor fitness are increasingly seen among patients presenting for cancer treatment. Thus, long-term health issues among those treated for cancer are increasingly important the longer the survival from initial diagnosis. As the risk of cancer relapse decreases, the relative contribution of other illnesses to morbidity and mortality increases. Furthermore, in many cancer types, patients who relapse after a long-term disease free interval or live long enough to develop a second cancer have an excellent chance of another long-term remission with further active therapy, so their fitness is very important.

1.1.2 Treatment of cancer and its associated physical side-effects

Current active treatments of cancer, many with curative intent, incorporate one or more of the modalities of surgery, radiation therapy and systemic therapy. Systemic therapy has expanded greatly in recent years with a new range of cytotoxic chemotherapy, hormone therapy and targeted biological therapies (Schmitz and Speck, 2010). Cancer treatment with curative intent potentially results in short and long-term cardiac, pulmonary, neurologic and musculoskeletal toxicities and it is likely that the multimodal approach may compound the potential for increased adverse side effects (Conn et al., 2006a, Spence et al 2010, Schmitz and Speck, 2010). Recently, there is much interest in how to reduce long-term side effects of therapy while preserving improved overall survival.

Some of the physical side-effects during cancer treatment are difficult to disentangle from the effects of the cancer itself or to attribute directly to one cancer treatment modality. Those which would be expected to be short-term include anaemia, pain, nausea, vomiting and sleep disorders (van Weert et al., 2008). However, many symptoms can be expected to persist over a more protracted time course and can be linked to specific treatment modalities as well as to individual cancers.

More than 50% of cancer patients undergo surgery, the complications of which include systemic infections, loss of function, decreased range of motion, altered bowel habit, dyspnoea, pain, numbness and lymphoedema (Courneya, 2003). The inactivity and bed rest which is often associated with surgery can also result in muscle atrophy and a loss of physical function (Schmitz and Speck, 2010). Naturally the effects of surgery vary according to the location and type of surgery. For example, breast cancer surgery may be associated with post-mastectomy pain syndrome and upper limb lymphoedema. These have been reported to occur in approximately 30% of cases (Stricker and Jacobs, 2008), but this figure is likely to decrease rapidly as lumpectomy and sentinel node sampling replace mastectomy and lymph node dissection. Lung cancer surgery, on the other hand, will by definition involve reduction in lung capacity and patients generally experience considerable decrements in exercise tolerance (Smulders et al., 2004). It is important to be cognisant of the heterogeneity of cancer populations. For example, breast cancer by itself is a very diverse group and different molecular subtypes behave differently which will have a bearing on the surgical approach and associated systemic treatments. These factors would be likely to have a knock-on effect on longer-term physical recovery.

Radiation therapy is usually administered in small doses termed 'fractions' over a period of weeks to maximise the eradication of cancer cells (Courneya, 2003) and reduce toxicity to surrounding normal tissues. Such toxicity can cause wound complications, infections, loss of function, decreased range of motion, diarrhoea, dyspnoea, pain, numbness and lymphoedema (Courneya 2003). Exposure to ionizing radiation from radiation therapy can also be associated with pulmonary (Lingos et al., 1991) and cardiac toxicities (Paszar et al., 1988) causing lung fibrosis and cardiomyopathy.

Systemic therapy is associated with a wide range of treatment-related side effects. Standard cytotoxic chemotherapy regimens may be administered intravenously or orally and are usually given in repeated cycles 2- 4 weeks apart over a 3 -6 month period (Courneya, 2003). The adverse effects of cytotoxic chemotherapy depend on the type and cumulative dosage and regimen of chemotherapy drugs.

Some combination regimens can affect autonomic function due to altered cardiovascular homeostatis (Ekholm et al., 2000), precipitate pulmonary fibrosis (Mao et al., 2007) and possibly peripheral vascular endothelial dysfunction (Jones et al., 2007a). It is now increasingly acknowledged that there are also negative short and long term cognitive side effects of chemotherapy (Stricker and Jacobs, 2008), sometimes termed 'chemo-brain'. Other chemotherapy related side-effects are anaemia and tachycardia (Perez et al., 2004, Jensen et al., 2002, Bohlius et al., 2006). A decline in muscle strength (Courneya and Friedenreich, 1997b, Courneya and Friedenreich, 1997a) and aerobic fitness generally also occurs. Chemotherapy agents are also frequently associated with weight gain (Demark-Wahnefried et al., 2001, Perez et al., 2004) which in turn may be associated with an earlier recurrence of cancer and shorter survival (Chlebowski et al., 2002, Kroenke et al., 2005).

Specific side effects of cytotoxic drugs include cardiotoxity, pulmonary toxicity and neuropathy. Anthracyclines and several other cytotoxics have also been associated with arrhythmias, cardiomyopathies and congestive heart failure (Carver et al., 2007). The cyclophosphamide and doxorubicin combination chemotherapy often used in adjuvant breast cancer treatment has been associated with decreases in left ventricular ejection fraction 3 weeks after completion of the 4^{th} cycle (Perez et al., 2004). Many non-anthracycline therapies can adversely affect cardio-vascular risk profile e.g. blood pressure, lipid profile, c-reactive protein) (possibly also due to the use of concomitant steroids) (Jones et al., 2007a). Bleomycin, and occasionally cyclophosphamide and paclitaxel, are associated with pulmonary damage (Carver et al., 2007). Taxanes and platinum drugs (especially oxaliplatin, commonly used in adjuvant colorectal cancer therapy), can be associated with peripheral sensory and motor neuropathies (Stricker and Jacobs, 2008).

Hormone therapy is usually administered orally for a prolonged time, usually years, and can be associated with a number of side effects such as weight gain, muscle loss, proximal muscle weakness, fat accumulation in the face and trunk, osteoporosis, fatigue

and hot flashes (Courneya, 2003). Aromatase inhibitors can be associated with arthralgias (Cella and Fallowfield, 2008), tenosynovitis and loss of grip (Friedman et al., 2010 , Lintermans and Neven, 2011).

Biologic therapies include interferons, interleukins, colony-stimulating factors, monoclonal antibodies, vaccines, gene therapy, and non specific immunomodulating agents. These work in different ways, for example monoclonal antibodies target growth factor receptors and tyrosine-kinase domains. The long term side effects of these new treatments vary widely, and can include cardiovascular and musculosketetal side-effects, alone or in combination with cytotoxic agents. For example, traztuzumab (herceptin), an anti-HER2 monoclonal antibody which has improved overall survival for a significant subgroup of breast cancer patients, can adversely affect left ventricular ejection fraction (Perez and Rodeheffer, 2004).

The treatment of specific cancers are also related to individual side effects; breast cancer survivors face issues such as body image as well as sexual and relationship problems (Avis et al., 2005), as well as physically disfiguring treatments (Milne et al., 2008). Patients with gynaecological cancers may face issues related to sexual dysfunction and premature menopause.

Many persistent effects after cancer treatment are difficult to attribute to a specific treatment modality or cancer, but cause significant effects on quality of life, physical functioning and future cardiovascular risk. A decrease in muscle strength affects roughly half of patients with cancer across most cancer types (al Majid and Mc Carthy, 2001, Tisdale, 2002, Lucia et al., 2003). This may be related to factors such as bed rest, reduced energy intake and pro-inflammatory cytokines (Lucia et al., 2003). Myopathy is also reported (Batchelor et al., 1997). A reduction in cardiopulmonary capacity may lead to decreases in quality of life (QOL) (Shapiro and Recht, 2001, Zabora et al., 2001). Other general symptoms experienced by cancer survivors include chronic fatigue (Beisecker et al., 1997, deJong et al., 2002), weight gain (Beisecker et al., 1997), difficulty

sleeping (deJong et al. 2002), cognitive dysfunction and psychosocial distress (Courneya, 2003).

Compared to the non-cancer population, cancer survivors are also at increased risk for being overweight and developing secondary tumours. The toxic effect of many cancer treatments also increases the risk for a chronic disease development such as cardiovascular disease (Loescher et al., 1989, Cardinale et al., 2002, Taghian et al., 2001), osteoporosis and diabetes (Bines and Gradishar, 1997, Yeh and Bickford, 2009, Albini et al., 2010).

1.1.3 The role of Physical Activity (PA) in cancer

PA has been proposed as a non-pharmacological treatment to address many of the adverse effects outlined above. PA refers to 'body movement that is produced by the contraction of skeletal muscles and that increases energy expenditure' as opposed to exercise which refers to 'planned, structured, and repetitive movement to improve or maintain one or more components of physical fitness' (Chodzko-Zajko et al., 2009).

Indeed, evidence suggests that PA after cancer treatment may not only be important in symptom management and reversing or ameliorating some of the adverse treatment effects described above, but it may also improve QOL, and impact positively on survival (Mc Neely et al., 2006) and be important for general health (Markes et al., 2007, Haskell et al., 2007). Thus, PA participation is increasingly regarded as an important element of the rehabilitation and long term management of cancer survivors (Spence et al., 2010).

Theoretically, PA may be influenced both by the disease and by its management. It may be expected that after diagnosis those receiving adjuvant therapy such as chemotherapy or radiotherapy, or hormonal therapy will decrease physical activity due to the physical rigors of treatment but this should gradually increase in the following months. However, the effects of de-conditioning may interfere with this process. In contrast, subjects with metastatic disease may actually increase physical activity as therapy shrinks or stabilises

the disease process. In both of these populations, and right across the cancer care spectrum, estimation of physical activity or performance status (PS) assumes great importance as a prognostic indicator (Loprinzi et al., 1994), and a guide to treatment options.

Some of the treatment-related side effects may increase the risk posed by exercise leading to the requirement of a modified exercise prescription to ensure safety (Schmitz and Speck, 2010). Guidelines from the American College of Sports Medicine (ACSM) (Schmitz et al., 2010), American Cancer Society (ACS), and the American Institute for Cancer Research advise at least 30 minutes of moderate-to-vigorous PA on at least 5 or more days per week, which mirrors recommendations from normal populations (Haskell et al., 2007) (Table 1.1). The recent roundtable consensus document from the ACSM (Schmitz et al., 2010) recommended the modification of exercise advice according to factors such as health status, treatment history, anticipated disease trajectory and highlighted the importance of also reducing sedentary time. While these recommendations are a useful first step, specific information is lacking about optimal exercise intensity, frequency, time and type of exercise in cancer populations.

Table 1.1 Physical activity recommendations for cancer populations

American Cancer Society[1]	World Cancer Research Fund/American Institute for Cancer Research[2]	American College of Sports Medicine (Schmitz et al., 2010)
-Adults: engage in at least 30 minutes of moderate-to-vigorous physical activity, above usual activities, on five or more days of the week (45–60 minutes of intentional physical activity are preferable) -Children and adolescents: engage in at least 60 minutes/day of moderate-to-vigorous physical activity at least five days per week. Limit screen time (TV, computer, games) to no more than two hours per day	-Be physically active as part of everyday life Be moderately physically active, equivalent to brisk walking, for at least 30 minutes each day -As fitness improves, aim for 60 minutes or more of moderate, or for 30 minutes or more of vigorous, physical activity every day -Limit sedentary habits such as watching television	-Avoid inactivity -Return to normal activities as quickly as possible after surgery -Continue normal daily activities and exercise as much as possible during/after nonsurgical treatments -Individuals with known metastatic bone disease and cardiac conditions may require modifications and greater supervision for safety -Aerobic, resistance training and flexibility exercise recommendations are the same as age-appropriate physical activity guidelines for Americans

A cancer diagnosis has been referred to as a 'teachable moment' (Demark-Wahnefried et al., 2005). However, it has been reported that few cancer survivors seem to make the positive lifestyle changes required (Irwin, 2009). Factors influencing PA in cancer survivors can be related to the physical and medical side effects associated with the disease and its treatment as well as the psychological stress of living with a chronic disease (Littman et al., 2010). Correlates of higher PA in cancer survivors include

[1] http://www.cancer.org/Healthy/EatHealthyGetActive/ACSGuidelinesonNutritionPhysicalActivityforCancerPrevention/acs-guidelines-on-nutrition-and-physical-activity-for-cancer-prevention-summary (accessed 20.03.12)

[2] http://www.aicr.org/patients-survivors/guidelines/patients_survivors_guidelines_physical_activity.html (accessed 20.03.12)

younger age, male gender, high education attainment, healthy weight and the absence of co-morbidities (Hong et al., 2007, Lynch et al., 2007a). Other factors such as having social support (Pinto et al., 2002a), an exercise role model or partner and a higher income (Rogers et al., 2005) have also been linked to higher PA participation. Factors associated with lower PA levels include treatment type (Irwin et al., 2003, Pinto et al., 1988, Pinto et al., 2002a), older age, higher body mass index (Pinto et al., 2004, Irwin et al., 2003) and depressive symptoms (Emery et al., 2009, Raison and Miller, 2003). Other barriers to carrying out PA include low social support (Courneya et al., 1999), and symptoms of disease and treatment-related symptoms affecting quality-of-life (Courneya et al., 2008b).

1.2 The Role of Physical Activity/Physical Function assessment at Cancer Diagnosis

Assessing a cancer patient's functional activity has been an integral part of everyday oncology practice for decades. During the interview process with a health care professional, a patient is subjectively evaluated and assigned a Performance Status (PS) using a numerical scoring system such as the Eastern Co-Operative Oncology Performance Status Scale (ECOG PS) (Zubrod et al., 1960) or the Karnofsky Performance Status (KPS) (Karnofsky and Burchenal, 1949) (Table 1.2). These scales are used at the point of cancer diagnosis and also throughout cancer treatment and management to quantify the effect of the cancer and its treatment on the patients' level of function, ability for self-care and level of ambulation (Taylor et al., 1999), reflecting the physical, physiological and psychological effects of the disease (Ma et al., 2010, Mor et al., 1984b).

The concept of PS was first mentioned in the 1940's when nitrogen mustard chemotherapy for primary lung carcinoma was introduced (Karnofsky et al., 1948). The Karnofsky Performance Status Scale (KPS) (Table 1.2) was developed in 1948 based on the criteria deemed to be most important to evaluate the effect of chemotherapeutic agents in cancer. These criteria included; objective improvement, subjective improvement, PS, length of remission and prolongation of life (Karnofsky and Burchenal,

1949, Karnofsky et al., 1948). The KPS ranges from 0 to 100, in 10-point increments, with 11 different PS levels from normal functioning (100) to dead (0).

The ECOG PS (Table 1.2) was devised in 1960 in an attempt to simplify the Karnofsky Performance Scale (KPS) by reducing the scale from 10 to 5 points. The ECOG PS is a six-point ordinal scale from 0 (fully ambulatory without symptoms) to 5 (dead). This is now termed the 'ECOG/WHO score' (Oken et al., 1982). The KPS and ECOG PS are generally considered to be inter-changeable (Taylor et al., 1999) and formulas have been derived to convert KPS scoring to ECOG PS and vice versa (Buccheri et al., 1996, Ma et al., 2010). The choice of PS scoring system is often related to institutional preference but, the ECOG PS, which has less options, is often preferred due to is simplicity (Blagden et al., 2003).

'Good' PS (ECOG 0 and 1, KPS > 70%) at diagnosis is associated with a better response to treatment (Sengelov et al., 2000, Maurer and Pajak, 1981) and quality of life (Jordhoy et al., 2001, Schaafsma and Osoba, 1994). 'Poor' PS (ECOG PS 2,3 and 4, KPS ≤ 70%) has been linked to fatigue (Brown et al., 2004a, Scott et al., 2002) and an increased systemic inflammatory response (Scott et al., 2002, O' Gorman et al., 1998, Brown et al., 2004a). It must be acknowledged that the ability to predict survival based on 'level of fitness' scores is low (Heyse-Moore, 1987, Forster and Lynn, 1988, Mackillop and Quirt, 1997, Muers et al., 1996). Many variables have been evaluated in terms of their ability to predict survival in patients with cancer (Brundage et al., 2002). These include quality-of-life (QOL) scores from the European Organization for Research and Treatment of Cancer (EORTC-QLQ C30) (Schaafsma and Osoba, 1994, Coates et al., 1997) , the Spritzer Quality of Life Index (Allard et al., 1995), the Linear Analog Self-assessment scale

Table 1.2 The ECOG PS and Karnofsky PS Scales

Grade	Karnofsky descriptors	Grade	ECOG PS descriptors
100	Fully active, able to carry on all pre-disease performance without restriction	0	Normal, no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease		
80	Normal activity with effort, some signs or symptoms of disease	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
70	Cares for self but unable to carry out normal activity or do active work		
60	Requires occasional assistance but is able to care for most of personal needs	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
50	Requires considerable assistance and frequent medical care		
40	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
30	Severely disabled; hospitalization is indicated although death is not imminent		
20	Very ill; hospitalization and active supportive care necessary	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
10	Moribund		
0	Dead	5	Dead

(Coates et al., 1992, Coates et al., 1993) and the Functional Assessment of Cancer-Therapy-Lung (FACT-L). The independent prognostic value of these measures has been demonstrated in various groups of patients with cancer. Physical symptom scores measured by symptom assessment instruments such as the Memorial Symptom assessment Scale (MSAS) (Chang et al., 2001), the Rotterdam Symptom Checklist (Earlam et al., 1996), and psychological symptom distress by MSAS-SF (Short Form)(Chang et al.,

2001) have also demonstrated independent prognostic value in predicting survival of cancer patients. Symptoms such as fatigue (Hwang et al., 2002), dyspnoea (Hetse-Moore et al., 1991, Maltoni et al., 1995, Vitetta et al., 2001), lack of appetite (Maltoni et al., 1995, Loprinzi et al., 1994), weight loss (Dewys et al., 1980), and pain (Vitetta et al., 2001, Herndon et al., 1999) have also been shown to predict survival in cancer patients.

However, among all these variables, 'poor' PS is still a robust predictor of shorter survival (Scott et al., 2002, Motzer et al., 1999, Mor et al., 1984b, Deans et al., 2007, Bill Musk et al., 2011). The Edinburgh Lung Group (Capewell and Sudlow, 1990) conducted a study in which the KPS of 651 newly registered patients with lung cancer was assessed by physicians and then correlated with patient survival. In patients not treated surgically, those with a KPS > 90% survived for a median 9.3 months compared to 6.2 months for those with a KPS of 80%, 4.5 months for a KPS of 60-70 and 1.2 months for a KPS of 50% or less. In a large longitudinal study in patients with renal cell carcinoma (n=2570) with a follow-up period of 23 years, it was found that 5 and 10 year survival rates were 82.9% and 76% respectively for patients with ECOG PS 0 versus 51.3 and 44.1% for patients with ECOG PS 1. Only patients assigned an ECOG PS 0 or 1 were included in this study (Karakiewicz et al., 2007). Similarly, in a population of patients with metastatic urothelial cancer (n=119) it was reported that PS was the most important predictor of response to cisplatin-based combination chemotherapy, and response to chemotherapy was a strong prognostic factor for survival (Sengelov et al., 2000).

Low KPS has been found to be reasonably reliable in predicting impending death (Hwang et al., 2004). However, a high KPS does not automatically mean a long survival (Yates et al., 1980). Cancer patients tend to choose life-extending therapy if they think their survival is more than 6 months (Christakis and Lamont, 2000), and clinical decisions in palliative care are based largely on survival prognostication (Hwang et al., 2004). Higher accuracy in predicting life expectancy enables better decision making and planning for patients with advanced disease with regard to therapeutic options and advance care planning (Hwang et al., 2004).

PS has also been combined with other variables to maximise the accuracy of predicting prognosis (Blagden et al., 2003) to aid patient management decisions. A prospective, longitudinal study following patients (n=220) with gastric or oesophageal cancer over a 2-year period reported on a prognostic score combining clinical disease stage, KPS, rate of weight loss and serum CRP concentration as independent prognostic indicators. A risk prediction score was developed based on these variables which improved prognostic accuracy and risk prediction of death within 12 and 24 months after diagnosis (Deans et al., 2007). This risk prediction score was devised to identify those unlikely to live more than 12-18 months following radical resection, so that these patients could be offered non-palliative therapies. In a recent study evaluating the oncological outcome of docetaxel-based chemotherapy in 257 men with metastatic castration-resistant prostate cancer, univariate analysis identified significant clinical pain, PS, bone metastasis, prior treatment with estramustine, treatment cycle, PSA value and prostate specific antigen (PSA) response as significant predictors of overall survival (Miyake et al., 2011). The only factors which were predictive of survival in multivariate analysis were PS, significant clinical pain, prior treatment with estramustine, treatment cycle and PSA response. Thus, PS in isolation and in combination with other factors is an important factor which aids prognostication in oncology patients.

ECOG PS has also been shown to be a powerful predictor of treatment-related toxicity (Akechi et al., 2004, LLoyd-Williams et al., 2004, Dimeo et al., 2004). The cut-off point between ECOG PS 2 and ECOG PS 3 is often used to select patients for clinical trials and for palliative systemic chemotherapy (Deans et al., 2007, Albain et al., 1991, Motzer et al., 1999). A study comparing survival in patients treated with different lung cancer chemotherapy regimens (cisplatin and paclitaxel, cisplatin and gemcitabine, cisplatin and docetaxel, or carboplatin and paclitaxel) for Stage IIIB, Stage IV or recurrent non-small cell lung cancer (n=1155), was initially designed to allow patients of ECOG PS 0,1 and 2 to receive chemotherapy within the trial (Schiller et al., 2001). However, after 66 patients with a PS of 2 at trial entry were enrolled, a high rate of toxicity and adverse effects including death within 30 days (from any cause) among those patients was noted and the study design was subsequently revised to include only those of PS 0 and 1. All of

the chemotherapy regimens were similar in response rate and survival. The final results showed that the median survival among patients with a PS of 0 was 10.8 months, it was 7.1 months for patients with a PS of 1 and 3.9 months for those with a PS of 2. Thus, as opposed to a cut-off point of PS ≥ 2, many lung cancer chemotherapy trials have a cut-off of PS ≤ 1 as patients with PS ≤ 2 have been shown to have particularly poor outcome in clinical trials after treatment (Sweeney et al., 2001, Bunn, 2002, Lilenbaum et al., 2008, Schiller et al., 2001).

1.2.1 Reliability of PS scoring between health professionals

In a study carried out over 30 years ago, inter-observer reliability of the KPS was investigated by health professionals in a group of patients with advanced cancer (n=75). A moderate inter-rater reliability (r=0.69) was reported between nurses and social workers (Yates et al., 1980). However, no measure of agreement was included in this study, which limits its interpretation. Furthermore, it was indicated that PS scoring was a component of the nurses' training, however it was not specified how familiar social workers were with PS scoring which may have influenced results of this study. Inter-observer variability of PS scoring was also investigated by Schag et al. (1984) in 75 patients with cancer. The only details supplied about the study population were that 60% had widespread disease and 73% were out-patients. Two sets of raters were involved in this study (the first set consisted of physicians and primary oncologists, the second set were psychologists and psychiatrists). A strong correlation (r=0.89) and high levels of agreement were (kappa statistic=0.53) were noted between raters. In terms of percentage agreement, it was reported that raters disagreed 42% of the time but 32% of the disagreements just had one level of a difference. The higher correlation noted by Schag et al. (1984) may have been related to the fact that the scoring was carried out on the same day as opposed to one week apart in the study by Yates et al. (1980). Patients with advanced cancer may be expected to fluctuate with regard to their clinical status in a one-week time-span. Higher levels of inter-observer correlation were reported between two oncologists in assessing both the KPS (r=0.92) and the ECOG PS (r=0.91) scores in 209 consecutive patients with cancer (Roila et al., 1991). However, although

high levels of reliability were noted, agreement was not quantified which is important in estimating the disparity in scores between testers.

A study by Conill et al. (1990) assessed the KPS and ECOG PS in 100 ambulatory heterogeneous cancer patients attending a radiotherapy clinic. The PS scales were completed on the same day by two radiation oncologists and rating was also reported by the patients themselves. High correlations were reported between oncologists (r=0.76[3] for the KPS, 0.75 for the ECOG PS), agreement[4] was 70% for the KPS, and lower at 59% for the ECOG PS. The lower agreement rate for the ECOG PS may have been related to raters being less familiar with this scale.

In a study exploring PS scoring assessed by patients, nurses and oncologists in advanced non-small cell lung cancer patients (n=206) (Ando et al., 2001), weighted kappa for inter-observer agreement between oncologists and nurses was 0.63 (95% confidence interval 0.54-0.71) indicating moderate-to-good agreement. Of note, oncologists evaluated PS most optimistically, however survival was better correlated with the oncologist-assessed PS rather than the nursing evaluation, suggesting oncologists were better at evaluating PS and may take other prognostic variables into account when assigning a value. Twelve oncologists and 45 nurses participated in this study. The large number of nurses may have introduced more variability into this study as their training and level of experience in terms of PA assignment is not detailed.

Sorenson et al. (1993) showed only moderate overall non-chance agreement among three oncologists who assessed the ECOG PS status of 100 consecutive patients with mixed cancer diagnoses in an outpatient clinic. A good range of ECOG PS scores from 0 – 4 were observed in this study. Overall the Kappa statistic for inter-observer variability was 0.44 indicating fair agreement (95% confidence limits 0.38 – 0.51). This level of agreement was lower than previous studies which may have been due to three different raters. As opposed to the studies described above, Sorensen et al. (1993) considered

[3] Kendall's correlation was carried out.

[4] Agreement referred to 'co-incidence degree'

agreement separately for discrete PS scores, and reported higher agreement with better PS (ECOG 0 having a Kappa value of 0.55 (95% confidence limits 0.44 – 0.67), and lower agreement in ECOG PS score 4 with a Kappa value of 0.33 (95% confidence limits 0.22 – 0.45) (Sorensen et al., 1993). It was stated that the three oncologists who rated patients had no specific training for the study, and worked in the oncology clinic, which would presumably be reflective of the clinical reality when assessing PS, lending weight to the applicability of this study. However, it is likely that oncologists would have more experience and a higher level of training in PS scoring than other professionals, and therefore, not surprisingly, display higher correlation and higher levels of agreement than other professionals. Higher agreement was shown with higher PS scores. The disparity in agreement noted with worsening PS may be indicative of the difficulty in scoring 'poor' i.e. higher PS. Assigning a higher PS value may be more clear-cut as it may be easier to identify patients who are 'functioning well'. On the other hand, PS scores at the lower end of the scale may be more open to varying interpretations - as some raters may interpret the functional status of patients more positively, while others may rate the patients more negatively.

1.2.1.1 PS scoring between health professionals and patients

Ando et al. (2001) reported over-estimation of PS when investigating inter-observer agreement of PS ratings assigned by health-care providers (oncologists and nurses) compared to PS self-assigned by the patients themselves in patients with Stage III or IV non-small cell lung cancer (n=206). Patient-assessed PS scores agreed with only half of oncologist-assigned scores. Oncologists were more optimistic in their scoring, assigning a 'good' PS to 71% of patients, whereas this figure was 59% for patients (weighted kappa of 0.53). However, survival was better predicted by the oncologist scoring meaning the more optimistic scoring by oncologists was a better reflection of overall patient status.
Doctors were also found to 'overestimate' PS when compared to patient estimates in a large study carried out in a large study of 1,115 patients with advanced colorectal or lung cancer (Loprinzi et al., 1994). Again, the strongest prognostic factor for survival was

physician estimates of PS. This was then followed by patient assessment of own PS (Loprinzi et al., 1994).

Blagden et al. (2003) compared PS scoring between oncologists and patients in a population (n=101) with a suspected lung cancer diagnosis. Scoring was carried out at the first patient-oncologist consultation. Agreement was reported in only 50% of cases, with a weighted kappa (95% CI) of 0.45 (0.33, 0.59), indicating moderate agreement. There was a narrow range of disparity in score differences, with only 6 cases where PS assigned by the patient and oncologist differed by more than 1 score. It was noted that a few patients rated themselves as having poor self-assessment scores-even though they appeared to be in good health. The authors proposed that this may have been due to pre-morbid depression-which is plausible, as depressive symptoms and major depression are found in up to 58% and 38% , respectively, of cancer patients (Massie, 2004). As with the study by Loprinzi et al. (1994) and Ando et al. (2001), oncologist scoring was more positive compared to the patient scoring. In agreement with the study by Loprinzi et al. (1994), no difference was found between patient-assessed and oncologist-assessed survival as opposed to results of the study by Ando et al. (2001).

Following on from the study by Blagden et al. (2003), ECOG PS was assessed by patients and oncologists in day-care patients (n=111) with heterogeneous cancer diagnoses (32.7% were in Stage III cancer) undergoing chemotherapy treatment (Jeon et al., 2007). Depression was assessed using the Hospital Anxiety and Depression Scale. Agreement was reported in just over half of cases, with a weighted kappa of 0.17 (95% confidence interval = 0.07 – 0.27) indicating a low level of agreement. Similar to previously described studies (Blagden et al., 2003, Ando et al., 2001, Loprinzi et al., 1994), discrepancies between scores indicated that patient scores were less optimistic than physician-assigned scores. Different factors explained the discrepancy in scores for the physician and patient assigned scores; using regression analyses, depression was found to be significantly associated (β=0.5, p=0.005) with discrepancies in patient scoring, which may be due to depression influencing patient's perception of their own physical ability. Of note, cancer stage was the only significant factor in the oncologist's scoring

(β=0.34, p=0.0004), indicating that the clinical status influenced PS scoring. The discrepancy in scores between patients' and oncologists' ratings is therefore not surprising.

In contrast with previously described studies, other work (Lilenbaum et al., 2008, Taylor et al., 1999) suggests that patient scoring of PS scales was more optimistic than health care providers. In a study investigating the prevalence of poor PS in a large population of patients with cancer (n=2,885) with a sub-population of lung cancer patients (n=503) (Lilenbaum et al., 2008), PS rated by the patients themselves was compared to PS assigned by 'health care providers'. Similar to agreement rates previously described (Blagden et al., 2003, Ando et al., 2001, Jeon et al., 2007), this study reported that only 47% of the overall sample agreed in terms of ECOG PS assigned, and 53% agreed in the lung cancer sample (overall weighted kappa was 0.45). When disagreement was present, it was more likely to be in the direction of the health care provider underestimation (39% underestimation versus 14% overestimation overall). This implies that patients tended to over-estimate their physical status, while the opposite was true for health care providers. Of note, patients in this study were not aware of their cancer diagnosis, which may have influenced results. It is possible that over-estimation of PS may have occurred to enable trial entry, or conversely - patients may have been overly pessimistic in their scoring to avoid entry to other trials. Details were not given about the clinical occupation of the 'health care providers' or their experience and training in PS scoring.

Similarly, another study reported that patients' PS rating was more optimistic than oncologists' (Taylor et al., 1999). Inter-observer reliability of the KPS and ECOG PS was investigated in a heterogeneous cancer population (n=100), admitted to an oncology ward for investigation of their malignancies or for chemotherapy treatment. PS was assessed by two resident medical officers, two clinical medical oncologists, two senior principal treating nurses and the patient. Reflecting the early stage disease of the majority of participants – the majority were assigned a 'good' PS of 0 or 1. There was a significant tendency for patients to rate both the ECOG PS (p=0.0007) and KPS (p=0.0054) scales better than the oncologists' rating.

Good agreement was reported between physicians and patients (KPS: 0.63 for the patient and physician 1 pair, 0.67 for the patient and physician 2 pair, ECOG PS: 0.61 for the patient and physician 1 pair, and 0.58 for the patient and physician 2 pair) in a study evaluating PS of 100 consecutive patients with mixed cancer diagnoses (Conill et al., 1990). Higher agreement between physicians than between patient and physician was reported, however no details were given whether physicians over or underestimated PS compared to patients.

Therefore, conflicting results emerge in terms of patient versus health care provider assessment of PS, although more studies report health care provider 'overestimation' of PS compared to patient self-assignment. It would be expected that patients would accurately judge their own level of functioning; however as oncologists' scoring generally correlated better with survival data - the status of health care providers assigning PS scores is likely to be the optimum. Proposed reasons for the discordance between PS scoring by the patient compared to healthcare providers may be related to several factors. First, oncologists probably, use available information about the clinical status of the patient when rating PS, although the PS descriptors suggest that PS score should most closely reflect PA and ability to perform activities of daily living. In the case of patients, factors such as their psychological status may influence perception of health and physical ability, thereby affecting PS ratings. Other sources of discordance may be underreporting of symptoms by patients so maximum treatment may be offered, non-specific questioning of patients relating to activity levels and self-care, a lack of training of health care professionals in using these scales, or 'dismissal of non-cancer-related causes of PS impairment' (Lilenbaum et al., 2008).

1.2.2 Validity of PS scoring

The scientific literature was reviewed via searches of the following databases; Medline, Embase and the Cochrane library. Searches were not limited by publication data, but

were limited to English language and to humans and adults studies. The literature was searched using a combination of the following key words; 'Cancer' OR 'Neoplasm' OR 'Tumour', AND 'Physical activity' OR 'Exercise', AND 'Accelerometer' OR 'Pedometer' OR 'Physical activity monitor' OR 'Physical function' AND 'Eastern Co-Operative Oncology Group Performance Status Score' OR 'Performance Status' OR 'Karnofsky Performance Status'. This search generated 59 articles and the references cited in each of the identified randomized trials were reviewed for potential papers missed during the original search.

Assessing the validity of PS scoring poses challenges, as there is a lack of consensus on which types of measures are most appropriate to compare with PS. A number of studies carried out almost 30 years ago compared KPS to patient functioning measures estimated by self-report (Yates et al., 1980, Schag et al., 1984, Mor et al., 1984b) and reported strong relationships between self-reported PA and the KPS. The construct validity of the KPS was explored in a population of terminally ill cancer patients (Mor et al., 1984b). This was carried out by comparing the KPS to two measures of physical function - The Katz ADL Index, and a severity index constructed from the variables of the Katz ADL Index. These scales assessed the following functional variables; continence, transferring in/out of bed/chair, walking, dressing, bathing, climbing stairs and mobility outside home, under categories of unable, with help or independent. This information was gained by an interview with the patient or with the patient's family – which may have limited its objectivity. Moderate relationships were reported between increasing KPS scores and higher functional scores on the Katz ADL Index (r=0.49). However, as this study was carried out in patients with advanced cancer, these relationships were not investigated at the upper range of KPS scoring, which is more representative of the general oncology population.

Yates et al. (1980) compared the KPS to a number of self-reported physical functioning measures including difficulty with balance and stair use using the questions "Have you been having any difficulty keeping your balance in the past few days?" (Yes/No), difficulty on stairs "Have you been having any difficulty going up and down stairs in the

past few days?'' (Yes/No). Strong correlations were noted between difficulty with stairs and the KPS (0.63 ($p < 0.001$)), and difficulty with balance (0.61 ($p < 0.001$)), although as previously mentioned, the value of self-reporting such factors may be questionable compared to objective evaluation.

The construct validity of the KPS was also explored in a study by Schag et al. (1984) in a sample of 293 patients with cancer. A self-report measure of physical capacity was used in this study, the Cancer Inventory of Problem Situations questionnaire which consists of 18 variables relating to domains of self-care, daily activity, evidence of disease and ability to work. Moderate correlations (-0.38 to 0.51) were reported between the physical components of this questionnaire and the KPS.

These early validity studies focussed on the comparison between PS and self-report measures of physical function. However, many limitations pertain to self-report measures and they are notoriously prone to bias (Sallis and Saelens, 2000a), because it is difficult to quantify volume and intensity of activity (Prince et al., 2008). In addition, these studies were performed almost 30 years ago. In recent years treatment regimes have become less toxic, and there is better supportive care (e.g. new antiemetics and analgesics), so many patients who might have previously been unable to tolerate chemotherapy can now do so. Since then, there has also been a paradigm shift towards more individualised medicine in oncology due to better identification of markers and molecular sub-types, resulting in a much more targeted - rather than a 'one size fits all' treatment approach. The effects of these factors on PS scoring patterns are not fully known.

Recent work in this field has compared physical function tests to PS. The Simmonds Functional Assessment Tool was compared to the KPS in 100 patients with stage III or IV lung cancer (Montoya et al., 2006). Participants were largely assigned a good PS and scored equal to or above the 80% on the KPS. The Simmonds Functional Assessment (Simmonds, 2002) is a test consisting of eight items; putting on a sock, tying a belt, putting coins into a cup, reaching above the head, walking for 50 feet and walking for 6

minutes. Results showed low to moderate (r = 0.21 to 0.51), but significant correlations between this physical function measure and KPS. However, while this measure provides a snapshot of physical function, the usefulness of essentially upper limb co-ordination tests such as putting coins in a cup and tying a belt is arguable, as these functions would be expected to be well preserved. Thus, the Simmonds Functional Assessment may not provide a comprehensive comparison with PS scores such as the KPS, as these scales take into account a more global measurement of physical activity which includes mobility and self-care. Furthermore, the research was carried out in patients with advanced lung cancer. Therefore, the applicability of results to a more general cancer population is unknown.

As a measure of functional capacity, the 6-minute walk test was compared to the KPS in 171 patients with recurrent glioma, with a median time from original diagnosis to study enrolment of 22 months (Jones et al. 2009). Median six-minute walk test distance was 400m which corresponded to 44% below age and gender predicted values. Self-report PA was assessed using the Godin Leisure Time Index and showed that a mean of 164 ± 201 total weekly minutes were spent exercising with 25% of participants meeting national exercise guidelines of ≥ 150 minutes of moderate and vigorous exercise per week (Haskell et al., 2007). Results indicated a moderately significant correlation between the KPS and the 6-minute walk test ($r=0.34$, $P < 0.01$) with the lowest KPS score among those with a 6-minute walk test distance <320m and the highest among those with a 6 minute walk test distance of ≥464m, with a similar pattern noted for self-report PA, assessed using the Godin Leisure Time Index (Jones et al., 2009). However, limitations in discriminating between individuals with good PS were found. Only patients with 'good' KPS (>70%) were included in the study as it was expected that patients with poor functional status may not have had the cardio-respiratory reserves to complete the 6-minute walk test. Moreover, although the validity of the 6-minute walk test is well established in patients with cardiovascular and respiratory diseases, the validity of this measure has not been established in patients with cancer. Of particular note, the median time to study enrolment was very wide in this study. Also, patients with recurrent glioma are a very heterogeneous group. Some may exhibit neurological

deficits which limit their ability to complete the six minute walk test, as opposed to a cardiovascular or respiratory test limitation (Ruden et al., 2011), therefore the applicability of this study to all patients could be questioned. The six-minute walk test is reflective of 'once-off' functional capacity, and is not reflective of free-living PA carried out throughout the day or ability to manage activities of daily living, thus may not be the most appropriate measure to compare with PS.

A recent study by Ruden et al. (2011) evaluated functional capacity using the 6-minute walk test and self-reported PA using the Godin Leisure Time Index in 243 patients with recurrent glioma and related these measures to survival. The mean 6-minute walk test result was 448 meters (range 102-825) which is equivalent to 38% ± 17% less than age and sex predicted values. The mean KPS was high at 90, (range 70 - 100). From the Godin Leisure Time Index, it was reported that 26% of patients were currently meeting national exercise guidelines (≥ 150 min/wk of moderate to vigorous intensity exercise (Haskell et al., 2007)), and 24% reported no exercise behaviour. There was no association between the 6-minute walk test and survival, however results indicated that exercise behaviour, measured by the Godin Leisure Time Index was a strong independent predictor of survival ($p=0.008$) which provided incremental information beyond the KPS alone ($p < 0.001$). However, the KPS still remained a strong predictor of mortality in multivariate analysis. Limitations of this study were that only patients with 'good' PS (KPS ≥ 70) were included and that the estimate of exercise behaviour was based on self-report, which is prone to inaccuracy. Also, this study along with the study by Jones et al. (2009), described above, was in patients with recurrent glioma; given the poor survival prospects of this cohort, their results may not be applicable to the general oncology population or the newly diagnosed glioma population.

A recently published study explored the relationship of the KPS and Physical Performance Test in a heterogeneous group (n=152) of elderly cancer patients with mixed cancer diagnoses and an even mix of local, loco-regional[5] and metastatic disease

[5] 'Loco-regional' disease generally refers to a cancer which has spread to regional lymph nodes and/or resectable tissues

(Terret et al., 2011). Patients with a KPS of < 60 (n=54) were excluded from the study. The KPS was assigned by a research nurse. The Physical Performance tests consisted of 7 items related to functioning; writing a sentence, eating, lifting a book and putting it on a shelf, putting on and removing a jacket, picking up a penny from the floor, turning 360° and completing 50-foot walk test. Most patients were assigned a high KPS of ≥ 80%, yet conversely 76% of patients had a Physical Performance Test score of < 20 which is indicative of some health impairment. Thus, KPS was found to be more optimistic than the Physical Performance Test in assessing the physical function of patients. Thus, a weak association between the Physical Performance Test and KPS scores was reported ($r=0.27$; $p < 0.001$). Extrapolating these results, the authors proposed that patients with Physical Performance Test scores of > 20 should be considered for standard cancer treatment, while those with a result ≤ 20 should be subjected to a further, more complex physical assessment. A limitation of this study was that only patients with a KPS of ≥ 60 were included. The Physical Performance Test may not be optimal for testing physical functioning over time as test elements such as writing a sentence and eating would be expected to be preserved in most cancer types.

PA is a key determinant of physical functioning (Ruden et al., 2011). The relationship between ECOG PS and objectively measured PA was explored in only one study previously (Dahele et al., 2007). Patients with advanced upper gastro-intestinal cancer (n=20) were recruited from an out-patient palliative care setting to wear an *activ*PAL™ accelerometer for 1 week as a measure of physical activity. Participants were compared to healthy controls (n=13). Not surprisingly, the cancer cohort spent more time lying and sitting ($p <0.001$) and less time in quiet standing or stepping ($p <0.001$) compared to controls. Estimated total energy expenditure measured by the accelerometer was compared to physician-assigned ECOG PS. Small numbers did not permit statistical relationships to be drawn; however results indicated a trend towards a reduction in energy expenditure with worsening clinical PS. A similar trend was observed in relation to the number of steps taken per day. This study was carried out in a very small sample of palliative care patients, which may not be generalisable to the general medical oncology population.

1.2.3 Summary of preceding section

PS scoring is clearly a useful tool for determining 'fitness' for cancer treatment and close relationships have been demonstrated between PS and prognostic factors as well as survival. The descriptors of the two most commonly used PS scales rely heavily on an assessment of current PA levels. This is particularly true of one of the most crucial distinctions between ECOG PS 2 and 3, frequently used to determine patients' fitness for active anti-cancer therapy. Oncologists generally show better consistency when scoring PS, compared to other health care professionals. Studies comparing physician-assigned to patient-assigned scores are conflicting, although the majority of studies indicate that oncologists score PS more favourably than patients. However, when survival data is taken into account, oncologists' PS generally predict survival more accurately, thus validating the current practice of oncologists, rather than patients, scoring PS. Validity study designs initially focussed on comparing PS to subjective measures of physical functioning. Although strong relationships were largely reported these studies are now dated and these measurements may not be a good measure of overall physical status. More recent studies have compared PS to more objective tests such as the 6-minute walk test. Although they provide a more comprehensive measurement of physical functioning, only patients with a relatively high level of function can carry out these tests, thus excluding patients with poor PS levels. In addition, these tests are just a 'snapshot' of function; they are a measure of functional capacity, and are not reflective of free-living day-to-day function as estimated by PS scales. Only one study compared PS to objective measures of PA, however this was in a small sample of patients receiving palliative care. There is clearly a need to advance research in this area to evaluate the relationship between PS and more robust measures of physical activity such as accelerometers. This research should ideally be carried out in a larger heterogeneous cohort more reflective of the general oncology population.

1.3 Physical Activity levels after cessation of chemotherapy

1.3.1 Epidemiology of Physical Activity and Cancer

The aetiology of cancer is complex and multi-factorial. Nonetheless strong epidemiological evidence attests to the role of physical activity in decreasing the risk of developing certain cancers, particularly colo-rectal cancer (Slattery, 2004, Samad et al., 2005) and breast cancer (Sprague et al., 2007, Mittendorf et al., 1995). Probable associations have been suggested between low PA levels and the risk of endometrial (Cust et al., 2007), prostate (Oliveria and Lee, 2005) and lung (Tardon et al., 2005) cancers. Evidence has also shown that higher PA levels may have a possible protective effect against ovarian (Patel et al., 2006), kidney (Pan et al., 2006) and pancreatic cancer (Lin et al., 2007). Indeed, according to the World Health Organization (WHO), physical activity (PA) is among the nine modifiable risk factors for cancer development and it has been reported that insufficient levels of PA may be linked to 19% of cancers in Europe (Friedenreich et al., 2010).

The exact biological mechanisms underlying these effects have not yet been fully elucidated, although numerous pathways have been proposed. The strongest evidence in breast cancer exists for the oestrogen pathway as a factor in the initiation and promotion of cancer by stimulating cell division, which increases the potential for DNA mutations and promotes the growth of oestrogen-dependent tumours (Rock and Demark-Wahnefried, 2002). Other possible aetiologies in breast cancer may consist of increased insulin resistance (Hoffman-Goetz et al., 1998, Goodwin et al., 2002) and enhanced immune function (Abrahamson and Gammon, 2006) associated with sustained increases in PA levels. In colon cancer, decreasing insulin concentrations may be also important as insulin may promote carcinogenesis in various organs (Westerlind, 2003). It is also thought that PA decreases bowel transit time, exerting an effect on prostaglandin levels and immune system function (Westerlind, 2003). These associations may also occur by beneficial changes in metabolic and growth factors, adipokines and inflammation (Chlebowski et al., 2002, McTiernan et al., 1998) as well as by decreases in C-reactive protein and blood pressure (Fairey et al., 2003).

PA and a healthy diet help to prevent the development of obesity. Obesity at cancer diagnosis is also associated with an increased risk of disease recurrence in breast cancer (Majed et al., 2008, Chlebowski et al., 2002) and this relationship holds for pre-menopausal and post-menopausal women (Chlebowski et al., 2002). The pathways which mediate these effects are complex and not fully known at this time. One possible mechanism is the presence of more circulating oestrogens from increased adipose tissue (Stephenson and Rose, 2003). Adipose tissue is also associated with increased circulating levels of insulin, insulin-like growth factors and leptin which are linked to cell proliferation and development of breast cancer (Stephenson and Rose, 2003). There are, however, also clear associations between obesity and the risk of non-oestrogen dependent cancers such as adenocarcinoma of the oesophagus and renal cancer (Corley et al., 2008). A recent study including post-menopausal breast cancer patients (n=105) found that patients with more advanced disease were significantly more likely to be obese, centrally obese, hyperglycaemic and hyperinsulinaemic which suggests that the metabolic syndrome may be associated with a more aggressive tumour phenotype (Healy et al., 2010).

1.3.1.1 The epidemiology of sedentary behaviour and cancer

At the other end of the PA continuum (Tremblay et al., 2010), newer evidence suggests that decreasing sedentary time may be even more important than additional vigorous activity. Sedentary behaviour is characterised by 'prolonged sitting or lying down and the absence of whole-body movement' such as watching television or working at a computer (Owen et al., 2009). Traditionally, the focus in exercise science has been on achieving sufficient volumes of moderate and vigorous activity, with a cursory nod to avoiding inactivity. More recently, non-exercise thermogenesis (Levine et al., 1999) and so called "inactivity physiology" (Hamilton et al., 2007) are becoming more widely considered within the exercise literature. Non-exercise thermogenesis has been defined as daily energy expenditure which is associated with "fidgeting, maintenance of posture, and other physical activities of daily life" (Levine et al., 1999). Of note, non-exercise

thermogenesis generally takes up a greater component of total energy expenditure than exercise (Tremblay et al., 2007, Hamilton et al., 2007). Inactivity physiology is concerned with the molecular and physiological effects of sedentary behaviour. Evidence is accumulating of different cellular processes associated with too much time spent sitting which are different from exercise responses (Hamilton et al., 2007). This has not been specifically studied in depth in oncology. However, one pathway associated with cancer occurrence is the lipid pathway (Khandekar et al., 2011). It has been shown experimentally in the rat model that reducing spontaneous standing and sitting time had a greater effect on lipoprotein lipase activity than adding vigorous exercise training on top of the normal level of non-exercise activity. A recent study using Actigraph accelerometers to assess sedentary time in over 4,000 participants showed that increased sedentary time was associated with elevated C-reactive protein levels (Healy et al., 2011), which may be of interest in the cancer context given that the inflammatory pathway has also been proposed as a causative factor in cancer aetiology. Therefore, increased sedentary time may be of greater concern than decreased time spent at higher intensity levels (Hamilton et al., 2007).

Epidemiological research in large population-based samples well-adjusted for confounding variables has linked sedentary behaviour with colo-rectal, endometrial, ovarian and prostate cancer development (Lynch, 2010). Sedentary behaviour is also associated with increased chronic disease in healthy populations (Hamilton et al., 2007).

A large prospective cohort study of 488,720 men and women aged 50-71 years; 'The National Institutes of Health-American Association of Retired Persons Diet and Health Study' evaluated the link between sedentary behaviour and cancer. The study showed that high levels of TV/video watching were associated with an increased risk of colon cancer for men and women and endometrial cancer in women (Howard et al., 2008). Similarly, a study by Gierach et al. (2009) which included 109,621 women – with a follow-up period of 12-13 years, during which time 1,052 of the cohort developed endometrial cancer, reported no associations of cancer risk with light/moderate, daily routine or occupational physical activities. However, risk of developing endometrial

cancer increased with number of hours daily spent sitting. Women who spent ≥7 hours per day sitting with those who spent < 3 hours per day sitting (Gierach et al., 2009).

1.3.2 Physical activity and survival benefits

This dose-response relationship between higher PA levels and a lower risk of cancer recurrence also appears to hold in certain circumstances after a cancer diagnosis (Holick et al., 2008, Irwin et al., 2008b, Holmes et al., 2005, Pierce et al., 2007). A number of large epidemiological studies have shown a reduced risk of cancer recurrence with increased PA.

These studies have largely used self-report measures of PA in which intensity is based on self-estimated activity levels or on metabolic equivalents (MET)[6] levels for specific activities (Ainsworth et al., 2000). In accordance with the Centres for Disease Control and Prevention and the American College of Sports Medicine guidelines (Pate et al., 1995), PA recommendations include duration of activity (e.g. 30 minutes per day), intensity (moderate, 3 - 6 METs; vigorous >6 METs) and frequency (e.g. 3 times per week) - therefore the minimum recommendations for moderate activity require 7.5 MET hr/wk[7] or 450 MET-minutes per week .

The Nurses' Health Study, a large prospective study, reported that women (n=2,987) who engaged in PA after a diagnosis of breast cancer had a 20% to 50% lower risk of death from breast cancer (Holmes et al., 2005). The greatest benefit was in breast cancer survivors who engaged in > 9 MET hr/wk of activity (the cut-off point chosen for

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[6] MET scores for specific activities are defined as 'the ratio of the metabolic rate associated with each activity divided by the resting metabolic rate' (Ainsworth, 2000). One MET-hour is the amount of energy expended when sitting quietly for 1 hour and is equivalent to $3.5mL.kg^{-1}.min^{-1}$ (i.e. of oxygen uptake per kilogram of body weight per minute)

[7] The time spent per week at each activity is multiplied by its typical energy expenditure requirements to derive a MET-hour per week (MET hr/wk) total recreational physical activity score. For example; 3 MET hr/wk METs is equivalent to walking at average pace of 2 to 2.9 miles per hour for 1 hour and 9 MET-hr is equivalent to walking 3-5 hours per week at an average pace.

classifying a patient as 'physically active'). However, only half of breast cancer survivors reported carrying out this level of activity. A Norwegian study reported a 64% decrease in all-cause mortality risk among post-menopausal breast cancer survivors (n=1,364) in the highest versus the lowest category of PA participation (Emaus et al., 2010). Similarly, a Canadian cohort of 1,233 women with breast cancer, showed that risks of breast cancer death and death from all causes were also lower among the highest versus lowest quartiles of both moderate and vigorous intensity recreational activity (Friedenreich et al., 2009).

A recent study carried out by Holick et al. (2008) in a breast cancer cohort (n=4,482) reported that compared to women who expended <2.8 MET-h/wk in physical activity, women who engaged in greater levels of activity had a significantly lower risk of death from breast cancer. This equated to a 35% to 49% decreased risk of death from breast cancer and all cause-mortality. Similarly, the protective effect of increased PA levels in terms of cancer recurrence and breast cancer death was also reported in The Health, Eating, Activity and Lifestyle (HEAL) study (n=933) (Irwin et al., 2008b). The HEAL study showed that women who increased PA levels after a cancer diagnosis had a 45% lower risk of death (from all causes, although the majority of deaths were cancer related) and women who decreased PA after diagnosis had a four-fold greater risk of death.
In a prospective study carried out by Pierce et al. (2007) of early stage breast cancer patients (n=1,490), the median level of PA reported was 636 MET-min/wk[8]. Women who reported no PA (7.7%) had a mortality rate similar to women in the lowest quartile and were combined with them. Mortality rates showed a linear trend (P_{trend}=0.02) with the highest mortality in the lowest quartile (<225 MET-min/wk) and reduced mortality in the highest two quartiles.

In contrast, findings from the Life After Cancer Epidemiology (LACE) study (n=1,970) did not support a protective effect of PA on breast cancer recurrence or mortality but

[8] MET-min/wk: total energy expenditure estimated as the product of time spent in activities (minutes) multiplied by METs

suggested that regular PA is beneficial for breast cancer survivors in terms of total mortality (Sternfeld et al., 2009).

Most of these studies have been carried out in the breast cancer population, but similar dose-response relationships were shown in a landmark study of colo-rectal cancer patients (Meyerhardt et al., 2006a). It was reported that the proportion of patients with colo-rectal cancer–specific deaths at 5 years was 14.1% for patients who engaged in less than 3 MET-hr/wk, 14.4% for patients who engaged in 3 to 17.9 MET-hr/wk, and 6.2% for patients who engaged in 18 or more MET-hr/wk (significant across each PA tertile). In a separate cohort of men and women with Stage III colon cancer (Meyerhardt et al., 2006b), a similar reduction in disease-free survival was reported among patients physically active after diagnosis. An approximate 50% lower rate of colon cancer recurrence and related death was shown in those who exercised > 6 hours per week (Meyerhardt et al., 2006b).

These findings have also been borne out in recent systematic reviews (Barbaric et al., 2010, Ibrahim and Al-Homaidh, 2011). The review by Barbaric et al. (2010) included 10 studies with almost 14,000 breast cancer and colo-rectal cancer patients and reported that engaging in higher MET hours (>9 MET-hr/wk) per week of activity may help to increase cancer survival rates (Barbaric et al., 2010). Ibrahim and Al-Homaidh (2010) included 6 studies and > 12,000 breast cancer patients and reported all levels of post-diagnosis PA reduced breast cancer deaths by 34% (HR = 0.66, 95% CI, 0.57–0.77, P< 0.00001), all causes mortality by 41% (HR = 0.59, 95% CI, 0.53–0.65, P< 0.00001), and disease recurrence by 24% (HR = 0.76, 95% CI, 0.66–0.87,P = 0.00001) (Ibrahim and Al-Homaidh, 2011).

Thus, the evidence appears to substantiate an inverse relationship between PA and cancer recurrence and mortality in breast cancer and colorectal cancer, at least, as well as wider health-related benefits in survivors. However, the threshold exercise volume for benefits has not been fully elucidated. The HEAL study (Irwin et al. 2008b) reported an inverse relationship between death and any recreational activity, including very low

volumes of activity. Minimal threshold PA levels to effect changes in mortality have also been reported to be walking at a normal pace of approximately 2-2.9 miles (per hour) at least once per week (3-MET-h per week) (Holick et al., 2008, Meyerhardt et al., 2006a, Holmes et al., 2005) and dose-response relationships seem to exist beyond this point, with the greatest benefits among those with the highest PA levels. A number of sources report that 2 to 3 h/wk of moderate-intensity (9-MET-h per week) PA after a breast cancer diagnosis is associated with a 40% to 50% lower risk of breast cancer death (Holmes et al., 2005, Pierce et al., 2007, Ibrahim and Al-Homaidh, 2011).

1.3.3 Physical activity and cardiovascular risk profile improvement

It has been consistently shown that regular aerobic PA improves cardiovascular functioning and leads to significant reductions in cardiovascular risk factors (Pate et al., 1995). It has been demonstrated by animal studies that coronary circulation may be modified by aerobic exercise, with an increase of the interior diameter of major coronary arteries and formation of new myocardial capillaries and arterioles (Franklin and Kahn, 1996). Aerobic exercise has been shown to have an anti-thrombotic effect by decreasing platelet adhesiveness (Billman, 2002). Improved endothelial function is also associated with aerobic exercise (Hambrecht et al., 2000). PA also has a positive effect on many established risk factors for cardiovascular diseases. These include the prevention or delay of high blood pressure development in normotensive subjects and the reduction of blood pressure in those with established hypertension. PA is also associated with an increase in high-density lipoprotein cholesterol levels, and a lowered risk of developing non-insulin-dependent diabetes mellitus (Fletcher et al., 2001). Taken together, these effects tend to improve the coronary risk profile and curb the development of atherosclerosis, thereby reducing the risk of cardiovascular and coronary artery disease mortality (Giannuzzi et al., 2003). The research in this area of cardiovascular improvement has been carried out in 'healthy' populations. Although the relationship between increased PA levels and improved cardiovascular risk is expected to hold in cancer subjects, the aetiologies elucidating these benefits are not fully known at this time.

1.4 Physical Activity levels of patients after completion of chemotherapy

Given the importance of PA levels after a cancer diagnosis, the question arises as to the PA levels of cancer survivors. A systematic approach to searching for literature in the area of PA levels of cancer survivors was undertaken. The scientific literature was reviewed via searches of the following databases; Medline, Embase and the Cochrane library. Searches were limited to the year 2000 onwards, and to the English language, humans and adults studies. The literature was searched using a combination of the following key words; 'Cancer' OR 'Neoplasm' OR 'Tumour', AND 'Physical activity' OR 'Exercise', 'Health Behaviour' OR 'Health Change', AND 'Quality of life' AND 'Fatigue' AND 'Survivorship'. This was supplemented by a manual search of reference lists from each paper, and relevant studies emanating from this search were also reviewed. This generated 40 articles and Table 1.3 summarises details of these studies. PA trends in cancer survivors have been assessed in a number of longitudinal and cross-sectional studies with conflicting results.

A small number of studies showed a trend of decreasing PA levels in the first year after diagnosis (Irwin et al., 2003, Harrison et al., 2009). Others reported a trend of increasing PA (Andrykowski et al., 2007, Meyerhardt et al., 2006a, Hawkes et al., 2008, Emery et al., 2009, Voskuil et al., 2010). The volume of PA after a cancer diagnosis performed varied widely between studies reporting a mean PA of 9.2 MET h/week (for recreational activity) (Littman et al., 2010) to 99 MET h/week for total PA (Voskuil et al., 2010).

Rather than quantify PA in terms of MET h/week, many studies assessed compliance with recommended guidelines (150 minutes of moderate intensity exercise per week (Schmitz et al., 2010)). Generally, it was found that no more than one–third of patients met PA guidelines (Irwin et al., 2004, Andrykowski et al., 2007, Pinto et al., 2002a, Courneya et al., 2008a, Milne et al., 2007, Bellizzi et al., 2005, Coups and Ostroff, 2005, Eakin et al., 2007), although some studies reported PA levels in excess of this (Holmes et al., 2005, Harrison et al., 2009).

Studies incorporating pre-diagnosis PA also reported that 30-60% of cancer survivors who were physically active pre-diagnosis do not return to their pre-diagnosis PA levels (Blanchard et al., 2003, Irwin et al., 2003). However, pre-diagnosis levels were estimated retrospectively which is prone to recall error (Prince et al., 2008, Sallis and Saelens, 2000a). Pre-diagnosis PA was also included for a sub-section of the HEAL study (Irwin et al., 2003) in which it was reported that breast cancer survivors decreased their PA levels by 2 hours per week on average and obese breast cancer survivors tended to show greater reductions in PA levels.

Table 1.3 Studies examining physical activity levels of cancer survivors

Author	Population	Study design	Time post treatment	PA measurement	Physical activity levels reported
(Irwin et al., 2004)	Breast Cancer (n=806)	Longitudinal	3 years post diagnosis	Based on the Modifiable Activity Questionnaire	Averaged 2.5 - 3.5 hours per week. 32% physically active 2.6 years after diagnosis
(Irwin et al., 2003)	Breast Cancer (n=812)	Cross-sectional	Approximately 6.6 months since diagnosis	Based on the Modifiable Activity Questionnaire	Significant decrease in total activity of breast cancer survivors by 11% (2 hours) per week from the year pre-diagnosis to within 12 months post-diagnosis
(Andrykowski et al., 2007)	Breast Cancer (n=231)	Longitudinal	Baseline, post cessation of radiotherapy (2 time points) and 2 and 6 months post cessation radiotherapy	Godin Leisure Time Index	Percentage meeting guidelines Baseline: 27.2% Post-treatment1:39%Post-treatment 2:14.7% 2 month follow-up: 24.5% 6 month follow-up:24.6%
(Pinto et al., 2002a)	Breast Cancer (n=69)	Longitudinal	Baseline, 3 months, 6 months, 9 months and 12 months	Asked about participation in vigorous (eg running, jogging) and moderate-intensity exercise (eg brisk walking), average duration and type of exercise	32% were sufficiently active an average of 1.6 years after diagnosis
(Courneya et al., 2008a)	Colo-rectal cancer, female melanoma, and breast cancer (n=114,355)	Cross-sectional	Not detailed	Minnesota Leisure-time Questionnaire	< 22% of cancer survivors reported to be physically active
(Milne et al., 2007)	Breast Cancer (n=558)	Longitudinal	Mean (SD) of 25.2 (3.4) months post-diagnosis	Godin Leisure Time Questionnaire	31% meeting PA guidelines after treatment

(Blanchard et al., 2008)	Breast, prostate, colorectal, bladder, uterine, skin melanoma (n = 9,105)	Cross sectional	2, 5 and 10 years post-diagnosis	Godin Leisure Time Index Questionnaire	29.6% - 47.3% meeting PA guidelines
(Holmes et al., 2005)	Breast Cancer (n=2,987)	Cancer diagnosis between 1984-1988 and followed up 2 yearly until death or June 2002	Median of 38 months after diagnosis	Unit: MET-hours per week Questioned 'During the last year, what was your average time per week spent at each of the following activities'. Choice of 8 activities including walking.	45% reported walking ≥ 5 hours per week, 28% reported bicycling 1 or more hours per week, and 28% reported participating in aerobics classes ≥1 hours per week.
(Meyerhardt et al., 2006a)	Colo-rectal Cancer (n=573)	Longitudinal	Followed up biennially until death or June 2004 (median time of follow-up 9.6 years)	Specific activities in MET-hours reported	At 2 years post-diagnosis; <3 MET-hours/wk: 28.8%, 3-18 MET-hours/wk: 44.6%, >18 MET-hours/wk :26.6% At 5 years post-diagnosis; <3 MET-hours/wk: 28.2%, 3-18 MET-hours/wk: 41.4%, >18 MET-hours/wk :30.4% At 10 years post-diagnosis; <3 MET-hours/wk: 22.8%, 3-18 MET-hours/wk: 51.7%, >18 MET-hours/wk :25.6%
(Bellizzi et al., 2005)	Breast, cervix, ovary, colon, uterus, melanoma, larynx, lung pharynx, leukemia, lymphoma (n=7,384)	Cross-sectional	<1 year:6.4% 1 year: 9.8% 2-4 years: 22.8% 5-9 years: 22.6% 10+ years: 38.3% Post diagnosis	Frequency of moderate and vigorous physical activity (per week) and duration of each activity asked	Overall 29.6% met PA guidelines

(Coups and Ostroff, 2005)	Digestive system, genital system, respiratory system, skin, urinary system, upper aero-digestive tract and othe (n=1,646)	Cross-sectional	Mean (SD) time since diagnosis: 9.5 (10) years	Physical inactivity defined as 'not engaging in 20 min (or more) of vigorous physical activities, 3 or more times per week, or 30 mins (or more) of light/moderate physical activities, 5 or more times per week'	Percentage 'physically active' 18-39 year olds: 40.7% 40-64: 25.2% ≥ 65: 20.6%
(Lynch et al., 2007b)	Colorectal Cancer (n=1,996)	Cross-sectional	Mean (SD) 4.5 (1.5) months post-diagnosis	Assessed using questions based on the Active Australia Study, asked to report time spent in walking for transport or recreation, on moderate-intensity PA and vigorous intensity PA	32% achieved 150 mins of PA per week after their diagnosis
(Lynch et al., 2010)	Breast Cancer (n=111)	Cross-sectional	Mean time since diagnosis 10.3 (9.3) years	Actigraph accelerometer	Majority of day (66%) was spent sedentary, 33% was spent in light activity
(Eakin et al., 2007)	Colo-rectal, breast , prostate cancers, cancer of female reproductive organs, 'other' (non-specificed) cancers and melanoma (n=968)	Cross-sectional	Not detailed	Based on guidelines of 150 or more minutes of physical activity per week) Participants classified as sufficiently active, insufficiently active, or sedentary	Mean (SD) 27.7% (±2.8) sufficiently active, 39.7% (±3.1) insufficiently active, 32.6% (±3.0)
(Hawkes et al., 2008)	Colo-rectal cancer (n=1,250)	Longitudinal	Pre-diagnosis, 7 and 12 months post-diagnosis	Active Australia Survey	Sufficiently active: Pre-diagnosis: 52.7% 6 months post diagnosis: 32.4%

					12 months post diagnosis: 37.8%
(Grimmett et al., 2009)	Breast, colo-rectal, lung, lymphoma/leukemia, skin cancer melanoma, other cancer (n=716)	Cross sectional	43% had received treatment for cancer within 2 years of survey completion	Categorised as taking part in vigorous or moderate activity more than once a week or less than once a week	51.4% of cancer survivors physically active
(Grimmett et al., 2011)	Colorectal cancer (n=495)	Cross-sectional	Mean (SD) years since diagnosis, males: 2.06 (1.45), Females 2.15 (1.52)	Godin Leisure Time Index	20% men and 15% women 'physically active' (as measured by number of exercise sessions per week)
(Littman et al., 2010)	Breast Cancer (n=315)	Longitudinal	2-year period pre-diagnosis, and 1-12, 13-18 and 19-30 months post diagnosis	Modifiable Activity Questionnaire	Mean recreational PA pre-diagnosis was 18.8 MET-hours per week, 0-12 months post diagnosis was 9.2 MET-hours per week, 13-18 months was 15.3 and 19-30 months was 15.0
(Emery et al., 2009)	Breast Cancer (n=227)	Longitudinal	Follow-up every 4 months during the first year post-diagnosis and every 6 months during the subsequent 4 years	Seven-Day Physical Activity Recall	Mean (SD) MET levels Baseline: 16.6 (27.1), 1 year 31.3 (49.7), 2 year 22.3 (35.7) 3 year 19.6 (28.6), 4 year 16.8 (29.5) 5 year 14.3 (22.5)
(Ligibel et al., 2009)	Breast Cancer	Longitudinal	At diagnosis and 18 months afterwards	Participants asked their frequency of moderate and vigorous exercise	% exercising > 3 times per week Baseline: Moderate (46.5%), Strenuous(19.9%) 18 months: Moderate (50.5%), Strenuous(24.5%)
(Voskuil et al., 2010)	Breast Cancer (n=435)	Longitudinal	Pre-diagnosis, 1 and 2 years after the start of endocrine therapy	Question from the EPIC questionnaire (European prospective Investigation into Cancer) 'How much	Total PA (MET h/week) 114 ± 65 pre-diagnosis, 96 ± 59 at 1 year, 99 ±61 at 2 years

				time did you approximately spend on the following activities walking, bicycling, housekeeping, sports'	
(Harrison et al., 2009)	Breast Cancer (n=287)	Longitudinal	6, 12 , 18 months post-diagnosis	Behavioural Risk Factor Surveillance System, and then converted to MET-hours/week	At 6 months 46.4% meeting guidelines, at 12 months 46.3%, at 19 months 44.3%
(Gjerset et al., 2011)	Lymphoma, testicular, breast gynaecological, and prostate cancers (n=975)	Cross-sectional	< 2 years (11%) > 2 years (89%)	Godin Leisure Time Questionnaire	45% physically active post-diagnosis

A number of studies took the approach of comparing cancer survivors to non-cancer controls (Bellizzi et al., 2005, Coups and Ostroff, 2005, Grimmett et al., 2009, Eakin et al., 2007, Courneya et al., 2008a). Generally, little difference was found in activity levels between the cancer cohort and the non-cancer controls (Grimmett et al., 2009, Eakin et al., 2007, Courneya et al., 2008a), although one study reported greater PA levels among cancer survivors (Bellizzi et al., 2005), and another study reported the same or lower PA levels among cancer survivors (Coups and Ostroff, 2005).

From a number of studies, a complex relationship between increased PA levels and a higher disease burden was outlined. In the Health, Eating, Activity and Lifestyle (HEAL) study, it was reported that women diagnosed with a higher disease stage reported 15% more time engaged in PA compared with women diagnosed with in situ disease, although this difference was accounted for by household and not by recreational activity (Irwin et al., 2004) and did not reach statistical significance. Similarly, Holmes et al (2005) reported that women in the two highest categories of activity were slightly more likely to have stage II cancer, and slightly less likely to have stage I cancer compared with women in the lower categories of PA. However, conversely more advanced disease has also been associated with a more sedentary lifestyle (Pinto et al., 1988).

Only one study used an objective quantification method (Actigraph accelerometer) (Lynch et al., 2010) in a cross-sectional study in breast cancer survivors (n=111). Accelerometers are small devices which register acceleration of the limbs and trunk, generating a measure of free-living (real-life) activity. This study by Lynch et al. (2010) showed that participants spent the majority of their day sedentary (66%) or in light activity (33%), therefore only 1% of time was spent in moderate/vigorous domains of activity and sedentary time was found to be positively associated with adiposity ($p<0.05$). However, although the PA quantification method was robust, this study investigated PA levels of long term cancer survivors with a mean (SD) time since cancer diagnosis of 10.3 (9.3) years.

1.4.1 Limitations to studies investigating physical activity patterns in Cancer survivors

Many limitations pertain to these studies and the variability in results may be due to a number of reasons. Firstly, the heterogeneity of populations studied renders comparison between studies difficult as cohorts vary with regard to participant characteristics such as cancer staging, age and treatment variables which limit the ability to pool results. The majority of studies investigated PA patterns in breast cancer populations (Irwin et al., 2004, Irwin et al., 2003, Andrykowski et al., 2007, Pinto et al., 2002a, Courneya et al., 2008a, Milne et al., 2007, Holmes et al., 2005, Lynch et al., 2010, Littman et al., 2010, Emery et al., 2009, Ligibel et al., 2009, Voskuil et al., 2010, Harrison et al., 2009). Bearing the diversity even within breast cancer populations in mind, it should be considered that brain metastases are more common in breast cancer patients which may affect PA levels, which is not always documented in studies. Four studies reported PA patterns in other populations such as colo-rectal cancer (Meyerhardt et al., 2006a, Lynch et al., 2007a, Hawkes et al., 2008, Grimmett et al., 2011) and a number of other studies investigated PA levels in mixed cancer populations (Courneya et al., 2008a, Blanchard et al., 2008, Bellizzi et al., 2005, Coups and Ostroff, 2005, Eakin et al., 2007, Grimmett et al., 2009, Gjerset et al., 2011).

Many of the studies were cross-sectional in design (Irwin et al., 2003, Courneya et al., 2008a, Blanchard et al., 2008, Bellizzi et al., 2005, Coups and Ostroff, 2005, Lynch et al., 2007b, Lynch et al., 2010, Eakin et al., 2007, Grimmett et al., 2009, Grimmett et al., 2011, Gjerset et al., 2011), so only provided a once-off 'snapshot' of PA, thus patterns of activity were impossible to assess. Other studies assessed PA levels in cancer survivors longitudinally (Emery et al., 2009, Irwin et al., 2004, Andrykowski et al., 2007, Ligibel et al., 2009, Pinto et al., 2002a, Milne et al., 2007, Meyerhardt et al., 2006b, Hawkes et al., 2008, Littman et al., 2010, Voskuil et al., 2010, Harrison et al., 2009). Although, timing of measurement varied widely from retrospective analysis of pre-diagnosis PA levels to assessing levels up to 10 years post cessation of treatment, which again limits the ability to pool study results.

A key aspect to consider in these studies is the quantification method used to assess PA. PA as a multi-dimensional construct incorporating frequency, time, type and duration, is difficult to measure accurately as no standard method of assessing PA exists within the oncology population. A limitation of studies in the cancer setting is that PA is generally measured by self-report instruments, due to factors such as low-cost, ease of use and administration, practicality and general acceptance. Reflecting the lack of consensus on an optimal questionnaire for use within this population, a variety of measures have been used.

The Modifiable Activity Questionnaire (Irwin et al., 2004) was used a number of studies (Irwin et al., 2004, Irwin et al., 2003, Littman et al., 2010) which includes leisure and occupational activity recalled over the past week and past year. The Godin Leisure Time Index (Godin and Shephard, 1985), which assesses leisure time PA only, was also used widely (Andrykowski et al., 2007, Milne et al., 2007, Blanchard et al., 2008, Grimmett et al., 2011, Gjerset et al., 2011). The Minnesota Leisure Time Questionnaire (Taylor et al., 1978) which assesses leisure and home/household activities over a 12-month time frame was used by Courneya et al. (2008). The Seven-Day physical activity recall (Sallis et al., 1985) was also used which assesses leisure and occupational activity over a recall period of the previous 7 days was used in the study by Emery et al. (2009). A number of other studies did not use a specific questionnaire, and simply asked participants about their PA levels over certain time periods such as over the previous week or previous year (Pinto et al., 2002a, Holmes et al., 2005, Bines and Gradishar, 1997, Coups and Ostroff, 2005, Eakin et al., 2007, Grimmett et al., 2009, Ligibel et al., 2009, Meyerhardt et al., 2006a).

Thus, PA quantification methods varied widely, and some studies quantified PA as MET-h per week, while others measured percentage adherence to PA guidelines. Also, estimating change in PA patterns in the oncology population is confounded by the lack of consistency in self-report measures used which limits comparability between studies, with different time-frames being assessed e.g. "in a usual week" or in the past week, month or even year. It is also difficult to compare across studies; as some assess

a wide variety of PA settings (recreational, household, and occupational) and others assess recreational activity only, and categorize results by setting type. Others focus on recreational or leisure time activity and categorize results by intensity (mild, moderate, vigorous, total).

1.4.2 Summary of preceding section

PA after a cancer diagnosis is likely to confer survival benefits beyond those associated with standard regimens such as chemotherapy and radiotherapy, as well as benefiting other factors such as QOL and fatigue. Even though PA is expected to decrease during active treatment and increase again post-treatment (Courneya and Friedenreich, 1997b, Courneya and Friedenreich, 1997a, Andrykowski et al., 2007), this does not seem to be consistently borne out in the literature, as PA levels of cancer survivors seems to be low. However, the majority of information is gleaned from self-report measures – with a lack of consistency in terms of which self-report measures were used, rendering comparison of results difficult. In addition, the heterogeneity of populations investigated in terms of cancer diagnosis, time since diagnosis, study design and time-frames chosen compounds the challenges in terms of evaluating the PA patterns of cancer survivors. There is a paucity of research which evaluates objective PA patterns of cancer survivors during the first year after cessation of cancer treatment when it might be expected that important lifestyle changes would be commenced. Establishing objective PA levels at this time-point is an important first step in terms of advising design of possible interventions in this population.

1.5 Interventions to increase physical performance and cardiovascular risk factors after treatment

Even though there is strong evidence for the benefits of PA post cancer-treatment, the majority of cancer survivors do not carry out sufficient levels necessary for health-related benefits (Pate et al., 1995, Bellizzi et al., 2005, Irwin et al., 2003, Irwin et al., 2004) as described in Section 1.4 (page 33) previously. High PA levels are associated

with multiple health benefits and may even be associated with a decreased cancer recurrence rate as described in Section 1.3.3 (page 29) and 1.3.2 (page 32) . Given the apparent low PA levels of cancer survivors and the benefits which pertain to sufficient PA levels; research has been directed towards interventions which aim to increase this parameter.

Rehabilitation of 'functional disability' as a result of rest and immobility in cancer was first mentioned in the late 1970's (Hinterbuchner, 1978). Thus, investigating the impact of exercise rehabilitation within the cancer area is a relatively new field of research. The first papers on intervention studies in this area appeared in the 1980's (Winningham et al., 1989, Winningham and Macvicar, 1989) and reported on the effect of low intensity aerobic exercise in breast cancer patients undergoing adjuvant chemotherapy. In the main, early trials were methodologically poor, including uncontrolled pre/post single group design studies (Conn et al., 2006b) rather than randomised designs. Literature reviews naturally followed which compiled the evidence from these early studies (Smith, 1996, Pinto and Maruyama, 1999, Courneya and Friedenreich, 1999, Courneya et al., 2000, Courneya, 2001), suggesting the positive effects of PA in terms of fatigue and quality of life. However, these reviews lacked a systematic approach and included non-randomised studies, which can lead to overestimation of intervention outcomes (McNeely et al. 2006). These reviews also summarised evidence of intervention studies including all patients throughout the cancer trajectory; those in treatment[9], those in the rehabilitation phase as well as long-term survivors. It is now known that rehabilitation needs can vary throughout the cancer continuum (Spence et al., 2010).

Indeed, the Physical Exercise across the Cancer Experience (PEACE) framework was developed by Courneya and Friedenreich in 2001, which suggests six possible 'cancer control' time periods to be considered when prescribing PA. These include; 'buffering before treatment, coping during treatment, rehabilitation immediately post-

[9] 'In treatment' is generally taken to mean on a chemotherapy regimen

treatment, long-term health promotion and survival for those with positive treatment outcome and palliation for those approaching the end of life'. A more recent framework devised by these authors, simplified this model, dividing survivorship into two time periods; the rehabilitation phase – the 3-6 month time period after cancer treatment has ceased, and the longer-term disease prevention/health promotion model which follows (Courneya and Friedenreich, 2007). Of particular interest is the 'rehabilitation' phase as it has been suggested that this phase may be especially important for initiating exercise regimes to promote return to pre-diagnosis health status, although the importance of exercise has been emphasised throughout the cancer trajectory (Courneya and Friedenreich, 2001).

Few programmes take place in the initial time after completion of chemotherapy (Conn et al., 2006a, McNeely et al., 2006a). Meta-analyses have shown that exercise produces larger effects in QOL and fatigue during the survivorship phase compared to the treatment phase, therefore timing exercise regimes during this post-adjuvant time period may be important (Conn et al., 2006a, Mc Neely et al., 2006, Speck et al., 2010). Moreover, a study investigating exercise programming preferences of patients with cancer, reported that the majority of cancer survivors prefer to commence an exercise programme after completion of treatment (Jones and Courneya, 2002a). The rehabilitation phase was identified to be a key focus for research to examine the feasibility and efficacy of exercise interventions (Courneya and Friedenreich, 2007). Exercise interventions may also offer social support to patients at a time when the number of medical appointments is decreasing. This sudden perceived drop in support can be a difficult transition for some patients (Stanton, 2006).

In terms of evidence for exercise intervention studies in cancer; a number of systematic reviews and meta-analyses have been completed in recent years, which have been summarised in Table 1.4. These have included larger and more methodologically robust randomised controlled trials than early reviews in this area. A comprehensive meta-analysis published in 2005 included 32 cancer and exercise intervention studies and 503 participants (Schmitz et al., 2005). It was reported that

twenty two were of "high quality" using the Van der Windt internal validity characteristics (van der Windt et al., 1999), and included 25 reported outcomes Reflecting this growing field, an updated review by these authors published in 2010 included 82 studies, almost 7,000 cancer survivors and detailed 60 outcomes (Speck et al., 2010). Also indicative of this expanding field; a number of systematic reviews and meta-analyses have moved from a generalist overview of the area to a more specific scope of reference. Some have been directed towards the effect of exercise on outcome measures such as fatigue (Watson and Mock, 2003, Kangas et al., 2008, Jacobsen et al., 2007, Luctkar-Flude et al., 2007), quality of life (Duijts et al., 2011, Ferrer et al., 2011), depression (Craft et al., 2011) and VO_2 peak (Jones et al., 2011). There are also disease-specific meta-analyses, such as the breast cancer meta-analysis conducted by Mc Neely et al. (2006).

Taken together, it would appear that exercise interventions have the potential to confer many physical and psychosocial benefits to patients with cancer as well as cancer survivors. Many systematic reviews combined on-treatment studies with those which took place during the survivorship stage (Oldervoll et al., 2004a, Stevinson et al., 2004, McNeely et al., 2006a). Other reviews reported effect sizes separately for post-treatment and on treatment trials (Knols et al., 2005, Schmitz et al., 2005, Galvao and Newton, 2005, Speck et al., 2010). This approach seems sensible as interventions are thought to be more beneficial when administered after-treatment with larger effect sizes as opposed to 'on treatment' studies (Speck et al., 2010, Conn et al., 2006a). This is thought to be due to a decreased 'signal' due to physiological and haematological changes related to the side-effects of treatment (Speck et al., 2010).

1.5.1 Evidence for exercise intervention studies in patients with cancer and cancer survivors focusing on the post-treatment setting

Physical measures have been shown to increase as a result of exercise interventions. Reviews including all cancer types, two during and nineteen after-treatment have shown that physical function improved as a result of exercise interventions (Oldervoll et al., 2004a, Stevinson et al., 2004). Moderate effects of exercise on physical function

were also shown in a meta-analysis carried out by Conn et al. 2006 (d[10]=0.45, based on 11 studies). Physical functioning improved in breast cancer populations as a result of exercise interventions, although this was only based on 4 studies (McNeely et al., 2006a). Body composition measures (Conn et al. 2006) (based on 10 studies, d=0.27) improved as a result of exercise interventions. Strong consistent evidence has also been reported for upper body strength and lower body strength (Speck et al., 2010), (based on 6 studies for upper body strength, d=0.99, 7 studies for lower body strength, d=0.90). Strength increases were reported for the bench press and leg press (each based on 3 studies in breast cancer studies) (Fong et al., 2012). Large positive effects have also been reported for cardio-respiratory fitness (Odervoll et al. (2004), based on 1 study, McNeely et al. (2006) based on 3 studies, d=1.14, Speck et al. (2010), based on 14 studies, d=0.32, Schmitz et al. (2005) based on 4 studies d=0.65).

A recent meta-analysis evaluated the effects of supervised exercise on peak oxygen consumption (VO_2peak) (Jones et al., 2011) and reported that exercise training was associated with a significant increase in VO_2 peak, with superior improvements in VO_2 peak for studies conducted for a shorter duration (<4 months) and following the completion of adjuvant therapy (WMD[11]= 2.9, based on 6 studies).

[10] d = standardised mean difference between the treatment and control group, Interpreted using the criteria proposed by Cohen (1988); 0.2 – 0.5: "small to moderate", 0.51 – 0.8: "moderate to large", > 0.8: "large"

[11] WMD=Weighted mean difference

Table 1.4 Systematic reviews and meta-analyses of post-treatment exercise interventions in cancer survivorship populations

Author	Systematic review or meta-analysis	Main criteria for study inclusion	Number of studies included	Main findings/ Statistically significant results	Comments
General systematic reviews/meta-analyses					
Fong et al. (2012)	Meta-analysis	RCTs which assessed the effects of PA in adults who had completed their main cancer treatment, except hormonal treatment	34 studies 65% on breast cancer 48 outcomes listed	**Statistically significant results shown for;** **Breast Cancer Studies** PA was associated with improvements in insulin-like growth factor-I, bench press, leg press, fatigue, depression, and QOL **Mixed solid tumours** Significant improvements in body mass index, body weight, peak oxygen consumption, peak power output, distance walked in six minutes, handgrip strength, and quality of life.	All post treatment studies. Results separated out for breast and mixed solid tumour patients. Combined supervised and unsupervised programmes.
Knols et al. (2005)	Systematic review	An RCT[a] or CCT[b] with outcome measures of physical fitness and/or psychological well-being	34 10 RCTs and 2 CCTs after treatment trials 680 patients in total	**Statistically significant results shown for;** **Breast Cancer Studies (Post treatment)** Mood status (Pinto et al., 2003), Fatigue (Segar et al., 1998, Courneya et al., 2003c), Anxiety and depression (Segar et al., 1998), Happiness and self esteem (Segar et al., 1998), QOL[c] (McKenzie and Kalda, 2003, Courneya et al., 2003c) **Mixed Solid Tumours (Post treatment)** Physical strength (Berglund et al., 1994b, Berglund et al., 1994a), Aerobic capacity and flexibility (Burnham and Wilcox, 2002), Body fat decrease (Burnham and Wilcox, 2002), Sleeping problems (Berglund et al., 1994a), QOL (Burnham and Wilcox, 2002, Courneya et al., 2003a)	Results separated out for breast cancer during and post treatment and mixed solid tumour populations during and post treatment. Combined supervised and unsupervised programmes.

Odervoll et al. (2004)	Systematic review	RCTs or CCTs of physical exercise during or after cancer treatment	12 studies Study sample sizes from 21 to 155 patients 62% were breast cancer	**Statistically significant results shown for;** QOL (Courneya et al., 2003c, Segal et al., 2003, Burnham and Wilcock, 2002), Physical functioning, physical capacity and/or muscular fitness (Courneya et al., 2003c, Segal et al., 2003, Burnham and Wilcock, 2002, Segal et al., 2001, Dimeo et al., 1997a, Mock et al., 1997, Macvicar et al., 1989), Fatigue (Segal et al., 2003, Dimeo et al., 1999, Mock et al., 1997), Body composition measures (Winningham et al., 1989)	Studies with multiple interventions and pilot studies were excluded. Included patients on and off treatment. Two studies incorporated resistance training, other 10 studies included aerobic training.
Stevinson et al. (2004)	Systematic review	Participants with any stage or type of cancer, Prospective intervention trials with a control arm	33 controlled trials - 25 randomized trials, 1,863 participants in total	**On and off treatment studies included;** Physical function increased (Patients who exercised had on average a 0.96 (95% CI: 0.49, 1.43) standard deviation greater physical function than control subjects	Data was pooled for 19 trials that assessed physical functioning and 12 trials that assessed fatigue. Exercise-only as well as multi-modal interventions were included.
Schmitz et al. (2005)	Systematic review and meta-analysis	Interventions designed to increase PA and include a concurrent comparison group,	32 studies 503 participants in total 183 participants post treatment	**Post-treatment studies**: **Large effect sizes** Vigour/vitality (0.82, p=0.04), Body image (1.21, p=0.03), Confusion (0.83, p=0.04), "Body size with a goal of avoiding arm volume gain" (1.64, p=0.008) **Moderate to large effect sizes** Cardio-respiratory fitness (0.65) p<0.003 **Small to moderate effect sizes** Multiple constructs of mental health (0.34, p=0.02)	Results were presented separately for treatment and comparison groups. All intervention studies included, regardless of quality. Supervised and unsupervised interventions mixed. Of note, interventions during or post treatment did not improve fatigue
Galvao and Newton (2005)	Systematic review		26 studies, (9 studies for post cancer treatment)	**Post treatment Studies** Increased physical capacity (Nieman et al., 1995b, Durak and Lilly, 1998, Durak et al., 1999), Increased QOL (Durak and Lilly, 1998), Decreased anxiety and depression (Porock et al., 2000)	Divided studies into during or after treatment

Conn et al. (2006)	Meta-analysis	Interventions designed to increase resistance, flexibility or endurance exercise	30 studies 21 were supervised interventions	**Moderate to large effect sizes** Physical function (0.52 p<0.001) **Small to moderate effect sizes** Body composition (0.27, p<0.05)	Published and unpublished studies included
Speck et al. (2010)	Systematic review and meta-analysis	Include interventions 'designed to increase PA' and include a concurrent parallel comparison group	82 studies and 6,838 subjects	**Post-treatment studies**: **Large effect sizes** Upper body strength (0.99, p<0.0001), Lower body strength (0.90, p=0.024). **Moderate effect sizes** Breast-cancer specific outcomes (0.62, p=0.003), Perception of physical condition (0.57, p=0.04),, Confusion (-0.57, p=0.05), Fatigue (-0.54, p=0.003) **Small to moderate effect sizes** Physical activity level (0.38, p<0.0001), Aerobic fitness (0.32, p=0.03), Body weight (-0.18, p=0.004), Body fat percentage (-0.18, p=0.006), BMI (-0.14, p=0.002), Overall QOL (0.29, p=0.03), Mood disturbance (-0.39, p=0.04), Body image (-0.26, p=0.03), General symptoms and side effects (-0.30, p=0.03), IGF-1 (-0.31, p=0.03).	Results were for the combined effect of breast cancer (83%) and other cancers (17%). supervised studies were combined with unsupervised studies, resistance programmes were combined with aerobic programmes
Spence et al. (2010)	Systematic review	Aerobic and/or flexibility intervention studies carried out with cancer patients who had completed adjuvant chemotherapy	13 articles (10 studies) included	**Post-treatment studies;** Improvements in fatigue (Dimeo et al., 1997c, Hsieh et al., 2008) Improvements in haematological/immunological markers (Dimeo et al., 1997a, Dimeo et al., 1997c, Hutnick et al., 2005) Improvements in fitness (Dimeo et al., 1997c, Hayes et al., 2004, Thorsen et al., 2005, Hutnick et al., 2005, Hsieh et al., 2008)	Included only studies which took place in the first 12 months post cessation of chemotherapy. Included mixed cancer populations, but were predominantly breast cancer

		within previous 12 months			
Jones et al. (2011)	Meta-analysis	Included patients allocated to a supervised exercise training with a concurrent non-exercise control group, with VO_2 peak as an outcome measure	6 studies and 571 subjects	Exercise training increased VO_2 peak Weighted mean difference =2.9mL.kg^{-1}.min^{-1}	Greater improvement for programmes < 4 months and carried out in post-adjuvant setting
Specific cancer reviews					
(McNeely, 2006)	Systematic review and meta-analysis	Randomized trials with QOL, fitness, or physical functioning as primary outcomes.	14 studies 717 participants	**Post treatment studies** **Large effect size** VO_2 peak (1.14), p<0.0001 **Moderate to large effect sizes** Physical functioning and physical well-being subscales of QOL (0.84) p<0.0001, Fatigue (0.72) p<0.001	Included breast cancer population only. Included studies during or post cessation of adjuvant therapy.
Systematic reviews/Meta-analyses focussing on specific outcomes					
Quality-of-life					
(Duijts et al., 2011)	Meta-analysis	RCTs with outcome measures of psychosocial functioning and HRQoL	17 studies	**Small to moderate effect sizes** Fatigue (0.32, p=0.004), depression (0.26, p=0.016), body-image (0.28, p=0.007) HRQoL (0.30, p=0.001)	Limited to women with breast cancer. Included studies during and after treatment for cancer
(Ferrer et al., 2011)	Meta-analysis	All intervention studies provided QOL was an outcome measure	78 studies 54% were breast cancer	**Small to moderate effect sizes** Immediate follow-up assessment: 0.24łł (95% CI: 0.20 - 0.28) Delayed follow-up assessment: 0.35łł (95% CI: 0.27 - 0.44)	Included controlled comparisons and one-group pre-test post-test

Depression					
(Craft et al., 2011)	Systematic review and meta-analysis	RCTs with depression as an outcome measure	15 RCTs included 60% of studies breast cancer	Overall Effect size -0.22, p=0.04	Included during and post treatment as well as supervised and non-supervised programmes.
Fatigue					
(Jacobsen et al., 2007)	Systematic review and meta-analysis	A controlled comparison with Fatigue as a study outcome	18 studies 384 control subjects 449 intervention subjects 59% breast cancer	Limited support for activity-based interventions 0.09 p <0.05	Psychological or activity-based intervention (results separated out for each), 10% of studies in metastatic disease patients. Only 15% of studies carried out in phase after cessation of cancer treatment. Included home based (61%) and supervised (39%) regimes.
(Kangas et al., 2008)	Meta-analysis	Only RCTs with fatigue as an outcome measure were included	17	Mean effect size 0.42, p < 0.001	

[a]RCT: Randomised controlled trial, [b]CCT: controlled clinical trial,
Effect sizes: 0.2 – 0.5 'small to moderate', 0.51 – 0.8 'moderate to large', >0.8 large (Cohen, 1988)
*WMD: Weighed mean difference (used when data were on a uniform scale, [ł]SMD: Standardized mean difference (used when data were on different scales), [ff]CI: Confidence interval, RCT-randomised controlled trial, CCT-controlled clinical trial, łł no p value provide

A meta-analysis specifically reporting on the effect of exercise interventions on fatigue was very weakly supportive of exercise interventions (effect size *d*=0.05, based on 12 studies). However, effect sizes were not separated out for studies investigating the effect of interventions during or post-treatment, and only a minority (15%) of studies were carried out in the post-treatment setting (Jacobsen et al. 2007), therefore the on-treatment studies may have diluted the results of the post-treatment studies. Likewise, a meta-analysis by Conn et al. (2006) reported poor outcomes of exercise interventions (*d*=0.11, based on six studies) which included non-randomized trials and unpublished studies and also by Schmitz et al. (2005) (*d*=0.16, based on 8 post-treatment studies). Similarly, Galvao and Newton, (2005) (based on 8 on and post-treatment studies) and Stevinson et al. (2004) (based on 33 controlled trials) reported no effect of PA interventions on fatigue, both during and after treatment.

Contrary to these reported findings, a meta-analysis specifically reporting the effect of exercise interventions on fatigue by Kangas et al. (2008), reported moderate effects of exercise on outcomes (*d*=0.42, based on 16 studies). Specifically, walking and multi-modal programmes were reported to confer most beneficial effects on fatigue. A systematic review by Oldervoll et al. (2004) also provided evidence that both aerobic and resistance exercise may decrease fatigue in patients during and after treatment for cancer, however this was only based on three studies. A recent review by Speck et al. (2010) (*d*=-0.54, based on 14 studies) reported that PA interventions reduced fatigue post treatment. A breast cancer specific meta-analysis showed a decrease in fatigue (McNeely et al., 2006a), although this was based on only 6 studies.

Reviews by Galvao and Newton (2005) and Odervoll et al. (2004) which included mixed cancer populations indicated that exercise interventions improved QOL. Modest effects of exercise on QOL were reported by meta-analysis (Speck et al. 2010, *d*=0.29 based on 16 studies, Duijs et al. (2011), d=0.3, based on 13 studies). Breast cancer specific meta-analyses have also indicated that exercise had a small but statistically significant effect on QOL, however these were based on a small number of studies (three studies, WMD=4.58 and seventeen studies, *d*=0.3 respectively). A recent meta-

analysis, based on 78 studies indicated that exercise interventions had a small to moderate effect on QOL (d=0.24 for immediate follow-up, and d=0.35 for delayed follow-up), indicating that positive changes in QOL remained intact on longer-term follow-up. Moderators of higher QOL were higher intensity aerobic programmes over longer time periods, with these effects seen particularly in females (Ferrer et al., 2011). A recent meta-analysis have also reported a modest effect of exercise on depression (Craft et al. 2011) (d=-0.22, based on 15 studies).

Only one systematic review, summarised the studies during the rehabilitation phase – during the first year after completion of chemotherapy (Spence et al., 2010). Ten studies were included in this review and only four of the studies were in a mixed cancer population, the rest were in breast cancer (four studies) and colo-rectal cancer (two studies). Methodological limitations and variations in study design, participants and interventions did not permit a synthesis of data, however the authors surmised that benefits were accrued in terms of fatigue (based on 2 studies), haematological markers (based on 3 studies), fitness (based on 4 studies) and strength (based on 2 studies). It was suggested that exercise programmes during this period could help the transition from the intense levels of support offered during treatment. However, the 'early' nature of intervention studies in the rehabilitation phase was particularly emphasised.

Therefore, there appears to be a gap in the literature regarding PA interventions soon after completion of chemotherapy, which may be the most opportune time for an intervention to take place. There is a need to capture the effect of interventions in heterogeneous cancer populations as the largest cohort studied was breast cancer patients (Speck et al., 2010). A distinction has been drawn between supervised programmes and non-supervised (i.e. home based programmes). Home programmes have the advantage of being more accessible to patients; but there is inherently less control over the exact exercise dosage administered. While home-based programmes are advantageous in terms of accessibility and convenience, a greater degree of control can be exerted in supervised regimes.

Many 'rehabilitation' programmes in cancer are based on psychotherapy or social support. Such therapies however do not usually deal with the physical problems encountered by many patients, such as loss of functional capacity, weight gain and fatigue (Wilmoth et al., 2004) as detailed above in Section 1.1.2 (page 2). It is possible that multi-modal programmes may exert greater effects than programmes offering one intervention mode, however clarity is lost as the contribution of the individual components and/or interaction between them in producing the effect. A more precise dose-response can be estimated when programme are one intervention only.

Many cancer rehabilitation programs and/or trials which include physical rehabilitation are lengthy in duration, extremely intensive (Adamsen et al., 2009) and have tight eligibility criteria. They would be expensive to translate into general clinical practice or to apply to the general cancer survivor population. It has been noted that the majority of exercise intervention studies have taken place in the breast cancer population (Speck et al. 2010), which limits their applicability to the wider oncology population. This is unsurprising as they tend to be a motivated cohort, willing to partake in exercise interventions. The dearth of research in heterogeneous cancer populations has been noted.

Taking all these points together; the focus of this element of the thesis will be directed towards studies (single group pre-post studies, controlled clinical trials or randomised controlled trials) which include a supervised exercise intervention, take place during the first year after cessation of chemotherapy in heterogeneous cancer populations and consist of an exercise intervention only.

A literature search was performed, limited to humans, English language and adults. The key words used for searching were "Cancer" OR "Oncology" OR "Neoplasm", AND "Physical Activity" OR "Exercise" OR "Exercise therapy" OR "Rehabilitation" OR "Physical fitness" OR "Exercise capacity". Publications generated were searched for further references. All studies had to include a heterogeneous cancer cohort, and take

place during the first year after cessation of chemotherapy. This generated six studies which are detailed in Table 1.5.

The effect of rehabilitation was investigated after high dose chemotherapy followed by autologous peripheral blood stem cell transplantation in 16 subjects with haematological malignancies soon (0.5 months) after completion of chemotherapy (Dimeo et al., 1997c). A treadmill stress test to volitional exhaustion was the primary outcome measure. Participants were not randomized, instead those living within 50km of the hospital were included in the exercise group, and remaining patients were assigned to the control group. The training program comprised of treadmill walking following an interval training pattern. The patients trained daily on weekdays for 6 weeks. During the first week, the exercise duration was 5 X 3 minutes per day. The exercise duration was gradually increased to 4 X 5 minutes per day in the second week, 3 X 8 minutes in the third week, 3 X 10 minutes in the fourth week and 2 X 15 minutes in the fifth week, during the sixth week, exercise was performed without interruption for 30 minutes. The intensity was regulated by modifying the training speed to correspond to a lactate concentration of 3 ± 0.5mmol/L in capillary blood (i.e. slightly below the anaerobic threshold). The lactate concentration and training heart rate were adapted throughout the programme to allow accommodation as fitness improved. Outcome measures were the exercise stress test and a personal interview which assessed patients' feelings of fatigue, and limitations in activities of daily living such as stair climbing, walking or shopping. The interview performed 7 weeks after discharge indicated that four patients in the training group (and none in the control group) experienced less fatigue with usual daily activities.

The role of a moderate intensity combined aerobic and resistance exercise programme was investigated in a mixed tumour population after peripheral blood stem cell transplantation (Hayes et al., 2004). As recruitment was reported to be challenging, instead of randomization, patients were allocated to either the exercise or control intervention, based on a process of matching baseline characteristics (age, gender,

marriage status, exercise history, weight, living distance from centre, diagnosis, number of transplants, chemotherapy regime) ''as closely as possible''. Despite the efforts to match the groups, there were baseline differences in the mean age (control group: 54.5 years, exercise group: 39.5 years) of the groups which may have affected results. Subjects allocated to the control group were required to participate in a supervised stretching programme of three months duration, three times a week - the premise of which was to standardise the contact time between groups.

The subjects allocated to the exercise group participated in a supervised three month moderate intensity programme of mixed aerobic and resistance exercises. The aerobic element consisted of treadmill walking and stationary cycling for 20–40 minutes, three times per week at an intensity of 70-90% maximum heart rate. The resistance element consisted of 3-6 machine and free weight exercises performed twice a week, which were progressed weekly, with the weight set to induce failure at 8-20 repetitions. An ancillary study invested the immunological effect of the exercise (Hayes et al., 2003).

Table 1.5 Intervention studies incorporating heterogeneous cancer populations within the first year after cessation of chemotherapy

Authors	Main Eligibility Criteria	Study design/ Participants	Details of control arm	Details of exercise intervention	Main end-points	Reported results
Stevinson et al. (2006)	Within 6 months of completing treatment	Single-group, pre-post study 12 participants, 9 analysed (Included lung, prostate, ovarian Breast, Non-Hodgkins, lymphoma)	No control arm included	Weekly circuit training class with a home based activity 4 days/week for 10 weeks Consisted of a light-moderate intensity, aerobic and resistance exercises in a circuit format	-PA: PA measure from the European Prospective Investigation into Cancer and Nutrition (EPIC) -Semi-structured interviews to explore opinions of programme	-Established this type of programme was feasible and acceptable -Self-reported improvements in PA, fitness, psychological well-being
(Hayes et al., 2003, Hayes et al., 2004)	Cancer patients after receiving high dose chemotherapy and autologous peripheral blood stem cell transplantation	CCT Exercise group: 6 participants Control group: 6 Mixed tumour types including haematological cancers	Stretching programme	Aerobic and resistive gym based training 3 days per week for 12 week intervention 20-40 min treadmill walking or stationary cycling and 3-6 month resistance machine exercises 70-90% MHR 2 resistance sessions/wk	- Aerobic capacity (VO_2 peak); maximal graded treadmill exercise test -Muscular strength; isometric handgrip -Immune function	-Increased VO_2 by 7.8mL.kg.min^{-1} ($p<0.05$) -Increased upper and lower body strength ($p<0.01$)
Burnham and Wilcox, 2002	Minimal 2 months after chemotherapy and/or radiation and/or surgery	RCT 21 breast and colon cancer patients allocated, 18 patients analyzed (Control group: 6 Low-intensity: 6,	'No exercise' Nil further details supplied	3 days per week for 10 weeks -Low intensity aerobic exercise (25-35% HRR week 1 → 40% HRR by week 10) -Moderate-high intensity exercise(40-50% HRR →60% HRR by week 10)	-Aerobic capacity (VO_2 max) -Flexibility (sit and reach test) -Body composition (calliper), -QOL (Quality of life	-No differences between low and high intensity groups. -Combined groups; In Exercise Group -↑ VO_2max ($p<0.001$) -↑ lower body flexibility

		Moderate intensity: 6)		Duration : 14 minutes week 1 → 32 min week 10 Exercise consisted of: Treadmill, stationary bike and stair-climber	Index for Cancer patients), and the Linear Analog Self-Assessment (LASA)	(p=0.027) -↓body fat (p<0.001)
(Dimeo et al., 1997c)	Participants after high dose chemotherapy and autologous peripheral blood stem cell transplantation	CCT Training group (n=16), Control group (n=16) Mixed solid tumours and non-Hodgkin's lymphoma	Performed 'normal daily activities' , did not take part in training group	6 weeks of treadmill walking daily Intensity-to elicit a blood lactate level of 3 mmol/L in capillary blood	-Maximal performance (Treadmill test) -Haemoglobin levels	-↑ Maximal performance (p<0.05) -↑ Haemoglobin concentration (p<0.05)
(Durak and Lilly, 1998)	Selected on KPS rating, Undergone chemotherapy +/- radiotherapy	Single group pre-post study 25 participants Prostate, leukemia, carcinoma	No control group	Cardiovascular and resistance programme 2/week Intensity-unspecified	-QOL (Modified Rotterdam Quality of Life Survey) -Endurance capacity, 4-6 RM strength test	-↑45% in whole body strength -↑41.4% increase in MET level

Abbreviations CCT: Controlled clinical trial, HDC: High dose chemotherapy, PBST: Peripheral blood stem-cell transplantationm, APMHR: age predicted maximum heart rate, MHR: Maximum heart rate, EE: Energy expenditure , FFM: Fat-free mass, HRR: Heart rate reserve, KPS Karnofsky performance status score,

A further study examined the effect of low (25-35% heart rate reserve(HRR)) intensity exercise compared to moderate intensity (40-50% HRR) and to a control group matched by aerobic capacity and quality of life (Burnham and Wilcock, 2002). This was the first study to compare different intensity levels to a control group. The intervention was carried out three times a week for 10 weeks. Participants were at least 2 months (mean (SD) time after cancer treatment - control group: 9.0 ± 5.3 months, low intensity group: 10.3 ± 5.1 months, moderate intensity group: 9.8 ± 4.2 months) after cancer treatment - which included surgery, radiation or chemotherapy. No details were given about the 'no exercise' control group, whether this was usual care, or whether it included some face-to-face time. Peak VO_2 to volitional exhaustion was the primary outcome measure. Quality of life was estimated using the Quality of life Index for Cancer patients (Padilla et al., 1983), and fatigue was measured using the Linear Analog Self-Assessment (LASA) Scale (Sutherland et al., 1988). A high attendance rate of 95% was reported. The mean (±SD) post-treatment aerobic capacity was 33.0 (±12.6) for the low intensity group and 34.3 (±9.7) for the moderate intensity group. As there was no difference in aerobic capacity between the low and moderate groups, these groups were combined for further analysis. It is not clear whether this study was powered sufficiently for these groups to be collapsed for statistical analysis. Baseline differences existed on some variables, most notably with regard to weight and QOL score, however it is not known whether these would have influenced results. This study was not randomised - subjects were matched by aerobic capacity and scores on a QOL questionnaire. There was also a significant improvement in QOL ($P<0.001$) in the exercise group compared to the control group.

The feasibility and acceptability of a group-based exercise intervention in the rehabilitation of patients after cancer was explored by Stevinson and Fox (2006). Subject numbers were small with a convenience sample of 12 participants. This programme included participants diagnosed with 'any type of cancer' including patients with metastatic disease. There was a drop-out rate of 25% (n=3) due to disease progression, with the result that only 9 participants completed the programme. The intervention consisted of a progressive aerobic warm-up, and ended

with a cool-down. The main part of the programme consisted of light-to-moderate intensity, aerobic and resistance exercises (step-ups, stationary cycling, forward lunges, star jumps, upright rows, bicep curls, abdominal crunches, ball squats and wall press-ups) in a circuit format. Exertion level was monitored using the CR-10 scale of perceived exertion (Borg, 1982). The exercise sessions were supplemented by a home programme which aimed to build up to 30 minutes of PA on at least four days of the week. An exercise diary was supplied to patients and a pedometer was provided as an additional motivational tool. This was very much an exploratory study investigating the feasibility and acceptability of a group based exercise programme, with much detail included on the perceptions of participants regarding aspects of the programme. This study indicated the feasibility of the group setting, that it was enjoyable, and no adverse effects were reported. A number of participants reported improvement in their physical conditioning but this was not tested scientifically. Only descriptive statistics were included and no empirical evidence on the physical or physiological effect of this intervention was gleaned.

The effect of an exercise intervention was also investigated by Durak et al. (1998) in a single-group pre-post study with 20 participants. The exercise programme was carried out twice-weekly over a 10-week period and consisted of cardiovascular training at participants' own level of perceived exertion. Resistance machines were used-although the intensity was not specified. The programme also consisted of flexibility exercises. Reported results were an average increase of 43% for upper and lower body strength, and a 41.4% increase in MET level from the first to the last session of the exercise programme.

Taken together, these studies suggest that positive physiological changes can result from exercise intervention trials in the post-treatment setting; such as improvements in aerobic capacity (Hayes et al., 2004, Burnham and Wilcock, 2002, Dimeo et al., 1997a, Durak and Lilly, 1998), muscular strength (Durak and Lilly, 1998, Hayes et al., 2004), flexibility (Burnham and Wilcock, 2002), body composition (Burnham and

Wilcock, 2002) and haemoglobin concentration (Dimeo et al., 1997a). However, it must be acknowledged that there were no effects on the majority of outcomes. Also, a number of caveats must be considered in the interpretation of these studies due to variability in methodological quality, outcomes, exercise regimens and statistical methods.

Most studies were weak methodologically. Only one study was an RCT (Burnham and Wilcock, 2002). Another study utilised a randomised design initially, but due to difficulties with recruitment then began to allocate participants by matching baseline characteristics (Hayes et al., 2004). The study by Dimeo et al. (1997a) allocated participants based on proximity to the study site, and the study by Burnham and Wilcox (2002) matched participants by aerobic capacity and QOL, while other studies were single group pre/post studies (Stevinson and Fox, 2006, Durak and Lilly, 1998).

None of these studies based eligibility criteria on the primary outcome measure. Indeed, it has been stated that the lack of consensus (Speck et al., 2010, Mc Neely et al., 2006) for physical activity interventions in cancer may be due to not selecting participants on "a needs-based approach", which may have lead to underestimation of the specific variable being measured, limiting the ability to detect any intervention effects.

Collectively, the trials apply different methodology with regard to content, frequency, intensity and duration of the exercise regime. Aerobic exercise regimes were carried out by Stevinson et al. (2006), Hayes et al. (2003), Burnham and Wilcox (2002) and Dimeo et al. (1997a) with differing exercise intensity levels. Aerobic and resistance regimes were carried out by Hayes et al. (2003). Compliance and adherence levels as well as adverse effects were not routinely reported and difficulties with recruitment were reported in two studies (Stevinson et al. 2006, Hayes et al. 2004). A sample size calculation was reported in only one study (Hayes et al., 2004), based on both aerobic capacity and muscular strength, but was lacking details on the difference to be

detected. No power analysis was carried out in any of the other studies described, and lack of power may have precluded the ability to detect results meaning large effect sizes would be needed to generate results. No study analysed data on an intention-to-treat basis and all assessed multiple outcomes which raises the possibility of false negative findings.

1.5.2 Summary to date

Even though this is a relatively new field of research, evidence from systematic reviews and meta-analyses attests to the benefits of exercise interventions in cancer populations. A recently published roundtable consensus document (Schmitz et al., 2010) provided some much needed guidance in terms of exercise prescription, however, the optimal intervention model and exact dose-response relationships are not fully known.

Research in this area has been directed towards intervention studies predominantly in breast cancer patients, and most have taken place during treatment or many years into survivorship. Many interventions are lengthy and would not be easily transferable into the clinical environment. The time soon after completion of treatment seems to be the most opportune for an intervention and there is a need to carry out methodologically robust randomised trials to assess the effect of interventions during this time period.

Chapter 2

This chapter will firstly outline the types of study design employed in this thesis; which consist of a cross-sectional study, a longitudinal study and a randomised controlled trial. The main outcome measures utilised throughout this thesis will also be described, these include; physical activity (PA), fitness, fatigue, and body mass index (BMI). A concise background to each outcome measure and the choice of its measurement tool as well as a description of its psychometric properties are detailed.

2.1 Study design

Clinical study designs within the medical sphere are generally categorised into observational or experimental studies. An observational study have been defined as 'a study in which no intervention is made (in contrast with an experimental study) which provide estimates and examines associations of events in their natural settings without recourse to experimental intervention' (Mann, 2003). Observational studies were carried out for Studies I and II. The main aim of Study I was to examine the relationship between ECOG PS and PA levels, and the aim of Study II was to examine PA levels over time; neither of which necessitated an experimental study. Contrastingly, an experimental study was carried out for Study III as a treatment effect was being investigated.

Study I was a cross-sectional study. This study design is normally utilised to determine prevalence of a particular condition or risk factor for example. Cross sectional studies are also used to study associations which were congruent with the aims of Study I which were to examine the relationship between ECOG PS and PA. In this type of study design, participants are assessed at one point in time only. Advantages of this type of study design include the relatively short time period required and the fact that multiple outcomes can be obtained. A disadvantage is that cross sectional studies do not provide explanations for the outcomes obtained (Mann, 2003).

Study II was a longitudinal cohort study. Longitudinal studies are a type of observational study which assesses trends over time. A cohort study is a subset of a longitudinal study as it observes the effect on a specific group of people over time. As Study II aimed to explore PA levels at three different time-points, this study design was deemed suitable. An advantage of this type of study design is that changes can be tracked over time and as the same participants are followed. Disadvantages are that these studies are relatively expensive and time consuming. Also, as this type of study design is observational, it limits the ability to assign causal relationships.

Study III was a randomised clinical trial (RCT). RCTs are performed to resolve uncertainty concerning the relative efficacy of interventions under comparison. As Study III investigated the effect of an exercise intervention compared to a control group, this study design was considered most appropriate. In RCTs, participants are randomly allocated to either one intervention or another, usually including a control group (Mann, 2003). Both groups are followed up for a specified period and analysed in terms of pre-defined outcomes. The randomisation process pre-supposes that all variables other than the proposed intervention are evenly distributed between the groups, which minimises bias. As the groups are presumed to be indistinguishable apart from the intervention, any differences in outcome are presumed to be attributable to the intervention.

Central to the execution of RCTs is the concept of 'equipoise' — which is a state of collective uncertainty which exists when "there is no consensus within the expert clinical community about the comparative merits of the alternatives to be tested'' (Freedman, 1987). Thus, neither the study personnel, nor participants should feel they are being administered with an inferior therapeutic regimen. The scientific rigor of RCTs has been enhanced by the CONSORT (Consolidated Standards of Reporting Trials) statement which was devised by a group of scientists and editors to improve the quality of reporting of RCTs. It was first published in 1996 and updated in 2001 and 2010 and consists of a checklist and flow diagram that authors can use for reporting an RCT.

Advantages of RCTs are the thorough evaluation of a single variable in a clearly defined patient group, and the minimisation of bias by comparing two otherwise identical groups. The outcome of RCTs are considered a strong source of evidence regarding the regimen of interest and results are used as tools to guide clinicians in making decisions about optimal medical care (Miller and Joffe, 2011). Disadvantages of RCTs are that they are expensive and time consuming (Greenhalgh, 1997). A well-designed, methodologically sound and adequately powered RCT is considered the best form of evidence.

2.2 Outcome measures used in this thesis

2.2.1 Reliability and validity of measures

A number of outcome measures were used in this study, as listed above. Key outcome measures were PA, and fitness. Other outcome measures also used were fatigue, QOL, and anthropometric measures. In the consideration of the most suitable measure to use, a number of factors were taken into account. These included the validity and reliability of the measure, issues of feasibility and clinical utility within the cancer context.

The validity of an instrument refers to the 'extent to which it measures what it is supposed to measure' (Berger and Patchner, 1988). Validity, as a more subtle construct is generally considered to be more difficult to quantify than reliability, which is more concerned with measuring technicalities (French, 1993). There are many aspects of validity to consider. Face validity refers to the credibility of a test, whether it appears or 'looks' like it measures what it professes to measure (French, 1993). Content validity refers to whether a test covers a representative sample of items-that is, it should express all aspects of a multi-faceted concept. Content validity refers to the degree to which the content of a test matches all domains associated with the construct. Criterion validity refers to whether the test correlates with other 'criterion measures' which are considered to be representative of the same measure. If test data

and criterion data are collected at the same time, this is referred to as concurrent validity. If the test data is collected first to predict criterion data collected at a later time point, this is referred to as predictive validity. Construct validity refers to whether a test measures the underlying theoretical constructs. Construct validity refers to the degree to which a measure quantifies a theoretical concept it is purported to measure, and involves testing of the internal structure of the measure. Convergent validity refers to the degree to which a measure is correlated with other measures of the same domain which they are predicted to correlate with (Hicks, 2004, French, 1993).

Reliability refers to the consistency or repeatability of a measure (Bruton et al., 2000) and is generally considered as the reliability between two or more testers or devices (inter-tester reliability or inter-instrument reliability), or repeated twice by the same tester or repeated twice by the same device (intra-tester reliability, intra-tester reliability or test-retest reliability). Both must be tested under the same conditions within a specific time period (Renemana and Helmus, 2010). These relationships are frequently measured using correlations which assess the strength of the straight line association between two continuous variables. Values generated are between 0 and 1. A positive correlation indicates that as one value increases, the other value also increases. A negative correlation indicates that as one value increases, the other decreases. A value of 1 indicates a perfect correlation, and values of 0.75 and higher are generally considered 'good' reliability, values from 0.50 to 0.74 as moderate reliability, and values under 0.50 as poor reliability (Portney and Watkins, 2000). A disadvantage of the correlation coefficient is that systematic errors are not detected in the case where two sets of scores are highly correlated, but not highly repeatable. Thus, correlation only explains how two sets of scores vary together, not the extent of agreement between them.

2.2.2 The Measurement of Physical Activity (PA)

2.2.2.1 Introduction to measurement of PA

PA has found to be associated with the occurrence and recurrence of several cancers as outlined in 1.3.2 (page 29). Thus, measurement of this construct requires careful consideration. PA is defined as any "bodily movement produced by skeletal muscles which results in energy expenditure"(Caspersen et al., 1985). Resting metabolic rate accounts for 60 – 75% of total bodily energy expenditure, while 10% of energy expenditure is due to the thermic effect of feeding. The balance of 15-30% is the most variable component and is related to posture, spontaneous and voluntary PA. This component also determines whether an individual is 'sedentary' or 'active' and is measured for the purposes of estimating PA levels. Indeed, PA is difficult to accurately measure as it incorporates frequency, time, type and duration, and as behaviour is not stable and is prone to daily, weekly and seasonal variation. The most commonly used methods of assessing PA include self report, direct observation, objective monitoring (eg accelerometers or pedometers) and indirect measures such as doubly labelled water (for explanations of these-see overleaf). No standard method of assessing PA exists in 'healthy' adult populations or in the oncology literature (Rogers, 2010).

PA measurement has been incorporated into epidemiological research in order to ascertain cause-and-effect relationships between certain health behaviours such as low PA levels and disease states. Large population-based studies outlined in Section 1.3.2 (page 29) have provided strong evidence that adequate PA levels can decrease the occurrence and recurrence of certain cancers such as colo-rectal, endometrial, ovarian and prostate (Lynch, 2010) as well as providing cardiovascular benefits as outlined in Section 1.3.3 (page 32). For the most part, self-report measures have generally been used in this setting by necessity. However, these measures lack specificity and can be prone to error (Bassett et al., 2008). Accelerometers increase the precision of measurement and have been used in a small number of large, surveillance studies (Troiano et al., 2008, Tucker et al., 2011), however issues with cost and feasibility preclude their widespread usage within this area.

In order to pursue the next generation of research questions which follow from epidemiological findings - such as dose-response relationships, the optimal method of increasing PA and the effect of interventions - more precise measurement tools such as pedometers and accelerometers are required (Colbert and Schoeller, 2011). Within the cancer context, an important consideration for those with a significant disease burden, extreme fatigue, receiving palliative care, or those undergoing intensive treatment would be measurement tools sensitive enough to discriminate between sedentary and very low levels of activity. However, a limitation of the cancer and exercise literature is that the vast majority of trials have utilised self-report measures of PA.

2.2.2.2 Objective Physical Activity Measures

"Gold standard'' methods of measuring PA are doubly labelled water and indirect calorimetry. Doubly labelled water measures the energy expended or metabolic rate as a result of PA (Schoeller and van Santen, 1982). This method is performed by the administration of doubly labelled water, followed by then measurement of the elimination rates of deuterium (^{2}H) and oxygen (^{18}O) or deuterium oxide-18 ($D_2{}^{18}O$) over time, through sampling of body water concentrations (saliva, urine or blood). Indirect calorimetry estimates energy expenditure by measuring oxygen consumed and carbon dioxide produced in a laboratory environment using either a closed collection system or an open circuit system. These techniques measure the energy cost of PA, but no information is gleaned about the behaviour itself-with regard to the frequency, intensity, duration, pattern or type of activity (Colbert and Schoeller, 2011), therefore were not deemed suitable for use within this research. Furthermore, feasibility issues as well the expense associated with these techniques would have been prohibitory.

Heart rate (HR) monitoring is based on the principal of a linear relationship between heart rate and energy expenditure (EE) over a wide range of activity levels (Christensen et al., 1983). As intensity of movement and PA levels increase, HR

increases in direct proportion of energy demands. There are however, a number of potential sources of error associated with this technique, namely the non-linearity of HR during sedentary and light activities which may instead be influenced by factors such as emotional state, nicotine or digestion (Spurr et al., 1988). Other sources of error are the inter-individual variations between HR and EE (Leonard, 2003) and the higher HR associated with upper body exercise or static exercise such as weight-lifting. An additional point to consider is that resting heart rate and heart rate for a given workload are related to the fitness level of the individual, and even after exercise has ceased, heart rate remains elevated. Individual fitness testing needs to be performed prior to using heart rate monitoring so that data obtained can be correctly interpreted.

Direct observation of PA measures the type, duration and frequency of activity in real time. The method also allows contextual and environmental data to be collected. Advances in technology have resulted in several bespoke software packages to collect, handle, analyse and present observational data. However, this method is problematic as the intensity of activity, or energy expenditure cannot be quantified and it relies on subjective classification which is an issue in mid ranges of intensity especially. Direct observation can only measure physical activity in controlled environments such as school break times in paediatric research or occupational activity in work-based place research and is therefore limited to short-term validation studies. As the research studies in this thesis aimed to assess PA in the home environment over a number of days, this measurement method was not deemed practical (Trost, 2007).

A recently published review explored objective monitoring in exercise and cancer trials (Rogers, 2010). Only ten randomised trials reported the use of objective PA measurement tools such as pedometers or accelerometers. Pedometers are small devices worn on the waist which generate a measure of step count (Bassett et al., 2008). In the cancer setting pedometers have been used in six studies (Pinto et al., 2005b, Matthews et al., 2007, Vallance et al., 2007, Irwin et al., 2008a, Mustian et al., 2009, Demark-Wahnefried et al., 2003). These have mostly been used as a motivational tool with a goal to increase step count as immediate feedback is given

(Rogers, 2010). Although pedometers are easy to use and are cost effective, these devices were deemed unsuitable for use in this study as pedometers only measures the volume of movement, and time spent in various intensities of activities (i.e. time spent in domains of sedentary, light, moderate and vigorous intensity activities) could not be measured.

Accelerometers are small devices which determine the amount of PA registered from acceleration of the limbs and trunk, generating a measure of free-living (real-life) activity. Data generated can estimate energy expenditure and of greater importance within this piece of work - time spent in various intensity categories can be obtained by translating accelerometer counts into PA measurements of light, moderate and vigorous domains of activity using established cut-off points. Accelerometers are generally placed on a belt or as close as possible to the body's centre of mass. The majority of accelerometers can store data at 1-minute epochs for up to several weeks.

There are many commercially available accelerometers and a review of accelerometers used in field-based research found that no one accelerometer was more valid or reliable than another (Trost et al., 2005). Considerations for accelerometer choice in this study included participant burden, memory capacity of the monitor, supply costs, and amount of data manipulation needed (Murphy, 2009). Another important aspect of accelerometer choice was whether very low levels of activity could be discriminated from sedentary behaviour, which was particularly important for Study I. Also decreasing sedentary time and increasing time spent in light and moderate domains of activity were important therapeutic goals in Study III, so accelerometer sensitivity to low levels of activity was important.

Despite the benefit of these devices, it is important to be cognisant of a number of disadvantages which pertain to these devices. Firstly, there is uncertainty over the appropriate interpretation of accelerometer counts (Matthews, 2005). Energy expenditure can be estimated, although linear regression models to predict Metabolic Equivalents (METs) associated with activities can be inaccurate, especially at high

levels of expenditure (Johannsen et al., 2010). This was not considered relevant to this piece of work as energy expenditure was not measured. Accelerometers are also unable to measure activities such as swimming, cycling and activities involving the use of upper extremities (Prince et al., 2008, Kozey et al., 2010) and the underestimation of certain activities such as walking while carrying a load or walking uphill (Welk, 2002) can be problematic. However, an accompanying activity diary would reveal if such activities occurred. Furthermore, the available literature would suggest that patients with cancer and cancer survivors are sedentary as outlined in Section 1.4 (Page 33), thus, may be less likely to carry out activities such as swimming or cycling. Other disadvantages are the financial cost of monitors, time taken to process and analyse data (Dale et al., 2002) and variability in terms of technical reliability (Esliger and Tremblay, 2006). Differentiating between non-wear time and true sedentary activity can be challenging and while a wearer log can be useful, this may not always be reliable.

Accelerometers are a relatively new PA measurement method used within the cancer context. The review by Rodgers et al. (2010) identified only 5 studies within the exercise and cancer literature which incorporated accelerometer technology. The Caltrac (Muscle Dynamics, Torrance, CA, US) was used in one trial (Pinto et al., 2005b), the RT3 (Stayhealthy, Inc., Monrovia, CA, USA) (Sloane et al., 2009), the MTI Actigraph (Actigraph, Pensacola, FL, USA), Actical (Mini-Mitter) (Matthews et al., 2007, Rogers et al., 2009a), triaxial accelerometer[12] (Newtest Oy, Oulu, Finland) (Nikander et al., 2007) and ActivPAL™ (PAL Technologies Ltd, Glasgow, UK (Maddocks et al., 2009). All of these studies assessed the outcome of a PA intervention, with the exception of the study by Maddocks et al. (2009) which investigated the effects of a neuromuscular electrical stimulation of the quadriceps muscle in an experimental and control group. A further longitudinal study on breast cancer survivors also incorporated accelerometer measurement (Actigraph accelerometer) (Lynch et al., 2010). As well as the various accelerometer models used within this research area, accelerometer outcomes varied and included; calorific expenditure (Pinto et al., 2005b, Demark-

[12] The name of this monitor was not specified, was simply termed 'triaxial accelerometer'

Wahnefried et al., 2008), PA minutes (Demark-Wahnefried et al., 2008, Rogers et al., 2009a) and PA counts (Matthews et al., 2007, Rogers et al., 2009a).

In terms of accelerometer choice for the studies in this thesis, a number of monitors were considered. The main accelerometers considered for this study were the Actigraph, the Actical, the ActivPAL and the RT3 accelerometer.

The Actigraph has been commercially available since the mid-1990s and has been validated extensively in laboratory and free-living settings to estimate energy expenditure and compared to other monitors (Welk et al., 2004, Esliger and Tremblay, 2006, Le Masurier and Tudor-Locke, 2003). There are both uni-axial (GT1M model) and tri-axial (the GT3X model) models. These devices generate activity counts per minute, discriminate well between different walking speeds in the range of 2-5 miles per hour, and display good inter-instrument reliability (Esliger and Tremblay, 2006). However these devices are reported to discriminate poorly with speeds above this value which can result in underestimation of time spent in moderate activity (Strath et al., 2003, Rowlands et al., 2007).

The Actical has also been shown to be a valid measure of PA (Heil, 2006, Esliger et al., 2007, Esliger and Tremblay, 2006, Paul et al., 2007). Good intra-instrument and inter-instrument reliability was found in a study using a mechanical shaker table (Esliger and Tremblay, 2006). Conversely, another study reported that the Actical had the lowest inter-instrument reliability out of four accelerometers tested (ActiGraph, Biotrainer Pro, Tritrac-R3D[13], Actical) (Welk et al., 2004). This is an omni-directional monitor-meaning that it records in multiple directions, but is most sensitive to vertical plane movement.

The validity and reliability of the RT3 accelerometer has been tested in laboratory-based settings which examined walking and running at standardised speeds on a treadmill (Hussey et al., 2009, Rowlands et al., 2004, Powell and Rowlands, 2004,

[13] The Tritrac R3D preceded the RT3 accelerometer

Rowlands et al., 2007, Stone et al., 2007, Chu et al., 2007, King et al., 2004), using a shaker table (Krasnoff et al., 2008, Powell et al., 2003), assessing various mobility tasks (Hale et al., 2007, Powell and Rowlands, 2004), and performing structured activities (Rothney et al., 2008). Populations tested have included healthy adults (Powell and Rowlands, 2004, Rowlands et al., 2004, King et al., 2004), children (Rowlands et al., 2004, Chu et al., 2007, Hussey et al., 2009) and neurological populations (Hale et al., 2008). Overall, results have mostly shown good levels of validity and good intra-monitor reliability, but lower levels of inter-monitor reliability. The utility efficacy i.e. overall usefulness and acceptability of the RT3 was explored in a sample of 21 subjects by Perry et al. (2010). Results indicated that most participants found the RT3 acceptable to wear, and total data loss was relatively low at 6.7%-due to participant factors and technical factors in equal measures.

The ActivPAL also displays high levels of reliability and validity (Ryan et al., 2006, Grant et al., 2006). Unlike other monitors, the ActivPAL is placed on the mid-line of the thigh, about a third of the way down between the hip to the knee, and self-adhesive 'PALstickies' secure the device to the thigh. The addition of additional dressings (e.g. 3M Tegaderm dressings) renders the device waterproof. The ActivPAL is a uniaxial accelerometer which generates energy expenditure, step count and time spent in three measures only; walking, quiet standing and sitting and lying.

The evidence is suggestive that the RT3 performs similarly to the ActiGraph and Actical (Bassett and Dinesh, 2010) and has become accepted as a PA measure in clinical studies (Bassett and Dinesh, 2010). To help decide which monitor would be suitable to use within the studies in this thesis, a small feasibility study was carried out on the first 10 patients of Study I using both the ActivPAL accelerometer and RT3 accelerometers. This resulted in the RT3 being chosen for the rest of the studies for a number of reasons; firstly, feedback from participants indicated that the ActivPAL was deemed to be burdensome as it could not be removed at night-time or during showering. As well, more data manipulation options were available with the RT3 as raw activity counts

were generated. Furthermore, the ActivPAL device could not be easily posted as monitoring begins as soon as the device is removed from the docking station.

Thus, the RT3 was chosen for use in this study based on practicality and clinical utility. (Technical details of the RT3 and a figure showing this instrument will follow later in this chapter). Trouble-shooting as well as technical support for the RT3 was available within the study research centre due a pool of other users. However, some limitations pertain to the RT3, as with all accelerometers, which are detailed below along with information pertaining to the psychometric properties of this monitor.

A number of studies investigating reliability and validity of the RT3 have been carried out in paediatric populations (Vanhelst et al., 2010, Hussey et al., 2009, Chu et al., 2007), as differences pertain to activity counts in adult and paediatric populations (Rowlands et al., 2004), validity and reliability studies carried out in the adult population will only be discussed.

Concurrent validity of the RT3 was explored in a study by Rowlands et al. (2004) by comparing RT3 output to oxygen consumption. This was carried out in a population of boys and men (n=34). Results separated out for the adult cohort (n=15), revealed that RT3 counts correlated significantly with oxygen consumption ($r=0.85$, $p < 0.01$) at various treadmill speeds.

Most validation studies of the RT3 have been performed in laboratory settings and the question of the difference between walking on a treadmill and normal gait arises.
The difference in vector magnitude counts, measured by the RT3 between treadmill walking and normal gait was investigated in 25 healthy volunteers by Hendrick et al. (2010). No significant difference was found between the RT3 accelerometer vector magnitude counts generated from level ground walking at the participant's normal and brisk walking speeds and walking on the treadmill at the same preset speeds, implying that this device operates similarly in these two conditions. Similarly, another study compared treadmill speeds to vector magnitude counts generated. Nine male

runners each wore two RT3s across a number of different walking and running speeds. Again, results showed that the RT3 was strongly related to all speeds ($r>0.96$, $p<0.001$) (Rowlands et al., 2007).

Intra-monitor and inter-monitor reliability were also investigated by testing 8 RT3s in two repeated trials which consisted of walking, running, and sit-stand (low activity counts) in a single subject. Results showed no difference between the RT3s at rest, at 4km/hour, and sit-stand between monitors and between trials. However, as intensity increased to 6-10 km/hour, the inter-monitor difference increased 21-82%. It would appear that at intense levels of activity eg running, inter-monitor variability increased. Only at rest and during sit-stand there was consistently no variation between the RT3s due to low activity counts (Powell and Rowlands, 2004). The reliability of 8 RT3s was also examined by Powell et al. (2004). This was investigated in 2 repeated trials of 6 activities. Again, it was found that the RT3 produced stable data and that there were no significant inter-monitor differences for lower levels of activity, but there was variability at higher intensity activities.

In a further study examining the inter-instrument reliability of the RT3, six healthy, adult participants wore six RT3s each simultaneously placed on a waist belt. Participants carried out three standardized activities each for five minutes; walking on a treadmill at 3.0 km/h and 5.0 km/h as well as sitting on a chair. Average levels of reliability reported were good (ICC=0.78, 95% CI: 0.46–0.97). Of note, the lower limit of the confidence interval was poor at 0.46. When data from a 'rogue' RT3 was removed, the lower limit of reliability was reported to be 0.50, indicating moderate reliability (Renemana and Helmus, 2010).

Intra-instrument reliability of the RT3 was explored in a mixed neurological and healthy population (Parkinsons disease n=7, multiple sclerosis n=11, stroke n=20, controls n=9), and was reported to be good for data collected over a 7 day period (ICC=0.85, 95% CI: 0.71 – 0.91, $p < 0.001$). Values were also reported to be similar when tested over a 3 day period (ICC=0.84, 95% CI=0.7-0.91, $p<0.001$). The standard

error of measurement indicated that repeated testing could differ from baseline by ± 23%, which was deemed to be reflective of normal variation in weekly PA (Hale et al., 2008).

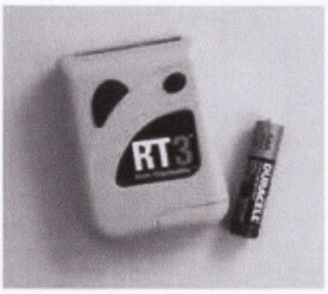
Thus, a number of studies indicate that reliability appears to vary depending on the frequency of movement. The inter-instrument and intra-instrument reliability of the RT3 was also examined by Powell et al. (2003) using a simulated motorised vibration table and 23 RT3s were tested on a motorised vibration table at frequencies of 2.1, 5.1 and 10.2 Hz. At the lowest frequency (2.1 Hz), there was no difference in counts between axes. However, as frequency increased, inter-instrument and intra-instrument coefficient of variance (CV) decreased, indicating that the largest variability was noted at the lower frequencies-thus the degree of differentiation decreased at higher intensities. This implies that the RT3 is a more sensitive measure for sedentary populations-of use within the cancer context. Of note, the inter-instrument ICC between the RT3s was 0.99 regardless of the axes. Consistent with these findings, other studies incorporating RT3 devices have shown higher levels of variability when testing across a lower range of frequencies (1.5-2.5Hz) (Powell and Rowlands, 2004, Esliger and Tremblay, 2006). Krasnoff et al. (2008) demonstrated good intra-device reliability but poor inter-instrument reliability for the RT3 using 22 accelerometers on a vibration table shaking at different speeds. Again, as intensity increased, the degree of differentiation decreased - greater levels of reliability were shown in more sedentary populations (Hale et al., 2008, Rowlands et al., 2004). The sensitivity of the RT3 was investigated in a recently published study, carried out in 30 subjects > 65 years, and 5 younger volunteers. Results demonstrated the ability of the RT3 accelerometer to discriminate between sedentary tasks and walking (Sumukadas et al., 2008). The work in this area to-date would indicate that the RT3 is a more sensitive measure for sedentary populations and for this reason may be particularly appropriate for using within the cancer context.

Inter-instrument reliability of the pool of RT3s used for the studies outlined in this thesis was evaluated as part of a departmental audit and acceptable inter-instrument reliability was found.

2.2.2.2.1 Technical Aspects and set-up of the RT3 accelerometer

The RT3 is a small, waistband mounted device about the size of a pager (dimensions 7·1 X 5·6 X 2·8 cm, weight 65·2g including AAA battery) (Fig. 2.1). It consists of a piezoelectric element and a seismic mass (Vanhelst et al., 2010). When the subject moves, the sensor registers acceleration or deceleration periodically, the seismic mass results in deformation of the piezoelectric element which then generates a voltage signal proportional to the acceleration applied. The accelerometer is sensitive to movement in three axes: vertical (x), anteroposterior (y), and mediolateral (z). The voltage signal is converted to a series of numbers called "activity counts" which was set as accumulated vector magnitude ($[X^2+Y^2+Z^2]^{0.5}$) activity over a one-minute epoch (Mode 4) and can store data for up to 21 days. The RT3 has a dynamic range of 0.5 - 19.6m.s^{-2}, and a frequency range of 2.0 - 10.0 Hz. Participants were advised to wear the device on their right hip (Appendix I).

Fig. 2.1 RT3 accelerometer



It has also been suggested that 3 – 5 days of monitoring is sufficient to estimate habitual PA (Trost et al., 2005). Subjects were asked to wear the monitor for 7 days to ensure sufficient data was collected. Data with less than 3 days of valid monitoring was not considered for further analysis as 3 days is considered the minimum number

of days to assess PA in daily life (Pitta et al., 2005). Little is known about wearer compliance in cancer patients, however an excellent compliance rate of 98% has been reported (Maddocks et al., 2010).

The RT3 captures time spent in light, moderate and vigorous domains of activity based on accumulated vector-magnitude cut-off points previously described (Rowlands et al., 2004). The sensor in the RT3 accelerometer measures in three directions of movement (X, Y, and Z), reflecting the vertical, antero-posterior, and medio-lateral axis, an averaged vector-magnitude count of the three axes was also generated which was utilised for the purposes of this research. A docking station (Fig. 2.2) is connected via a USB port to download data from the monitors (Trost et al., 2005).

A new battery was used each time to minimise data loss due to battery fault. An activity diary (Appendix I) was completed to "cross-reference" the activity output (Buchheit et al., 2007), to calculate 'non-wear time' and as a prompt for the participant to remember to wear the monitor (Perry et al., 2010). The raw data (counts/minute) of the RT3 accelerometers were read with the software provided by the manufacturer. The period interval for the accelerometer was set at 1 min, and output was expressed as mean counts of vector magnitude per minute. Cut-off points for the activity domains of sedentary, light, moderate and vigorous intensities were based on previously defined values (Rowlands et al., 2004, Healy et al., 2007b). Time spent in domains of activity was determined by summing minutes in a day where the count met the criterion for that activity, as outlined in Appendix I. To assess compliance with American College of Sports Medicine (ACSM) PA guidelines (150 minutes per week of moderate and physical activity, over 5 days of the week, and no less than 10 minutes in each bout (Haskell et al., 2007)) in Studies II and III, the Macros function of Microsoft Excel was used to develop a code (Appendix I). The VM data was copied and pasted into a new file, and the file was run to extract 10 minute blocks of moderate and vigorous activity.

Fig. 2.2 RT3 accelerometer in docking station

Hours of RT3 wear time were calculated by subtracting the hours of non-wear time from 24 hours (Troiano et al., 2008, Matthews et al., 2008). Hours of RT3 wear time were compared to the number of hours recorded as 'awake' in the activity diary Appendix I). Periods of RT3 non-wear were cross-referenced to the activity diary. Participants were asked to detail any reasons for taking off the monitor such as for showering, or forgetting the monitor. Hours of sleep were taken away from the total.

2.2.2.3 Subjective measures of assessing PA

2.2.2.3.1 Introduction to subjective measurement of PA

Subjective measures of PA include questionnaires, diaries/logs, and interviews. These are the most commonly used methods of assessing PA at the population level in epidemiological studies (Kriska and Caspersen, 1997) and are almost exclusively used in oncology settings due to their low cost, ease of administration, practicality and general acceptance.

Until as recently as the mid 1990s, the main focus of PA surveys was on leisure time PA, as this type of activity was thought to be most related to energy expenditure. Since this time, the contribution of work and transport domains to total energy expenditure has changed the focus from leisure time activity to an estimation of total activity (Brown et al., 2004b).

Self-report questionnaires generally assess the prevalence of PA subjectively over the domains of frequency, intensity, duration and type. The frequency of an activity can be measured "in a usual week", or "in the past week/month/year" or even over ones' life-time. Many questionnaires ask about the total time accumulated in three areas: walking, moderate-intensity PA, vigorous intensity PA and a number of questionnaires incorporate specific questions on occupational activity. The intensity of activity may be based on self-estimated activity levels or on metabolic equivalent (MET) levels for specific activities (Ainsworth et al., 2000).

Self-report questionnaires have been found to be reliable over time (Brown et al., 2004b), and are reported to be reasonably accurate in recalling vigorous activity (Craig et al., 2003) which is usually a premeditated and 'remembered' specific activity bout (eg exercise class, brisk walking, running). 'Highly stable' activities like sleep (Jacobs et al., 1993) are also generally well recalled. However, habitual, non-planned episodes of low-moderate intensity activities such as walking throughout the day, and day-to-day house work are difficult to recall and can be a key determinant of variability in total daily energy expenditure (Donahoo et al., 2004, Craig et al., 2003). There are other well-known limitations of these measures including recall bias and under or more commonly over-estimation of activity (Sallis and Saelens, 2000b, Bauman and Merom, 2002). Self-report methods are also prone to other sources of bias such as social desirability factors, poor memory and the inability to capture the absolute level of PA (Prince et al., 2008). Thus, questionnaire-estimates of PA have been called into question in terms of accuracy and reliability (Prince et al., 2008).

Despite these limitations, self-report PA questionnaires are widely used due to their convenience and practicality and many self-report measures have been developed. A recently published review of PA questionnaires for adults included 85 questionnaires and concluded that no one questionnaire was superior to others (Van Poppel et al., 2010). No cancer-specific self report PA measure exists, and a wide variety of

questionnaires are used as outlined in Section 1.4 (page 33) as there appears to be no consensus on a specific self-report measure to use within this area.

The self-report questionnaire chosen for Study I and II was the International PA Questionnaire, and one reason for its choice was to enable comparison with other studies due to its widespread use. Also, the IPAQ assessed occupational, household and transport-related activities which were deemed important domains to consider as leisure time PA was expected to be low. A number of other questionnaires were included in Study III, and to minimise participant burden, a more concise measure of PA, the Godin Leisure Time Index was selected.

2.2.2.3.2 The International PA Questionnaire (IPAQ)

The IPAQ (long version) (Appendix II) was used to assess habitual PA participation over a recall period of the previous 7 days. This questionnaire was developed between 1997 and 1998 by an International Consensus Group as an instrument to enhance comparison of PA levels across countries (Craig et al., 2003). The long version of the IPAQ utilised in this study is recommended for research purposes or studies requiring more detail on the separate domains or dimensions of PA (Craig et al., 2003). The long-form has been shown to have acceptable validity for assessing different domains of PA, PA intensities and total PA in healthy adults (Hagstromer et al., 2006). The long version of the IPAQ takes approximately ten minutes to complete.

The scoring of the IPAQ was completed according to guidelines (Appendix II). Data from this 31-item questionnaire were recorded in a categorical score, classified as "low", "moderate" or "high" PA across the following domains; leisure time PA, domestic and gardening activities, work-related PA, transport-related PA. Walking time was also included for the work, transport and leisure domains. Total time spent sitting per day as an indicator of sedentary behaviour was also estimated by each patient.

Total time spent in PA (MET-minutes) during the previous 7 days was calculated using the following formula as per the IPAQ scoring protocol (Appendix II);
[Number of days the activity was carried out * amount of time spent in each activity (minutes)] * MET intensity.

Acceptable validity and reliability of the IPAQ across 12 countries has been reported (Craig et al., 2003). Criterion validity was assessed against an accelerometer (Manufacturing Technologies Inc. (MTI) Actigraph), and a median correlation of 0.33 (Spearman's rho) for the long form was reported (Craig et al., 2003), which was deemed acceptable and was comparable to results from previous self-reported PA validation studies using objective instruments such as accelerometers (Sallis and Saelens, 2000a). A further study examining construct validity compared the IPAQ to an accelerometer and a pedometer with reasonable associations reported (r=0.23) and (r=0.25) respectively) (Dinger et al., 2006). The construct validity of the IPAQ was also tested in a population of 108 males by comparing the IPAQ to an accelerometer (total r=0.26), the domain of vigorous activity was compared to VO_{2max} with an association of r=0.41 reported. The IPAQ was also compared to doubly labelled water in a population of 16 males and 20 females with an association of 0.33 noted (Hagstromer et al., 2006). A Japanese study compared the IPAQ to doubly-labelled water in a population of 74 males and 76 females. Results may call into question the sensitivity of the IPAQ, as while a significant difference between "insufficiently active" and "highly active" categories was found, non-significant differences between "insufficiently active" and "sufficiently active" or "sufficiently active" and "highly active" groups were reported (Ishikawa-Takata et al., 2008).

The test re-test reliability of the IPAQ was investigated by Dinger et al. (2006) over a 4-6 day period, with a total ICC of 0.86 reported. Test re-test reliability was also investigated by Craig et al. (2003) over a 3-7 day period with ICCs of 0.75 – 0.83 reported across various age-groups.

2.2.2.3.3 Godin Leisure Time Index

The Godin Leisure Time Index (Appendix III) is a short questionnaire, which takes approximately 2 minutes to complete and contains three questions which assess the average frequency and duration of mild, moderate, and strenuous exercise of at least ten minutes duration in a typical week. The activity is then multiplied by the MET-levels associated with these; strenuous (9 METS), moderate (5 METS) and mild exercise (3 METS) generating an arbitrary total score as outlined in Appendix III. This questionnaire assesses the prevalence of sport and recreational activity over a recall period of a typical week.

The Godin Leisure Time Exercise Questionnaire has been shown to be a reliable and valid self-report measure of PA (Godin and Shephard, 1985). The test-retest reliability of this questionnaire was examined over a 2-week time period in 53 healthy adults and the correlation coefficient was reported to be 0.74 (Godin and Shephard, 1985). In a similar experimental set-up, the test-retest reliability was reported to be 0.81 for a sample of 319 male and female students (Sallis et al., 1993), again over a 2-week time period. A further reliability study with 28 males and 50 females reported the correlation coefficients of 0.62 over a 1-month retesting time period (Jacobs et al., 1993).

Moderate associations were also reported between the Godin Leisure Time Index and other PA questionnaires; the NASA/Johnson Space Centre PA Scale and Baecke of 0.54 and 0.61 respectively (Miller et al., 1994). Jacobs et al. (1993) compared the Godin Leisure Time Questionnaire to VO_{2max} in a population of 28 males and 50 females, reporting a correlation coefficient of 0.56 (Jacobs et al., 1993). Jacobs et al. (1993) also compared results from this questionnaire to those from an accelerometer and percentage body fat with reasonable associations reported (r=0.32 and r=-0.43 respectively). The construct validity of this questionnaire was also assessed by Godin et al. (1985) in a sample of 163 males and 143 females by comparing this questionnaire to VO_2 max (total r=0.24, strenuous r=0.38) and percentage body fat (total: r=0.13, strenuous r=0.21). Validation studies examined the relationship

between the total Godin score and the Caltrac accelerometer and reported a moderate association (Spearman's rho = 0.45) (Miller et al., 1994) in a population of 7 males and 26 females.

2.2.2.3.4 Summary to date of PA measurement

Physical activity (PA) is a key outcome measure to be considered within the cancer and exercise literature, although to-date there is no consensus on which PA measure is most suitable for use within this area. Self-report measures are predominantly used, but these measures are prone to inaccuracies, mostly in the direction of overestimation and other factors such as social desirability bias pertain to this measurement method. Furthermore, planned bouts of moderate and vigorous activity are generally remembered, but low level habitual exercise or sedentary behaviour are not accurately recalled. However, to enable comparison with other studies, a well validated measure, the IPAQ questionnaire was chosen for Studies I and II, and a more concise measure, the Godin Leisure Time Questionnaire was chosen for Study III to minimise participant burden, due to the evaluation of a number of other outcome measures. Objective measures are generally considered to be more robust tools for evaluating PA. Indirect calorimetry and the doubly-labelled water technique provide accurate measurements of energy expenditure, but these are costly techniques which are generally not feasible outside of the laboratory environment. Accelerometers are suitable to use in field-based research, and measure sedentary behaviour as well as time in light, moderate and vigorous domains of activity. A number of accelerometers are commercially available but the RT3 accelerometer was deemed most suitable for use within this thesis. This monitor is commonly used in research settings, has good clinical utility and has been validated across a number of populations.

2.2.3 The measurement of cardio-respiratory fitness

2.2.3.1 Introduction to the measurement of cardio-respiratory fitness

Cardio-respiratory fitness is influenced by variables such as age, sex, exercise habits, heredity and cardiovascular status (Fletcher et al., 2001) and may decline in many patients with cancer due to de-conditioning as well as the effects of treatment on the cardiovascular, respiratory and musculoskeletal systems (Schmitz et al., 2005, Hayes et al., 2004). The causes are thought to be related to toxic loco-regional and systemic treatments which adversely affect a number of steps of the O_2 transport system (ie pulmonary diffusion capacity, cardiovascular O_2 delivery and oxidative phosphorylation) (Jones et al., 2007b) as detailed in Section 1.1.2 (page 2).

In a heterogeneous series of patients with cancer and cancer survivors (n=17) - from diagnosis to palliation, it was reported that VO_2 peak[14] was consistently 30% below that of age and gender matched sedentary non-cancer controls (Haykowsky et al., 2009). Similarly, a study including 543 cancer survivors, reported that most participants scored within the 'poor' fitness classification when compared to normative age and gender matched values (Repka et al., 2010), measured using the Bruce treadmill protocol. The authors stated that the low VO_2 peak levels were due to low fitness levels and may have also been due to too large speed and grade increments in the testing protocol, leading to an underestimation of VO_2 peak. The physical performance of 70% of patients with solid tumours and haematological cancers was also classified as 'poor' (50-54% of reference VO_2 max) or 'very poor' (< 50% of reference VO_2 max) (Dimeo et al., 1997b) in mixed population of 78 cancer survivors. All patients were 'on treatment' and were being considered for high-dose chemotherapy with peripheral autologous blood stem cell transplantation, so VO_2 max values may be expected to be especially low in this cohort. Similarly, a decreased

[14] VO_2 peak refers to when a plateau in oxygen consumption is observed, while workload continues to increase during aerobic capacity testing

maximal oxygen uptake (VO_2max[15] < 20mL.kg.min^{-1}) was reported in 13-30% of survivors of 'aggressive' non-Hodgkin's disease (Elbi et al., 2006), one year after treatment with CHOP regimen (cyclophosphamide, doxorubicin, vincristin, and prednisone).

Cardiovascular fitness capacity can be measured directly by testing maximal oxygen consumption (VO_2 max), which is highly accurate and is considered the gold standard or alternatively it can be estimated indirectly using sub-maximal testing.

Maximal exercise testing is the most precise method of measuring absolute fitness levels, and can also identify underlying exercise limitations (Jones et al., 2008). However, the test requires the individual to exercise to volitional exhaustion or symptom limitation which may have inherent safety concerns. Trained personnel are needed to carry out maximal exercise testing and medical supervision is required. Careful calibration of equipment and collection of expired air and lactate levels is necessary. Therefore testing is difficult and expensive to perform in non-laboratory settings. In Study III, a sub-maximal fitness measure was chosen due to resource issues as well as safety concerns in carrying out a maximal test in individuals with varying degrees of left ventricular dysfunction and potentially occult treatment related cardio-toxic damage or other co-morbid conditions. A recently published meta-analysis by Jones et al. (2011) which explored the effect of exercise training on peak oxygen consumption in patients with cancer identified only 6 exercise trials which incorporated a measurement of VO_2 peak using a gas exchange analysis system. Thus, the majority of trials have used sub-maximal fitness measures.

However, sub-maximal testing is based on a derived maximum heart rate which may be inaccurate due to a 10-12 standard deviation in beats per minute for maximum heart rate in healthy individuals (Fleg et al., 2000). These methods are based on the

[15] Maximal oxygen consumption (VO_2 max) is the greatest amount of oxygen a person can take in from inspired air while performing dynamic exercise which involves large areas of muscle mass and represents the amount of oxygen transported by the cellular metabolism (Fletcher, 2001).

assumption of a normal exercise response, which may not be the case post chemotherapy (McNeely et al., 2006b) as heart-rate variability may be a factor in patients who have had autonomic dysfunction exacerbated by systemic cancer treatment (Jones et al., 2008).

There appears to be no gold standard sub-maximal exercise test for the oncology population (Schmitz et al., 2010). Sub-maximal tests estimate cardio-respiratory fitness based on workload achieved at a pre-determined sub-maximal heart rate (Jones et al., 2008). A large number of sub-maximal fitness tests have been devised. These exercise testing regimens are mostly carried out on motorised treadmills or cycle ergometers. A number of studies within the cancer area have used cycle-ergometer based tests such as the Astrand-Rhyming test (Thorsen et al., 2005) and the Monark cycle ergometer test (Courneya et al., 2003c). However, a treadmill-based test was deemed more appropriate as walking was a more familiar activity than cycling within this population. A number of treadmill-based sub-maximal fitness tests have been devised. The Modified Bruce Protocol, a standard sub-maximal measurement method frequently used in the cardiovascular area was chosen as the measure of fitness in Study III (Chapter 5). This protocol was chosen over the Bruce protocol as it is more suitable for use in sedentary populations. This has been used previously in cancer populations (Spence et al., 2007, Monga et al., 1997).

2.2.3.2 Sub-maximal Fitness Measure

The measurement of VO_{2max} was shown to be reproducible in young men performing the Bruce protocol to exhaustion with a coefficient of variation of 3% (range, 0-9%) (Nordrehaug et al., 1991). The Modified Bruce Protocol was developed from the Bruce Protocol (Bruce et al., 1949). The reproducibility of this protocol for the determination of maximal aerobic capacity was evaluated in sedentary older women (n=17, age range 51-68) (Fielding et al., 1997). Strong psychometric properties were shown with a mean coefficient of variation of 6.5% (range, 2.0-14%) and Pearson's correlation coefficients for the study variables was significant (r: between 0.70 to 0.89).

The first two stages of the Modified Bruce Test are performed at a 1.7 mph and 0% grade and 1.7 mph and 5% grade, and the third stage corresponds to the first stage of the Standard Bruce Test protocol.

A full description of the Modified Bruce Test is detailed in APPENDIX IV. Contraindications and precautions to exercise testing as per the American College of Sports Medicine (2009) were adhered to and standard guidelines were determined before testing (APPENDIX IV). VO_{2max} values were calculated for females as VO_{2max} ($mL/kg^{-1}/min^{-1}$) = 2.94 x T + 3.74 and men VO_{2max} ($mL.kg^{-1}.min^{-1}$) = 2.94 x T + 7.65 as described in ACSM (2009a) "Guidelines for Exercise Testing and Prescription'. Cardiovascular cut-off points for 'poor', 'fair', 'average', 'good' and 'excellent' were (McArdle et al., 2001) used to differentiate cardiovascular fitness test scores. Verbal encouragement during the exercise test was standardised.

2.2.4 The Measurement of Fatigue

2.2.4.1 Introduction to the measurement of fatigue

Fatigue is the most commonly reported symptom associated with chemotherapy, and radiotherapy treatment and advanced disease (Ahlberg et al., 2003b, Stone, 2002). Fatigue is characterised by tiredness, reduced energy levels and cognitive impairments (Yun et al., 2008) and has been defined as "a persistent subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning" (Mock et al., 2000). The figures quoted of patients with cancer suffering from fatigue vary from 61-99% (Stone et al., 2001, Stone, 2002) and some suffer from debilitating and persistent fatigue for many months or years after the cancer has been treated and cured (Oldervoll et al., 2004b, Bower et al., 2006, Cramp and Daniel, 2008).

Cancer-related fatigue is thought to be multi-dimensional in nature (Ahlberg et al., 2003b). The aetiology of cancer-related fatigue is not fully known but has been associated with co-occurring medical conditions such as anaemia, hypothyroidism,

cytokines, sleep problems, and psychological factors such as anxiety and depression (Lucia et al., 2003, Wagner and Cella, 2004, Mustian et al., 2007, Kangas et al., 2008). Side effects of cancer and its treatment may cause fatigue. In an effort to avoid fatigue, patients may down-regulate their level of activity which may in turn induce a further reduction in muscular and cardio-respiratory fitness (Hayes et al., 2004, Dimeo et al., 1999), thereby resulting in a vicious self-perpetuating cycle of decreased PA and fatigue (Dimeo et al., 1999, Ahlberg et al., 2003a, Dimeo et al., 1998, Hayes et al., 2009, Lucia et al., 2003). Fatigue may also be related to factors such as the release of cytokines, cancer-induced anaemia and tumour necrosis (van Weert et al., 2008). Mood and personality factors have also been associated with the onset and persistence of cancer related fatigue (Ahlberg et al., 2003a).

Exercise has been proposed as a non-pharmacological tool to manage fatigue (Jacobsen et al., 2007) and can help to reduce fatigue symptoms both during and after treatment for cancer (Cramp and Daniel, 2008). As fatigue is subjectively experienced, self-report questionnaires are considered the best method of measuring this variable (Ahlberg et al., 2003a).

However, consensus is required on consistent assessment tools for use within this area. Self-report tools which measure uni-dimensional and multi-dimensional aspects of this variable are utilised within the cancer context (Kangas et al., 2008). Uni-dimensional questionnaires assess the presence and intensity of fatigue, usually within the previous 7- day period. Examples of these questionnaires would be the Profile of Mood States Fatigue subscale (McNair, Lorr, & Droppelman, 1992) and the Brief Fatigue Inventory (Mendoza et al., 1999). Multidimensional scales are more comprehensive tools and assess the impact of fatigue across several dimensions such as physical, emotional/affective, and cognitive components of fatigue. Examples would be the Revised Piper Fatigue Scale, (Piper et al. 1998) and the FACTIT-F scale.

A recent review compared the psychometric properties and user-friendliness of a number of one-dimensional and multi-dimensional self-report fatigue scales. The Brief

Fatigue Inventory (BFI) scored the highest on 'quality criteria' (15/18), and also scored the highest in terms of user-friendliness (4/4) in a recently published review of self-report questionnaires of cancer-related fatigue (Agasi-Idenburga et al., 2010). Thus, due to its strong psychometric properties and brevity, the BFI was chosen for use for Studies I and II. The FACIT-F is a widely used measure in intervention studies within the cancer literature. This scale displays 'excellent' psychometric properties, with the total score for the psychometric properties of this scale scoring highest overall in terms of uni-dimensional measures of fatigue (Agasi-Idenburga et al., 2010). For these reasons, the FACIT-F questionnaire was chosen for use in Study III.

2.2.4.2 The Brief Fatigue Inventory (BFI)

The BFI (Appendix V) was developed from the Brief Pain Inventory (Cleeland, 1989) which measures severity of pain and interference caused by pain using 0-10 scales. The BFI was designed to assess severity of fatigue in cancer patients and the impact of fatigue on daily functioning. Psychometric properties of this scale including construct, concurrent and discriminant validity and reliability were tested and established on almost 600 adults with cancer (Mendoza et al., 1999).

The BFI is a self-administered questionnaire on a single page which takes approximately five minutes to complete and consists of 9 numerical scales of 0 to 10. Out of the 9 numerical scales: 3 items measure severity and 6 items measure interference with daily activities from 0 (none) to 10 (severe) with anchor points 'no fatigue' and 'fatigue as bad as you can imagine'. It is based on recall over the past 24 hours. Items 1-3 assess the severity 'now', 'over the last 24 hours' and 'at worst in the past 24 hours'. The final six items on the questionnaire rate how fatigue has interfered with various aspects of daily activity in the past 24 hours. These items are general activity, mood, walking ability, normal work (both work outside the home and daily chores), relations with other people, and enjoyment of life.

The global score for the BFI is calculated as the mean value of these 9 items. It displays good internal consistency with a Cronbach's alpha reliability range from 0.82 to 0.97

and correlates well with other similar fatigue measures. Categorical Fatigue severity is the score from Item 3 only, that is 'fatigue worst' and a score of 7-10 is 'severe' and 0-6 'not severe' (Mendoza et al., 1999).

2.2.4.3 The Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F)

The 13-item Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) (APPENDIX VI) of the Functional Assessment of Chronic Illness Therapy measurement system which has been developed specifically for the cancer population (Cella, 1997b, Cella et al., 1993). The FACIT-F is a subset of the longer (47-item Functional Assessment of Cancer therapy Anaemia (FACT-An) Scale, which includes the 27-item FACT-G and a 20-item subscale addressing concerns associated with the anaemia of cancer and its treatment. The FACIT-F contains the FACT-G plus a 13-item subscale addressing concerns specific to fatigue and uses a 5-point Likert-type scale (0=Not at all; 1=A little bit; 2=Somewhat; 3-Quite a bit; and 4=Very much). The questionnaire is based on a 7-day recall period. The FACIT-F is devised to be suitable to a (U.S.) 4^{th} grade reading level and takes 2-3 minutes to complete. It can be self-administered or administered using face-to-face interview.

The reliability of the FACIT-F scale has been reported to be 0.84 and it has been shown to have good validity when compared with other measures of fatigue, and a significant negative relationship with domains of vigour and with social desirability (Cella, 1997a). Internal consistency of this questionnaire is high with Cronbach's Alpha Coefficients ranging from 0.93-0.95. Each of the 13 items of the FACIT-F scale ranges from 0-4, so the range of possible scores is 0-52, with 0 being the worst possible score and 52 the best. To obtain the 0-52 score, each negatively-worded response is recoded so that 0 is a bad response and 4 is a good response. All responses are added with equal weight to obtain the total score (Appendix VI). Minimally important differences appears to be in the range of 3-4 points, representing 6-8% of the 0-52 score range of the instrument (Cella et al., 2002c). Normative data collected from 1,075 men and women drawn from the US population provides useful comparisons with test data.

2.2.5 The measurement of Quality-of-life (QOL)

2.2.5.1 Introduction to the measurement of QOL

Quality-of-life and, more specifically, health-related QOL refers to the 'physical, psychological, and social domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations, and perceptions' (Patrick et al., 1973).

Physical and functional well-being are essential dimensions for overall QOL (Cella and Tulsky, 1990) and may, in part, underlie some of the psychological distress experienced by cancer survivors (Williamson and Schulz, 1992). Moreover, it has been shown that functional well-being may a key element underlying satisfaction with life in cancer survivors both during and after treatment for cancer (Courneya et al., 1999, 2000a). Cancer and its treatment can result in physical and psychological consequences which can decrease QOL (deJong et al., 2002, Victorson et al., 2008). It is expected that QOL reduces in the initial phase after a cancer diagnosis, but that it gradually increases over time (Jansen et al., 2010). Thus the assessment of QOL is of importance within the cancer area and QOL has become a key patient-centred clinical and therapeutic outcome measure in cancer clinical trials to assess the effects of the disease and its treatment (Dahele et al., 2007, Fayers, 2001) and is next only to survival as a main outcome measure (Jansen et al., 2010).

Several tools have been devised to measure QOL and broadly consist of general measures, cancer-specific measures, disease-specific measures, psychological measures and symptom measures (Montazeri, 2011). A recently published meta-analysis on QOL outcomes of exercise interventions for cancer survivors included 78 studies, all which included a measure of QOL. The main questionnaires used were the FACT questionnaires (36 studies), the EORTC QLQ C30 (13 studies) and the SF-36 (16 studies).

QOL was not examined in Study I, as the aim was solely to compare PS to objective and self-reported measures of PA, and to examine if fatigue influenced these measures. For Study II the multi-dimensional EORTC-QLQ C30 (see overleaf) was chosen to enable comprehensive evaluation of this construct over time. To maximise comparability with other intervention studies within the cancer area, the FACT-G (see overleaf) was chosen for Study III as this measure is widely used in intervention studies within the cancer area. Both of these tools are cancer-specific measures. In addition, as physical outcomes and their impact on QOL were the focus of Study III, the Physical Functioning Component of the SF-36 was also included as the FACT-G alone may have been too broad a measure to examine this construct in depth.

2.2.5.2 The EORTC-QLQ C30 V3

Quality-of-life (Appendix VII) was measured using the EORTC-QLQ C30 V3 (Aaronson et al., 1993) questionnaire. This questionnaire includes multi-item scales and single-item scales. The multi-item components evaluate physical, role, cognitive, emotional social, fatigue, pain, and nausea and vomiting. Single items include dyspnoea, appetite loss sleep disturbance, constipation & diarrhoea. The scoring of the EORTC QLQ C30 was performed according to the EORTC scoring manual (Fayers et al., 2001) (Appendix VII). Thus, scores were linearly transformed to a 0-100 scale and missing items in the multi-item section were calculated as the mean of non-missing items if at least half of the items were completed (Fayers et al., 2001). This questionnaire takes approximately ten minutes to complete.

The items comprise five functional scales, three symptom scales, a global health status/QOL scale, and six items. A high score for a functional scale represents a high level of functioning, a high score for the global health status/QOL represents a high QOL, but a high score for a symptom scale/item represents a high level of symptomology/problems.

The reliability (i.e. internal consistency) of the multi-item questionnaire scales was assessed by Chronbach's alpha (Cronbach, 1951). Internal consistency estimates

greater than 0.7 are recommended (Nunnally, 1978). Similarly, role functioning has been identified to be the weakest from a psychometric point of view, due to the restricted range of responses (Aaronson et al., 1993). Internal reliability estimates were > 0.7 for physical functioning (0.86), emotional functioning (0.75), cognitive function (0.9), social function (0.73), fatigue (0.82) and pain (0.75). Only the multi-item scale did not reach the minimal standards for reliability (Aaronson et al., 1993).

2.2.5.3 The FACT-G

The Fact-G (version 4) (Appendix VI) is a 27-item questionnaire initially developed by Cella et al. and has been validated in a mixed cancer population (Cella et al., 1993). This is a core questionnaire of the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system available through the www.facit.org website. The FACT-G is considered a "core" questionnaire and there are site-specific additions to the core questionnaire for specific patient groups such as breast, colon and lung cancers. There is also a symptom specific addition for fatigue described above (the FACIT F). The FACT-G takes about 5 minutes to complete and was devised to be suitable for 6th grade reading level. Patients rate all items using a 5-point Likert-type rating scale ranging from 0 = "not at all" to 4 = "very much".

This questionnaire is divided into 4 primary QOL domains: physical well-being (seven items, range 0-28), social/family well-being (seven items range 0-28), emotional well-being (six items, range: 0-24), and functional well-being (seven items, range: 0-28) and an overall quality of life level is also yielded. The range of the FACT-G total score is 0-108. 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 (Victorson et al., 2008). The internal consistency of the subscales of the questionnaire was evaluated using Chronbach's alpha, which is considered acceptable if the coefficient is > 0.7 (DeVellis, 1991).

The scoring algorithms (Cella, 1997b) were used to compute all the FACT analyses (Appendix VI). 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 (Cella et al., 2002b). Effect sizes of 0.33 approximate minimally important differences (Yost and Eton, 2005). FACT-G normative data was reported for a sample of the general US adult population and for a sample of adult patients with cancer (Brucker et al., 2005). A 2-3 point difference on the FACT-G subscale scores and a 3-7 point difference on the FACT-G total score is associated with a meaningful difference on clinical and subjective indicators. Minimally important differences (MID) for the FACT-G most often fall in the range of 0.3 to 0.5 SDs. The Trial Outcome Index (TOI) is the sum of the Physical, Functional, and Lung Cancer subscales. The TOI is reported to be a precise summary index of physical and functional outcomes. 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 (Cella et al., 2002a).

2.2.5.4 The SF-36 v2 (Physical functioning component)

The SF-36v2 (Appendix VIII) is a widely used generic measure of health-related quality-of-life and overall health status. Psychometric properties of the SF-36 have been well established (Ware et al., 1993). This scale consists of 36 items, which 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. The Physical Functioning (PF) measure of the SF-36 was used for the purposes of this study (Appendix IX). The PF component of the SF-36 does not have a recall period. The PF scale has been shown to be the best all around measure of physical health (Ware et al., 2000, Ware et al., 1993). A higher functioning score indicates better functioning. The PF component of the SF-36 takes approximately 2 minutes to complete.

Responses from the SF-36 were scored and summed using a scoring algorithm and transformed to give scores with a 0-100 scale where higher scores indicate better function (Appendix VIII). T-scores (norm-based scores) have been developed for the health domain scales. Transformation of 0-100 scores to T scores allows scores for each of the health domain scales and component summary measures to have a mean of 50 and a standard deviation of 10 (Ware et al., 2000). The 10-item PF scale contains questions pertaining to a wide range of physical limitations from minor to severe, including lifting and carrying groceries, climbing stairs, bending, kneeling or stooping and walking moderate distances. One self-care item is also included. Low scores indicate limitations in performing physical activities and high scores reflect few limitations.

2.2.6 The measurement of body composition

2.2.6.1 Introduction to the measurement of body composition

Body composition is expected to change after a cancer diagnosis, mostly related to the side-effects of treatment. Body composition has clinical implications in many areas of cancer; increased prevalence or recurrence of many cancers including breast, prostate, colorectal and specific gastro-oesophageal cancers are associated with obesity (Demark-Wahnefried et al., 2001). Cancer cachexia associated with involuntary muscle and fat loss is associated with advanced disease and a poor prognosis (Dewys et al., 1980).

Dual energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and computed tomography (CT) are regarded as gold standard methods of assessing body composition (Mourtzakis et al., 2008). Bioelectrical impedance analysis (BIA) is another measurement method which is a more cost and time efficient method of assessing body composition in clinical populations (Kyle et al., 1988, Kyle et al., 2004). BIA is safe, accessible and does not involve exposure to radiation (Mourtzakis et al., 2008).

In a study of 50 patients with cancer, BIA measurement was compared to DXA measurement. It was reported that BIA over-estimated or under-estimated fat-free mass 'substantially' compared to DXA measurement. A sub-set of 21 patients were followed and significant changes in fat-free mass over time were detected with the DXA measurement-but the BIA measurement was unable to detect these changes (Mourtzakis et al., 2008). The sensitivity of BIA measurement could therefore be questioned, but DXA and CT were not available for the purposes of the studies in this thesis, and BIA measurement was performed.

2.2.6.2 Bioelectrical Impedance Analysis

Body composition was analysed using the 'Multi-frequency Body Composition Analyzer' (MC-180 MA) (Appendix IX). This is a multi-frequency 8-electrode method which provides estimated values based on the bioelectrical impedance analysis (BIA) method for fat, percentage fat, fat-free mass, muscle mass, and bone mass. This is carried out using a regression formula derived from specifying the height, weight, age, and using the generated impedance values between the arms and legs. The manufacturers reported a repeated accuracy of ± 2% for the impedance element, and an accuracy of ±0.2kg for the weighing scales element.

2.2.6.3 Waist circumference

Waist circumference (APPENDIX X) measurement was performed to complement the BIA assessment. This provides a measure of central fat. Even though this is a simple measure to complete, high reliability values have been reported with an intra-observer ICC for WC of 0.987 (95% confidence interval [CI]: 0.983 to 0.990), and an inter-observer ICC for WC was 0.988 (95% CI: 0.982 to 0.993) (Chen et al., 2001).

2.2.7 Summary of measurement methods (other than Physical Activity)

Besides PA, a number of other outcome measures were used throughout this thesis. These included fitness, fatigue, quality-of-life and body composition measures.

Cardiovascular fitness generally declines after a cancer diagnosis, due to toxic effects of treatment and inactivity related to its side-effects. The gold standard for measuring fitness is VO_2 max. For the purposes of this research, this test was deemed prohibitively expensive and time-consuming. A commonly used sub-maximal fitness measure, suitable for more sedentary populations, the Modified Bruce Protocol was chosen for use in Study III.

Fatigue is a prevalent side effect of cancer and its treatment. The Brief Fatigue Inventory, a concise questionnaire with strong psychometric properties was chosen for use in Study I and II. In order to enable comparison with a number of other intervention studies, the FACIT-F was chosen for use in Study III.

Quality-of-life is an important criterion, commonly assessed within cancer research. The EORTC-QLQ C30 was chosen for use in Study II, a measure with strong psychometric properties and again to enable comparison with other intervention studies, the FACT-G was chosen for use in Study III.

Body composition measures are considered an important outcome of physical intervention studies. In Study III, bio-impedance measurement, body mass index and waist circumference were measured to determine changes in body composition.

Chapter 3

3.1 Introduction

Performance status scales are functional classification scales widely used in oncology practice. These are evaluated by interview with a health care professional. Several scales are used; these have been shown to be robust tools in predicting treatment-related toxicity (Akechi et al., 2004, LLoyd-Williams et al., 2004, Dimeo et al., 2004) and prognosis (Blagden et al., 2003, Scott et al., 2002, Motzer et al., 1999, Mor et al., 1984b, Deans et al., 2007, Bill Musk et al., 2011, Hwang et al., 2004) and are therefore used as tools to aid decisions about appropriate cancer therapy for individual patients as outlined in Section 1.2 (page 9).

Although (PA) levels feature in the description of each point in the ECOG PS, there are no existing published data about the relationship to actual, objectively measured PA. Some studies have attempted to separate PS assessment from the patient / health care provider interview. Doctors (Blagden et al., 2003, Loprinzi et al., 1994) and health care providers (Lilenbaum et al., 2008) have been reported to "over-estimate" PS in clinical practice, when compared with PS estimated by the patient (Ando et al., 2001, Loprinzi et al., 1994). In a few studies comparing KPS to patient functioning measures estimated by self-report (Mor et al., 1984a, Yates et al., 1980, Schag et al., 1984), strong relationships between self-reported PA and the KPS were found. However, self-reported PA is notoriously prone to bias (Sallis and Saelens, 2000a) and it is difficult to quantify volume and intensity of activity. Even in everyday clinical assignment of ECOG PS, patients often struggle to recall how much of the day they spend in bed or chair or "up and about". Therefore, these knowledge gaps raise the question of whether objective PA measurement (Section 2.2.2.2, Page 70) using newer accelerometry technology, might be useful. As a global measure of free-living PA, accelerometry is also likely to be a more suitable method of assessing the validity of PS scales than self-report scales (Yates et al., 1980, Schag et al., 1984, Mor et al., 1984a) or physical function/capacity measures (Terret et al., 2011, Ruden et al., 2011). Fatigue, which is a tremendously prevalent symptom within cancer populations (Stone

et al., 2001, Stone et al., 2000) may also help to explain the relationship between PA levels and PS assigned.

The overall aim of this study was to investigate the relationship between PS assigned and PA.

Objectives of this Study were

1. To determine the relationship between physician-assigned ECOG PS and objectively measured PA at diagnosis assessed by accelerometer (RT3 accelerometer, Stayhealthy Inc., Monrovia, CA)
2. To compare the ECOG PS and objectively measured physical activity to subjective physical activity estimated by self-report questionnaire (International Physical Activity Questionnaire)
3. To examine the relationship between fatigue (Brief Fatigue Inventory) and ECOG PS

3.2 Methods

3.2.1 Setting and Participants

This study was carried out on 100 patients from a single cancer centre in St. James's Hospital, Dublin, Ireland from November 2008 to March 2010. Institutional ethical (Appendix XI) board approval was granted and all participants gave written informed consent.

The Eligibility Criteria were as follows;

Inclusion Criteria

1. Recent diagnosis of a potentially curable non-haematological malignancy
2. Being considered for chemotherapy and/or radiotherapy
3. Age ≥ 18 years
4. Capable of completing questionnaires

Exclusion criteria

1. Significant chronic lung disease or cardiovascular disease which interfered with mobility or any other co-morbid condition which significantly impaired functional ability

3.2.2 Study procedure

Potential participants were sourced through oncology multi-disciplinary meetings or via communication with relevant medical/nursing personnel and were subsequently approached and given study information (Appendix XII). Twenty-four hours was given for study participation to be considered. If interest was indicated, participants were supplied with an RT3 accelerometer (Fig. 2.1), an activity diary (Appendix I), the International Physical Activity Questionnaire (Appendix II) and the Brief Fatigue Inventory (Appendix V). RT3 set-up and data retrieval was carried out as outlined in Section 2.2.2.2.1 (page 79).

Participants wore the monitor for up to 7 days in the home environment during the immediate lead-up to their initial evaluation appointment with their medical or radiation oncology team. At that visit, the ECOG PS was assigned by the physician and the International Physical Activity Questionnaire (IPAQ) and the Brief Fatigue Inventory were completed. At the commencement of the study, the ECOG PS was reviewed with participating physicians. Crib sheets with the ECOG PS scale were routinely displayed in clinic rooms in St. James's Hospital.

3.2.3 Study Measures

The International Physical Activity Questionnaire (IPAQ) (long version) was used to assess subjective or self-report habitual physical activity participation during the previous 7 days. This was described previously (Section 2.2.2.3.2 page 83). The Brief Fatigue Inventory (Mendoza et al., 1999) was used to quantify fatigue levels as described previously in (Section 2.2.4.2, page 92).

3.2.4 Statistical analysis

Normality of distribution was tested using a 1-sample Kolmogorov-Smirnof test. As all data were normally distributed, parametric statistics were used to analyse data. Means for > 2 groups were compared using a 1-way Analysis of variance (ANOVA) with post-hoc testing using the Least Significant Difference (LSD) method. Associations between domains of activity and the ECOG PS were evaluated using a Spearman's rank correlation coefficient (rho). All reported *p* values were two-tailed and p values < 0·05 were considered statistically significant. Data were analysed using SPSS (SPSS16.0 Inc., Chicago, IL).

3.3 Results

3.3.1 Demographic details

The progress of patients through the study is shown in Fig. 3.1. The mean (SD) number of days monitored before ECOG PS assignment was 5.6 (1.1) days (range 3-8 days). All patients had localised disease and sixty-eight percent (n=68) of patients had breast cancer, 10% (n=10) lung/thoracic cancer, 9% (n=9) colorectal cancer, 10% (n=10) gynaecological cancer and 3% (n=3) prostate cancer. The mean (SD) age of participants was 54.7 (12.5) years with a range of 37 to 82 years. Patient characteristics including the number of co-morbidities are listed in Table 3.1.

Fourteen consultant or registrar grade physicians in medical or radiation oncology assessed patients and assigned ECOG PS in the course of the study.

Table 3.1 Baseline characteristics of patients

	Overall	ECOG PS 0	ECOG PS 1	ECOG PS 2-3
Age (years)				
Mean	54.7	50.2	55.8	60.7
SD	12.5	12.5	11.8	14.0
Gender				
% female	89	100	85.3	81.8
Number of Co-morbidities[16]				
0 (%)	58 (n=58)	67.9 (n=19)	55.7(n=34)	45.5 (n=5)
1 (%)	28 (n=28)	25 (n=7)	29.5(n=18)	27.3 (n=3)
≥ 2 (%)	14 (n=14)	7.1 (n=2)	14.8 (n=9)	27.3 (n=3)

Abbreviations: SD, standard deviation

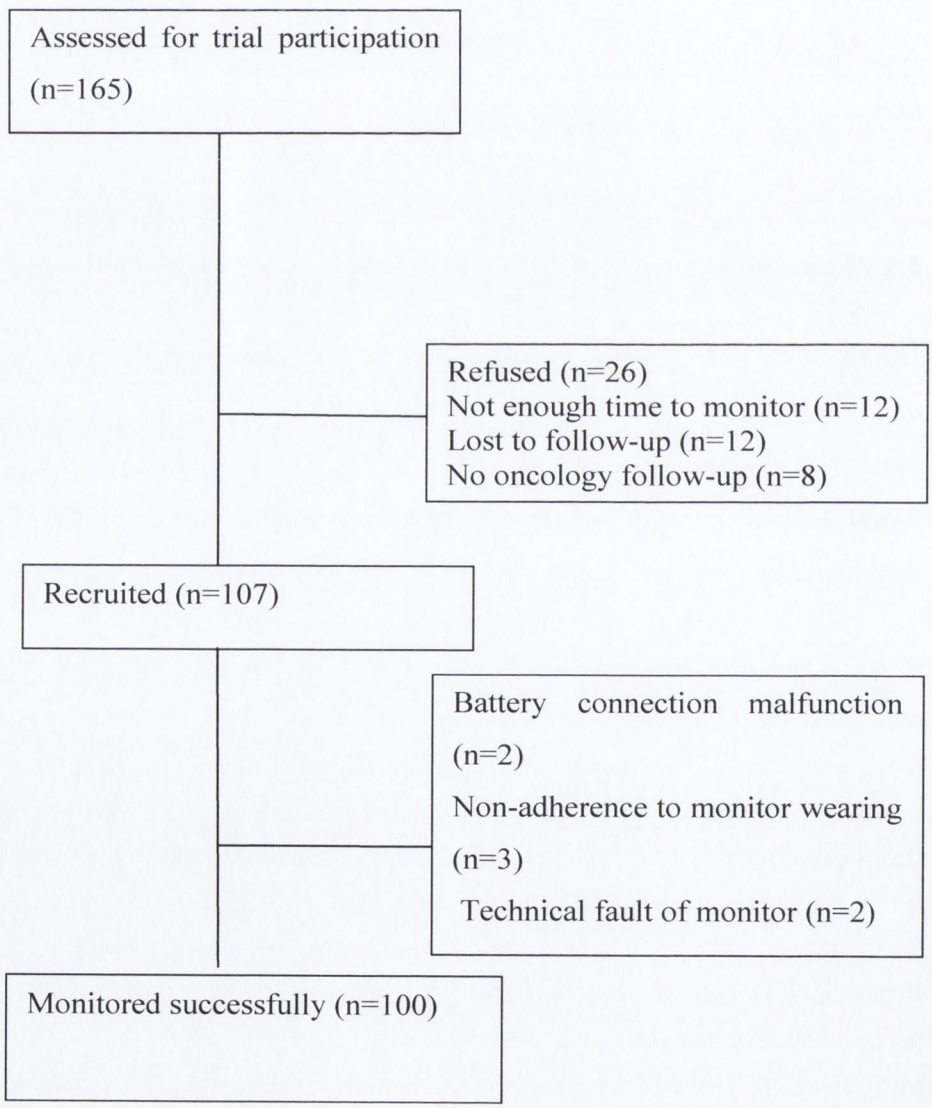
3.3.2 PS assigned

The majority (89%) of these ambulatory patients were assigned a good PS (ECOG PS 0 or 1). Twenty-eight patients were assigned an ECOG PS of 0, 61 patients a PS of 1, 6 patients a PS of 2 and 5 patients a PS of 3. Due to small numbers in ECOG PS categories 2 and 3, these categories were collapsed for further analysis. One hundred patients were successfully monitored and PS was assigned to these patients. Due to factors

[16] The breakdown of co-morbidities was as follows; Cardiac related diseases: (Hypertension n=20, previous MI (n=2), ischaemic heart disease (n=2), hypercholesteraemia (n=8), congestive cardiac disease (n=2), angina (n=1), atrial fibrillation (n=2), diabetes (n=2), TIA/Stroke (n=2)), Previous other primary cancer (n=5), Hypo or hyperthyroidism (n=10), Respiratory conditions: Asthma (n=9), Chronic Obstructive Pulmonary disease (n=4), Arthritic Conditions: (Osteo-arthritis (n=6), Rheumatoid arthritis (n=1)), Psychiatric/Psychological conditions: (Depression (n=8), schitzo-affective disorder (n=1), bipolar (n=1), Other: systemic lupus erythematosus (n=1), HIV (n=1), Peripheral neuropathy (n=1), Osteopenia/Osteoporosis (n=3), Irritable bowel disorder/Chrons Disease (n=4), diverticular disease (n=2), peptic ulcer disease (n=1), sarcoidosis (n=1), anaemia (n=1), polycytaemia (n=1), Oesophagitis (n=2), vertigo (n=4), ulcerative colitis (n=1), renal failure (n=1), peripheral neuropathy (n=1).

such as lack of time in oncology clinics and the BFI not used in the initial exploratory study, the number of completed questionnaires was 91 and 93 for the BFI and IPAQ respectively. Although not outlined in study objectives, the influence of age and co-morbidities on PS scoring was explored for completeness. It was found that age was significantly related to ECOG PS assigned (between groups $p = 0.04$) with differences identified between ECOG PS 0 and ECOG PS 2-3 categories ($p = 0.02$). There was no statistical relationship between PS assigned and number of co-morbidities (rho = 0.17, $p = 0.1$).

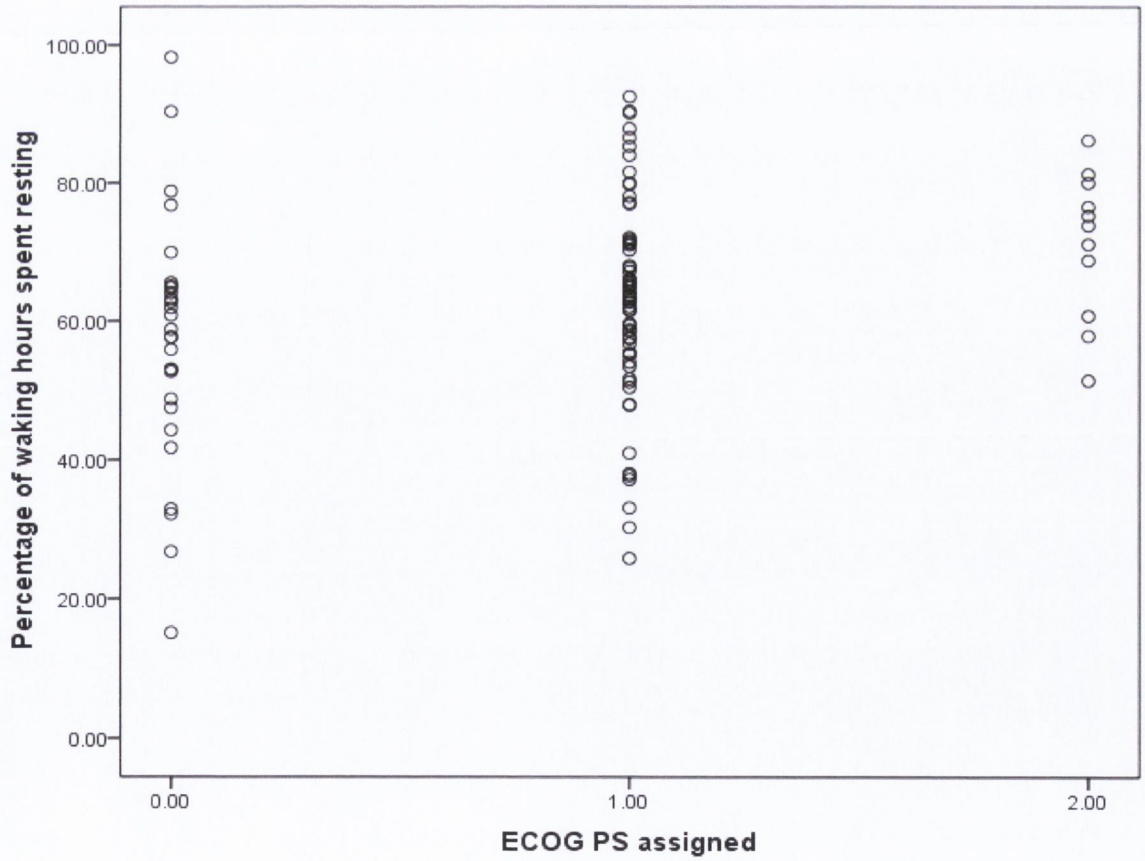
Fig. 3.1 Progress of patients through the study



3.3.3 PS assigned and PA levels of participants

Analysis of accelerometry data showed that participants spent a mean (SD) 8.1 (2.1) hours (66% of waking hours) at rest per day. Time spent in light activities was 4.4 (1.9) hours (33.5% of waking hours), moderate activities was 0.5 (0.7) hours (0.7% of waking hours), 0.2 (1.2) hours in vigorous activity (0.5% of waking hours). There was a trend towards increased time spent resting with worsening PS assigned (PS 0: 7.5(2.5) hours, PS 1: 8.2 (2.0) hours, PS 2-3: 9.2(1.2)) hours. Time spent at rest by each subject, expressed as percentage of waking hours, is shown in Fig. 3.2. There was no difference between percentage time spent resting of those patients > 65 years (n=76) compared to < 65 years (n=24) (mean (SD) 63·8% (16.9) versus 61.9% (15.7).

Fig. 3.2 Time spent at rest by each subject as a percentage of waking hours



ANOVA testing showed that ECOG PS was significantly related to percentage time spent resting as measured by accelerometer (p = 0.04). Post-hoc tests revealed the difference was between time spent resting by participants assigned a PS of 0 and by those assigned a PS of 2-3 (p = 0.01). No difference was identified between PS 0 and 1, or between PS 1 and 2-3. A weak but significant inverse association was found between objectively measured percentage of waking hours spent in activity and ECOG PS (rho = - 0.27 and p = 0.01). The mean (SD) percentage time 'in activity' per day, was 42.9% (17.9) for PS 0, 36.9% (15.1) for ECOG PS 1, and 28·9% (10.7) for ECOG PS 2-3. Only 17 of 100 patients spent more than 50% of waking hours in any activity, however light; all of those were assigned an ECOG PS of 0 or 1. No patient who was assigned an ECOG PS of 2 or 3 met this cut-off.

Table 3.2 IPAQ and ECOG PS assigned

ECOG PS assigned	**0 (n=28)**	**1 (n=54)**	**2-3 (n=11)**	**p value**
IPAQ				
Total physical activity (MET minutes per week)				
Mean	2861.20	2515.79	759.00	0.10
SD	2221.28	3219.32	1193.01	
Average estimated time spent sitting per day (hours)				
Mean	5.71	7.15	7.15	0.07
SD	2.47	2.69	3.09	

Abbreviations: IPAQ, International Physical Activity Questionnaire; SD, standard deviation

Subjective physical activity data (IPAQ) is presented in Table 3.2. ECOG PS was not significantly related to total estimated PA levels (p = 0.10) or average hours spent

sitting (p = 0.07). Associations between ECOG PS and subjectively measured PA are presented in Table 3.3.

Table 3.3 Correlation between percentage time in activity and subscales of the IPAQ

	Total Physical activity (IPAQ)	Hours spent sitting (IPAQ)
Percentage time 'in activity' (RT3)	rho = 0.59 p= < 0.001	rho = - 0.48 p = < 0.001
ECOG PS	rho = - 0.34 p = 0.001	rho = 0.02 p = 0.03

3.3.4 PS assigned and fatigue levels of participants

Results of the Brief Fatigue Inventory showed that 42.3% (n=26) of participants with a PS of 0 had 'severe fatigue', this was 51.9% (n=54) for PS 1 and 63.6% (n=11) for PS 2-3. ANOVA testing revealed that the Global fatigue score was significantly related to assigned PS ($p<0.001$), with differences shown between PS 0 and 1 ($p=0.04$), between 0 and 2 ($p<0.001$) and between PS 1 and 2 ($p=< 0.001$). There was a significant inverse association between the Global fatigue score and percentage time 'in activity' from the RT3 (rho=-0.31, $p=<0.001$) and between the Global fatigue score and total physical activity (from IPAQ) (rho=- 0.42, $p< 0.001$).

3.4 Discussion

This appears to be the first study comparing ECOG PS assigned to objectively measured PA in newly-diagnosed cancer patients. Dahele et al. (2007) previously investigated 20 patients in a palliative care setting and also reported a trend towards lower objectively measured PA levels with poorer PS assigned (Dahele et al., 2007). Strengths of the current study were a heterogeneous population of treatment-naive,

ambulatory patients, each measured at first treatment decision, and the assignment of PS in the course of the initial cancer consultation by medical or radiation oncology physicians who regularly selected patients for clinical trials.

The main finding of this study was the extent of time most patients, even those assigned a good PS, spent sedentary. This may relate to the fact that all patients had undergone surgery or at least biopsy. On the other hand, the majority of patients had breast cancer and would therefore have undergone relatively non-invasive surgery, frequently as a day surgery. Of note, within ECOG PS categories 0 and 1, a small number of participants were very active. However, very few patients, even those of PS 0, spent less than 50% of their waking hours at rest, and consistent with Dahele et al. (2007), very few patients when assessed objectively reached the 50% threshold between ECOG PS 2 and 3. However, Dahele et al. (2007) compared PS assigned to 'total hours quiet standing per week' and to 'total hours stepping per week' rather than to time spent in 'light, moderate and vigorous activity domains'. The verbal descriptors of the ECOG PS refer to 'time up and about', self-care and whether restricted in physically strenuous activity, so the parameters of 'total hours quiet standing per week' and 'total hours stepping per week' used by Dahele et al. (2007) may not provide as useful a comparison, although trends would be expected to hold, even though time 'up and about' cannot be accurately quantified by these methods.

The difficulty of comparing ECOG PS - an ordinal scale, to PA, a continuous multidimensional measure is acknowledged. Also, the ECOG PS scale was devised based on physician-patient interaction, not objective assessment. ECOG PS was designed to reflect physical function including "self-care" and occupational activity as well as absolute PA levels. A small number of studies have been carried out comparing PS to physical functioning measures such as the Edmonton Simmonds Assessment Scale (Montoya et al., 2006) and the six-minute walk test (Jones et al., 2009). While they potentially assess physical functioning more comprehensively, they are reflective of a 'once-off' effort to complete the test, and not reflective of real-time day long activity and self-care patterns assessed by performance status scoring. Exercise

behaviour is a key determinant of functional capacity (Ruden et al., 2011), and accelerometers by integrating self-care, incidental physical activity as well as planned exercise, may be a better measure to explore comparison with the ECOG PS.

There was no significant correlation between patients' own estimation of physical activity (from IPAQ) and ECOG PS, but a moderate association between IPAQ and accelerometer data. That suggests that a patient's estimation of his or her own activity levels using the recall questionnaire may reflect PA more accurately than the ECOG PS. This may also to some extent endorse the methods of earlier studies which compared PS to self-report (Yates et al., 1980, Mor et al., 1984b, Schag et al., 1984). However, generally higher associations between PS and self-report measures of physical functioning were noted in these studies compared to the value reported in the present study. Of note, all questionnaires pertaining to these studies measured different constructs, some were self-assessed by patients while others were evaluated by health-care professionals which makes comparisons across studies difficult. The IPAQ self-evaluated exercise behaviour encompassing domestic, occupational and planned exercise behaviour over the previous 7 days. The questions used by Yates et al. (1980) self-estimated difficulty on stairs, balance, the Katz ADL Index assessed independence of various activities of daily living, and was assessed by hospice staff, and Schag et al. (1984) used the Cancer Inventory of Problem Situations Questionnaire, which was filled out by patients and was mainly related to domains of self-care and activity levels.

Fatigue levels were surprisingly high, given that systemic cancer treatment or radiotherapy had not yet commenced at this point so presumably was related to the impact of the disease and the fact that patients had undergone surgery or at least biopsy as discussed above. It was noted that fatigue was significantly related to assigned PS, however, surprisingly, almost half of patients allocated a PS of 0 were classified as having 'severe' fatigue using the Categorical Fatigue Severity Score of the BFI. This would suggest that physicians did not question patients regarding fatigue, or patients did not impart this information, as it is unlikely that patients subjectively reporting high levels of fatigue would have been allocated a PS of 0. In the study by

Dahele et al. (2007), a moderate correlation between fatigue (FACIT-F TOI) and estimated energy expenditure and the average steps taken per day (r=0.59, p=0.009 and r=0.59, p=0.008) was reported. Lower but significant associations were noted between fatigue and objectively measured PA in the current study, so it would appear that one measure could not replace another. This highlights the complex relationship between fatigue and physical function - it is not known whether fatigue is a causative factor or a consequence of poor physical function (Brown et al., 2004a). A further complicating factor in comparing fatigue to PA in this population is the overlap of fatigue and depression in patients with cancer (Reuter and Härter, 2004).

The first question raised by these results is why time spent resting by most patients is so much more than might be expected based on the ECOG PS categories to which they were assigned. The vast majority of participants spent > 50% of the day at rest (whether "confined" or not), which would appear to correspond to an ECOG PS of 3. Systematic underestimation of activity with the RT3 accelerometer is unlikely. The device has been widely validated in other populations (Rowlands et al., 2004) is highly sensitive and registers minor activity. As a small number of patients registered as highly active, that suggests the others were genuinely inactive. It is not clear whether the low PA levels were related to disease-related decrements in PA or habitually low activity levels. Also, patients would be expected to be less active than normal as they were recovering from surgery. It would be expected that patients who underwent larger surgery such as pneumonectomy for lung cancer would have more functional decrements post-operatively than those who underwent more minimally invasive surgery, which should be reflected in terms of ECOG PS assignment. However, the majority would have had relatively small breast cancer surgery such as lumpectomies and/or sentinel lymph node sampling which would not be expected to cause large decrements in PA levels. It has been suggested that cancer patients decrease their PA by about 45% to maintain energy equilibrium, but this is more relevant in advanced cancer patients with cachexia (Moses et al., 2004) and would not be likely to be a consideration in this population of treatment naive patients being considered for first

line therapy. Therefore, this is unlikely to be a reason for the lower than expected levels of PA reported in this study.

Perhaps physicians in this study simply assigned "too high" an ECOG PS. This has been found in many studies in which PS scoring was over-estimated compared to patient scoring (Ando et al., 2001, Loprinzi et al., 1994, Blagden et al., 2003, Jeon et al., 2007). Post-hoc interviews with participating physicians about why specific ECOG PS scores were assigned were not conducted in this study. Although this could be considered a limitation, it was deliberate, as it was felt too much debriefing could influence doctors' scoring practices through the Hawthorne effect. Fourteen physicians participated, making systematic bias by a few unlikely. All participating consultants had experience in large academic comprehensive cancer centres in the US or UK, it is therefore likely that the spread of grade, experience and oncological subspecialty mean the doctors' assignment of PA is likely to reflect current clinical practice elsewhere.

The physician-patient interview is a dynamic interaction which involves both linguistic and non-verbal signals. The meanings of the verbal descriptors of the ECOG PS scale are likely to have shifted as the population has become more sedentary over this time. This is supported by the fact that participants were still sub-classified appropriately according to relative PA levels; PA levels were significantly lower in patients assigned an ECOG PS 2-3 compared to those assigned an ECOG PS of 0. The vocabulary and phrasing of the ECOG PS scale appears based on the premise that periods spent at rest reflect disease-related restriction rather than habitual inactivity. However, in our automated society, patients could be very sedentary, yet maintain the ability to function and feel unrestricted. Sitting awake, completely immobile, could be regarded as time spent "up and about" rather than "at rest" by those habitually inactive. There is an increasing perception by both doctors and patients that active treatment and inclusion in clinical trials is beneficial. Physicians might expect younger patients to be active; in support of this, many patients ≤ 65 years were assigned a better PS than those > 65, even though their activity levels were no higher than the older cohort. Thus the drifting societal perception of activity norms and medical expectations could

affect a patient's perception of activity, how that functional status is conveyed and interpreted and what PS is assigned. It can only be speculated whether patients who nowadays score 0 or 1 are less physically active than their counterparts 50 years ago when the ECOG PS was devised, in parallel with an increasingly sedentary society.

The ECOG PS remains a well-validated cancer assessment tool, but its "construct validity" as a measure of PA in our cohort was poor. In fact, one of the original aims of this study was to explore whether accelerometry could refine the often difficult cut-off between PS 2 and PS 3; clearly the results of this study precluded that. The biological implications of low PA levels found in this study are not fully known. If ECOG PS does not reflect actual PA, what of the underlying assumption that it predicts for treatment toxicity and survival because prolonged periods at rest reflect morbidity? Many chemo- and radiotherapy treatments are less toxic than decades ago, and supportive care measures have advanced, as outlined in Chapter 1, so cancer therapies can be tolerated by less "fit" patients. ECOG PS scoring is a health provider judgement call and may always have reflected patients' desire to present as well enough to tolerate, and the physician's assessment of fitness for, the treatment available. If PS assigned in this cohort had reflected actual PA, most would have received a PS score of 3.

Disturbances in the 'sleep-wake' cycle can adversely affect many cancer patients (Dahele et al., 2007). Night time PA was not measured. It is possible that some patients were 'up and about' at night while unable to sleep which was not taken into account in this study, however as the ECOG PS refers to 'waking hours' it was felt that measuring night time PA would be overly burdensome to participants in this study.

There has been a paradigm shift in oncology towards more personalised medicine, with the use of highly advanced nuclear medicine imaging techniques and molecular sub-classification of cancers as outlined in Section 1.1.2 (page 2). However, highly subjective PS scoring still remains a core element of the decision-making process in cancer patients (Terret et al., 2011). This study extends prior work in the area by comparing accelerometry - a more global measure of PA and an essential determinant

of physical function, to physician assigned PS in a relatively large heterogeneous cancer population. It would be premature to advocate the immediate incorporation of new technology to assess PA levels into the clinical assessment of patients. Nonetheless, this study using accelerometry raises questions about how fitness for cancer therapy is assessed in a sedentary society. It was found that the ECOG PS score did not reflect objective activity levels but it still differentiated between the activity levels of patient groups. This study showed it was practical to measure PA using accelerometry in this population and this measure may merit further investigation as an adjunct to clinical decision-making and clinical trial entry, especially for intensive treatment.

Chapter 4

4.1 Introduction

From Study I, (Chapter 3) PA levels were low at the time of cancer diagnosis. These findings may have been disease or treatment related, e.g. due to the effects of recovering from surgery, or due to habitually low levels of activity. PA levels would be expected to decrease during the active treatment phase due to the side effects of treatment (Section 1.1.2 page 2).

However, once treatment has ceased and its acute effects have subsided, PA levels would be expected to increase. The impact of the cancer diagnosis and its resultant 'teachable moment' (Demark-Wahnefried et al., 2005) might be expected to prompt behavioural change which could be reflected in higher PA levels after treatment has ceased. However, most research as outlined in Section 1.4 (page 33), does not appear to support this expectation of higher PA levels after treatment has ceased.

In much of this research, self-report measures, which are prone to inaccuracies (Prince et al., 2008, Sallis and Saelens, 2000a) were predominantly used (Table 1.3 page 35). The review by Rodgers et al. (2010) only identified five studies within the cancer literature which incorporated objective PA measurement using accelerometers as outlined in Section 2.2.2.2 (page 71). As detailed in Section 2.2.2.2 (page 72), accelerometers are a more robust and precise tool for measuring PA. No study has previously measured PA levels serially over the first year after chemotherapy has been completed using a robust objective method. Measuring PA levels objectively during this time period is important to inform interventions which should ideally take place within this time period (Courneya and Friedenreich, 2001).

The overall aim of this study was to assess objective and self-reported PA levels of breast and colo-rectal cancer survivors during the first year after completion of chemotherapy, and to compare activity with that of a matched non-cancer control group.

Objectives of this Study were

1. To describe the objective and self-reported PA levels of a breast and colo-rectal cohort at time points of 6 weeks (T0), 6 months (T1) and 1 (T2) year after cessation of curative-intent chemotherapy.
2. To ascertain fatigue and quality-of-life (QOL) levels of the breast and colo-rectal cancer cohort at the above time-points.
3. To compare PA levels of the cancer cohort with an age, gender and highest educational attainment matched non-cancer controls.

4.2 Methods

4.2.1 Setting and Participants

4.2.1.1 Cancer Cohort

Potential participants were approached in the chemotherapy day ward in St. James's Hospital during scheduled appointments for treatment or physician visits. The study was explained to each patient and an information leaflet as well as a consent form was supplied to prospective participants.

The eligibility criteria of the cancer cohort was as follows;
Inclusion Criteria:

1. Breast and colon cancer patients who had completed > 80% of scheduled adjuvant chemotherapy treatment for a first primary cancer.

Exclusion Criteria:

1. Evidence of confirmed active cancer spread or metastasis development.
2. A confirmed pregnancy.
3. A myocardial infarction in the previous year, significant chronic lung disease or cardiovascular disease which could have interfered with their mobility level or any co-morbidity which significantly impaired functional ability.

Participants were withdrawn before the 12 month time point if there was an intervening severe cardiac or respiratory illness or other disease which caused significant functional impairment or if there was confirmed return or spread of the cancer before the 1-year time-point post cessation of chemotherapy. Informed written consent was collected and institutional ethical approval was granted prior to the commencement of the study (Appendix XI and XIII). An additional ethical amendment (Appendix XI) was granted to seek additional information from participants on highest educational achievement, as this information was not initially sought[17]. The categories given were until primary education, until inter-certificate (or equivalent), leaving certificate (or equivalent), certificate/diploma level course, degree level or post-graduate level.

4.2.1.2 Non-Cancer Controls

As pre-diagnosis PA levels are impossible to measure accurately, a comparison was made between age, gender and highest educational achievement matched non-cancer controls corresponding with eligibility criteria detailed above. This design facilitated that, as far as possible, the only variable which differed between study participants and control subjects was the cancer diagnosis itself. The non-cancer control subjects were recruited through institutional e-mails as well as from those known to the researcher. Activity levels were assessed using the RT3 accelerometer and IPAQ questionnaire at a single time-point only.

Matched data was available for 23 participants. Two matches were generated for eleven of the participants and 1 match for twelve of the participants. In the case of

[17] Statistical advice (subsequent to the original design and ethical application) emphasised the need for accurate information on highest educational achievement for optimal matching of non-cancer controls to study participants. The medical chart was deemed insufficient to provide this information, therefore an ethical amendment was sought to allow written contact with participants to provide detail of their highest educational achievement. Out of 29 participants contacted, no response was received for three participants, and one participant was unwilling to divulge this information for study purposes.

two matches for a participant, random number tables were used to choose the match used for comparison purposes.

4.2.2 Study Procedure

The purpose of the study was explained and an information leaflet as well as consent form was supplied to each potential participant. If interest was expressed, participants received a follow-up phone call leading up to their 6-week time-point post-completion of chemotherapy. All participants gave written informed consent (Appendix XIII) and an RT3 accelerometer (Section 2.2.2.2.1 page 79), an activity diary, the IPAQ questionnaire (Section 2.2.2.3.2, page 83) and the EORTC-QLQ C-30 questionnaire (Section 2.2.5.2 page 95), as well as a stamped-addressed envelope was posted to each patient leading up to the time-points of 6 weeks (T0), 6 months (T1) and 1 year (T2) post-cessation of chemotherapy. A follow-up phone call confirmed instructions for wearing the accelerometer. Participants were required to wear the monitor for 7 days, and to post the completed questionnaires back in the stamped-addressed envelopes provided. This procedure was repeated at the 6-month and 1-year time-points. Questionnaires were completed in the participant's home, and the accelerometer was worn for the duration of seven days.

4.2.3 Study Measures Used

Objective PA was measured using the RT3 accelerometer (Section 2.2.2.2.1 page 79) (Appendix I). Self-report PA was measured using was the International Physical Activity Questionnaire (IPAQ), (Appendix II), which is outlined in Section 2.2.2.3.2 (page 83). The QOL questionnaire used in this study was the EORTC QLQ C-30, (Appendix VII), which is outlined in Section 2.2.5.2 The fatigue measure used in this study was the Brief Fatigue Inventory (Appendix V), as detailed in Section 2.2.4.2 (page 92). Body mass and height were measured by oncology nursing staff using a Seca 764 electronic weighting and measuring station during scheduled appointments in the oncology day ward of St. James's Hospital. Weight was measured at T0 and T2. Weight at the time of cancer diagnosis was also available from the medical charts. As some of the study time

points may not have corresponded exactly with patient appointments in St. James's Hospital during which weight was recorded; the weight which corresponded closest with the study assessment date was taken. In cases of missing data (17.3% of cases) or a time difference of greater than 12 weeks (24% of cases) from the time weighed in St. James's Hospital, self-reported weight was used, if available. Additional measures extracted from the medical chart included socio-demographic data such as age and sex and clinical variables included disease stage, nature and schedule of treatment as well as co-morbidities and medications.

4.2.4 Statistics

Data were tested for normality using a Kolmorgorov-Smirnof test. Normally distributed data were compared across time-points using the general linear model (GLM) procedure. Sphericity was tested, and if violated, the F value generated by Greenhouse-Geiser test was taken. The Least Significant Difference was used to control for multiple pair-wise corrections. The GLM procedure was also used to compare participants with matched controls. F-values were reported where appropriate which refer to the test-statistic. This value is the variance of the group means/mean of the within group variances. Non-normally distributed data was compared using the Friedman's test. Data was examined to assess where significance existed. Associations between variables were measured using Pearson's Product Moment Correlation Coefficient.

The clinical relevance of changes in the EORTC scale was calculated using the effect size, in which an effect size of 0.20-0.49 reflected a clinically relevant difference, an effect size of between 0.5-0.8 reflected a moderate clinically relevant difference, and >0.8 reflects a large clinically relevant difference (Cohen, 1988). A difference of 5-10 points on the QOL subscale of the EORTC-QLQ-C30 was indicative of a small clinically relevant difference, a difference of 10-20 points indicated a moderate clinically relevant difference, and a difference of > 20 points a large clinically relevant difference (Osoba et al., 1988). The internal consistency of the multi-item questionnaire scales was assessed by Chronbach's alpha (Cronbach, 1951).

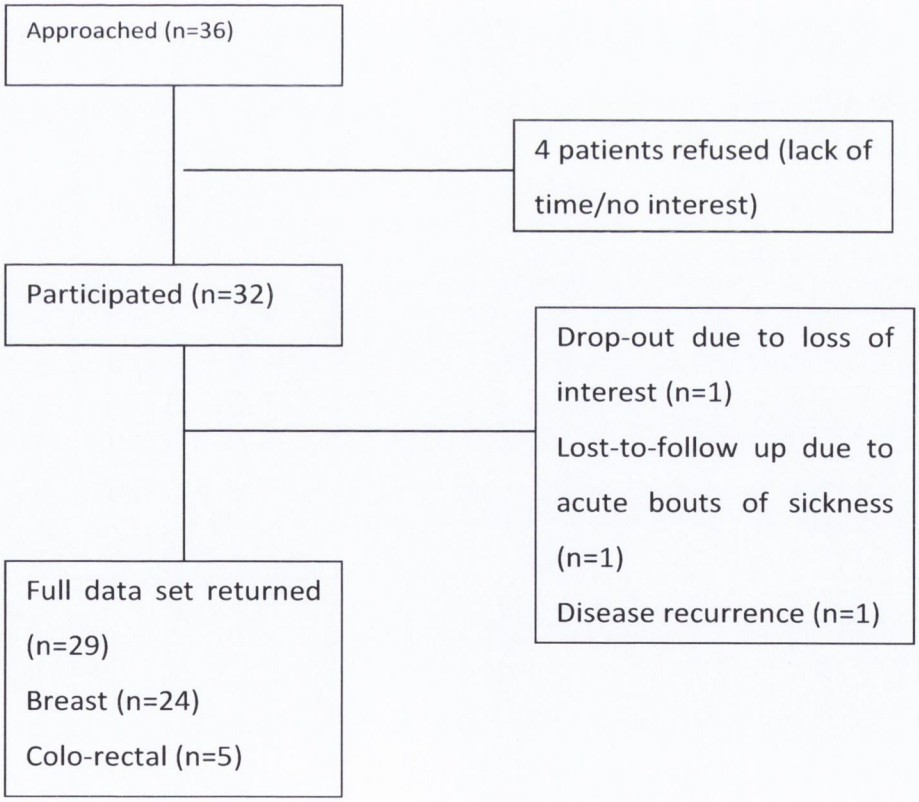
Recommended internal consistency estimates greater than 0.7 are recommended (Nunnally, 1978). In this study, internal reliability estimates for the functioning scales were high at 0.81 at T0, 0.88 at T1 and 0.82 at T2. Estimates for the symptom scales were acceptable at 0.71 at T0, 0.79 at T1 and 0.74 at T2. P values <0.05 were taken to be significant. Data was analysed using SPSS 16.0.

4.3 Results

4.3.1 Demographic details

The original intent was to accrue a minimum of 25 patients. Fig. 4.1 reports the flow of participants through the study.

Fig. 4.1 Flow-chart of participants through the study



The mean (SD) age of the combined study participants was 52 (11.8) years, with a range of 25-75 years. The mean (SD) age of the breast cancer cohort was 50.9 (11.6)

years, range 25 – 70 years and the colo-rectal cancer cohort was 57.4 (12.8) years, range 41-75 years. Table 4.1 details personal characteristics of the cancer cohort.

At T0[18] 19.2% (n=5) had a healthy BMI (<25), at T1 this remained at 19% (n=5) and at T2 this decreased to 12% (n=3). At T0 and T1 80.8% were overweight or obese (BMI> 25), and this increased to 88% at T2. Table 1 presents the descriptive characteristics of study participants.

At T0 7% (n=2) of participants were engaged in paid work outside the home. At T1 this was 38% (n=11), and at T2 this was 48% (n=14).

Table 4.1 Personal demographics of cancer cohort.

Demographic Characteristic	**% (n=28)**
Gender	
Female	89.7% (26)
Male	10.4% (3)
Marital Status	
Married	72.4% (21)
Separated	6.9% (2)
Single	20.7% (6)
Ethnicity	
Irish	89.7% (26)
Eastern European	3.5% (1)
Indian	3.5% (1)
Phillipino	3.5% (1)

[18] BMI data was based on available recorded weight, this was available for n=26 participants at T0, n=26 for T1, and n=25 for T2.

4.3.2 Disease and Treatment Characteristics

Details of breast and colo-rectal cancer diagnosis are shown in Table 4.2A and treatment details are shown in Table 4.2B.

Table 4.2a Disease details of participants.

Breast Cancer cohort	**% (n=24)**
Cancer Stage	
Grade II disease	21.7% (5)
Grade III disease	65.2% (15)
Not stated	17.4% (4)
TNM Staging[19]	
T1N0M0	25% (6)
T1N1M0	8.3% (2)
T1N3M0	4.2% (1)
T2N0M0	16.7% (4)
T2N1M0	16.7% (4)
T2N2M0	16.7% (4)
T2N3M0	8.3% (2)
T3N2M0	4.2% (1)
Colo-rectal Cancer Cohort	**% (n=5)**
Adenocarcinoma	80% (4)
Not Stated	20% (1)
TNM Grading	
T1N1M0	20% (1)
T3N0M0	40% (2)
T3N1M0	20% (1)
T2N0M0	20% (1)

[19] TNM refers to the TMN staging system, T: Describes the size of the tumour, T3 is bigger than T1, N: Describes regional lymph nodes involved, N0: No tumour cells in regional lymph nodes, N3: tumour has spread to distant regional lymph nodes, M0: no distant metastasis.

Table 4.2b Treatment details of participants.

Breast Cancer Surgery	**% (n=24)**
Wide-local excision & Sentinel Node Biopsy	45.8 (11)
Wide-local excision & Axillary Clearance	8.3 (2)
Mastectomy & Sentinel Node Biopsy	4.2 (1)
Mastectomy & Axillary Clearance	41.7 (10)
Colo-rectal Cancer Surgery	**% (n=5)**
Anterior Resection	40 (2)
Hemicolectomy	60 (3)
Chemotherapy Regime	
Docetaxol, cyclophosphamide	16.7 (4)
Docetaxol, cyclophosphamide, bevacizumab	20.8 (5)
Docetaxol, , trastuzumab	4.2 (1)
Adriamycin, cyclophosphamide, paclitaxol	20.8 (5)
Adriamycin, cyclophosphamide, paclitaxol	4.2 (1)
Docetaxol, cyclophosphamide, paclitaxel, herceptin	8.3 (2)
Doxorubicin, cyclophosphamide, paclitaxel, herceptin	4.2 (1)
Doxorubicin, cyclophosphamide, taxotere	4.2 (1)
Docetaxol, carboplatin, herceptin	12.5 (3)
Docetaxol, carboplatin, herceptin, paclitaxol	4.2 (1)
m-Folfox 6	20.8 (5)
Chemotherapy Dose Density	
< 6 cycles	12.5 (3)
≥ 6 cycles	68 (17)
Not stated	16.7 (4)
Radiotherapy	
Treated with Radiotherapy	87.5 (21)
Not treated with Radiotherapy	12.5 (3)

Abbreviations: m-FOLFOX 6=Folinic acid, fluorouracil, oxilaplatin,

The mean number of days from surgery date to T0 (6 week assessment date) was 209.2 (±52.6) days. This was 201.4 (±53.4) days in the breast cancer cohort and 252.3 (±15.0) days in the colo-rectal cancer cohort.

No problems were associated with the study measures. The majority of questionnaires were completed without assistance. Seven percent of patients (n=2) patients expressed a wish to do the questionnaire over the telephone or in person due to reading/writing difficulties.

4.3.3 Changes in Study Outcome Measures

4.3.3.1 Physical Activity

Objective PA levels were measured using the RT3 accelerometer. Table 4.3 reports minutes spent in each domain of activity during waking hours. Figures 4.2a and 4.2b demonstrate time spent in moderate and vigorous activity and sedentary domains over the time course of the study. There were no significant changes over time for time spent in moderate and vigorous domains of activity ($F(2,56)=0.61$, $p=0.55$, effect size=0.02), or for time spent sedentary ($F(2,56)=1.5$, $p=0.23$, effect size=0.05).

Table 4.3 Minutes (mean(SD)) spent in sedentary, light, moderate and vigorous domains of activity and percentage of day in each domain at T0 (6 weeks), T1 (6 months) and T2 (12 months) after cessation of chemotherapy (n=29).

	T0	**T1**	**T2**	**P**
Sedentary (mins)	407.3 (115.2)	436.2 (126.5)	452.7(130.5)	0.23
Percentage (%)	52.4	54.7	56.6	
Light (mins)	315.7 (87.6)	317.8 (116.0)	304.3 (96.4)	0.68
Percentage (%)	40.5	39.9	38.1	
Moderate (mins)	43.4 (39.6)	35.5 (34.4)	35.3 (29.9)	0.62
Percentage (%)	5.6	4.5	4.4	
Vigorous (mins)	11.7 (21.9)	8.0 (12.3)	6.5 (9.5)	0.31
Percentage (%)	1.5	1.0	0.8	

Matched control data was available for 23 participants with a mean (SD) age difference between the cancer subjects and non-cancer controls of 2.1 (1.7) years. The mean (SD) BMI of the control group was 25.2 (3.9) with a range of 20.2 – 39.5. Sixty-one percent (n=14) had a normal BMI (<25), 35% were over-weight (n=8) and 4% were obese (n=1)). Mean (SD) time in minutes per day spent in sedentary activity was 388.7 (82.0), light was 391.2 (70.0), moderate was 58.9 (40.6) and vigorous was 19.0 (21.4). Time spent in moderate and vigorous domains of activity was compared across time to the matched control group, and although there was a trend towards significance between the control group and T2, no difference emerged ($F(3,66)=1.9$, $p=0.15$). There was a significant difference between the BMI of the control group and the cancer cohort at T3 ($p=0.01$).

Fig. 4.2a Time in moderate and vigorous activity at T0 (6 weeks), T1 (6 months), T2 (12 months) and matched control data (error bars represent 95% confidence intervals)

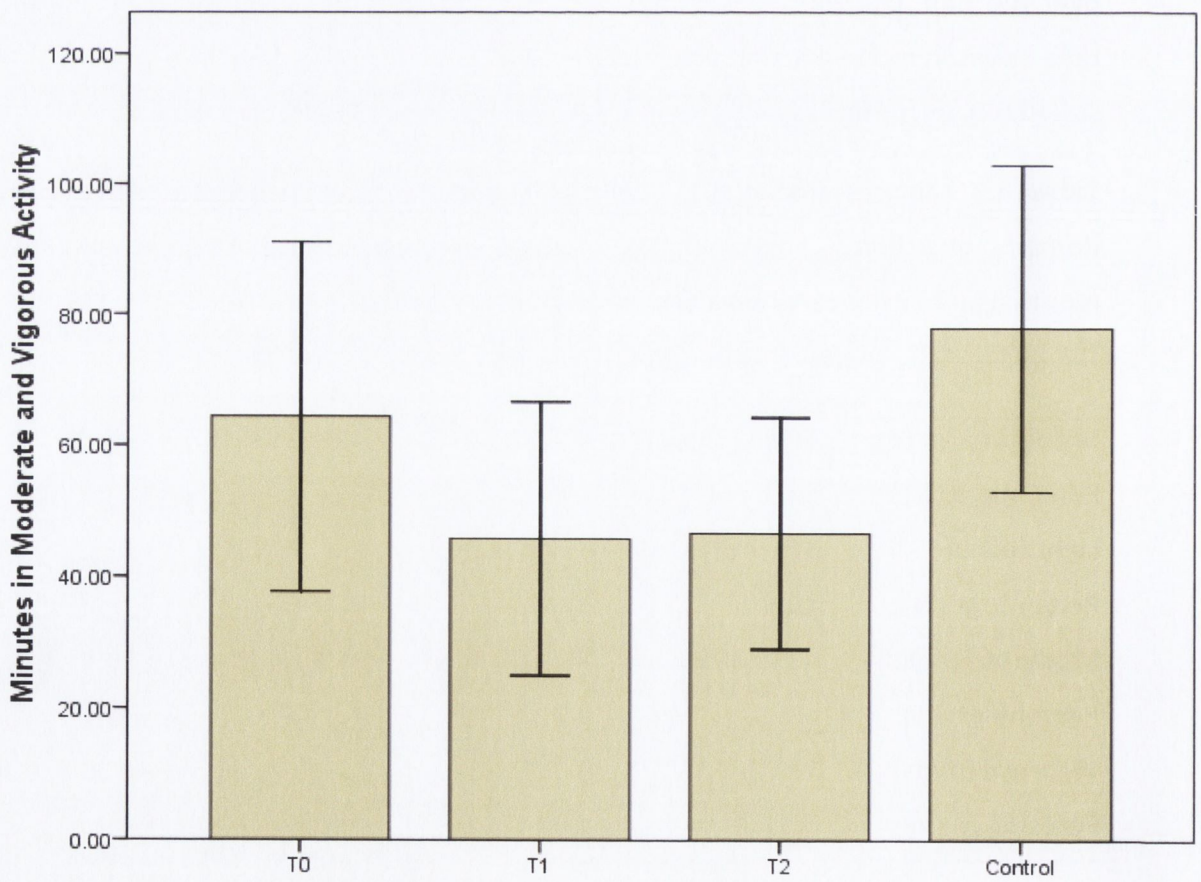


Fig. 4.2b Time spent sedentary at T0 (6 weeks), T1 (6 months), T2 (12 months) and matched control data (error bars represent 95% confidence intervals)

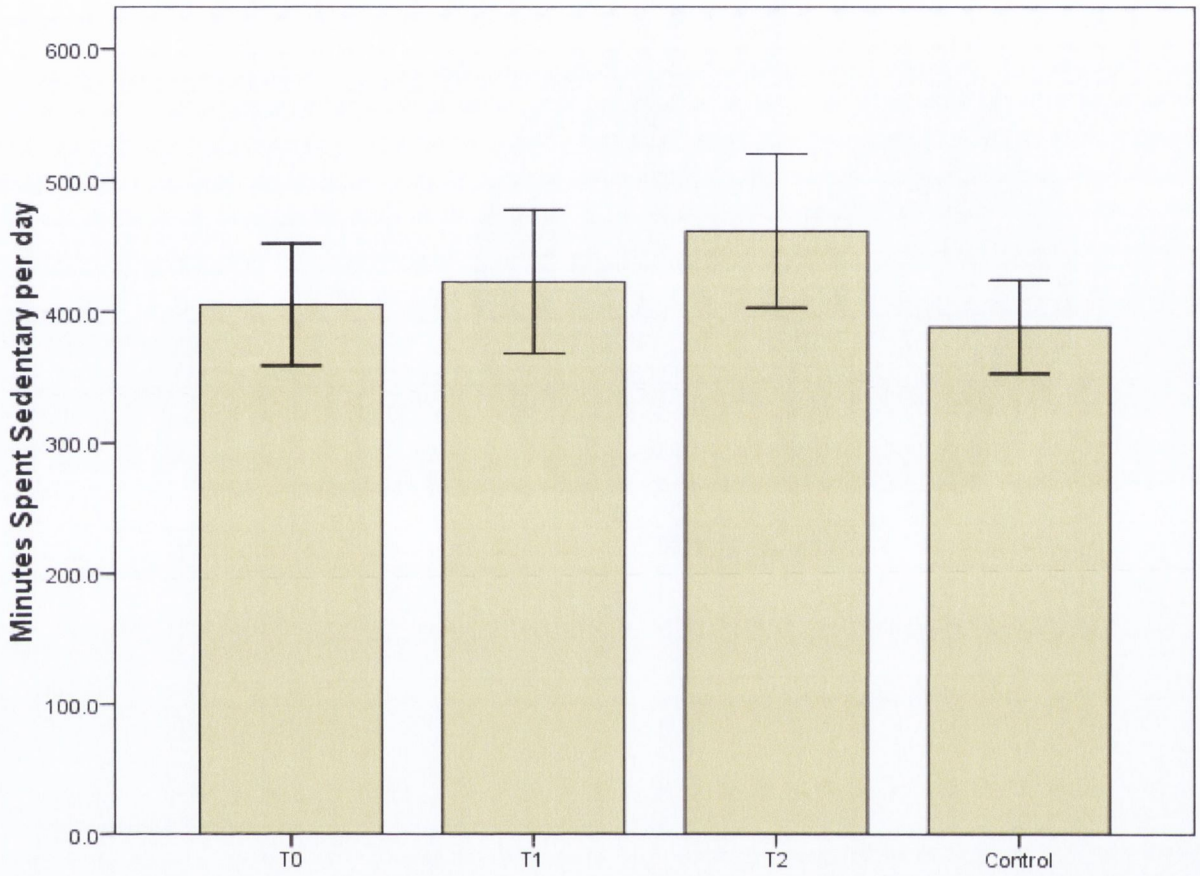


Fig. 4.3a Pie chart of objectively measured time in sedentary, light, moderate and vigorous domains of activity for cancer cohort at T0

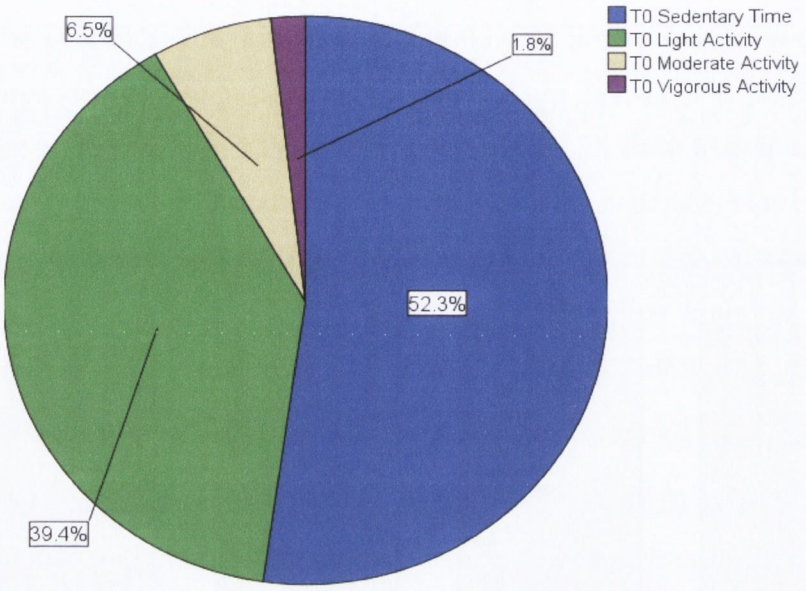


Fig. 4.3b Pie chart of objectively measured time in sedentary, light, moderate and vigorous domains of activity for cancer cohort at T1

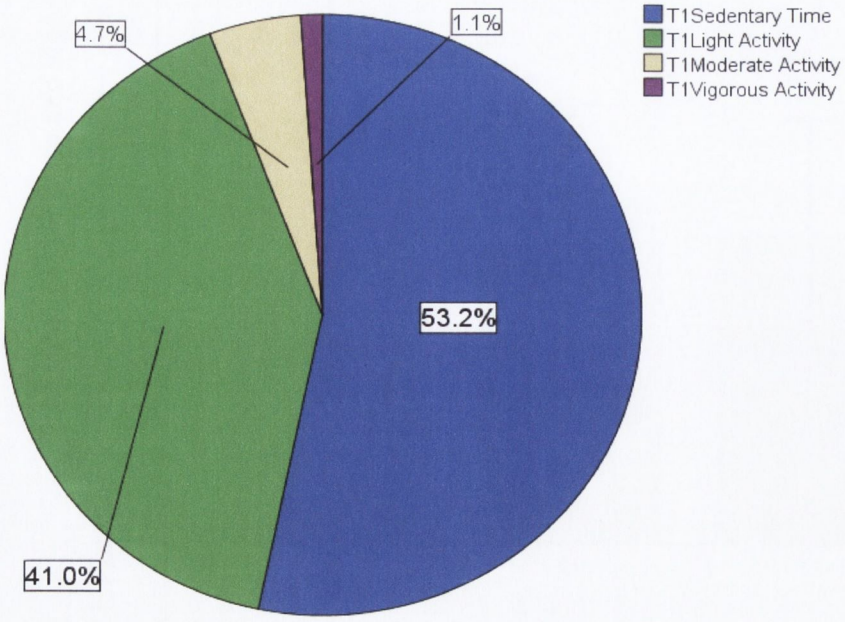


Fig. 4.4a Pie chart of objectively measured time in sedentary, light, moderate and vigorous domains of activity for cancer cohort at T2

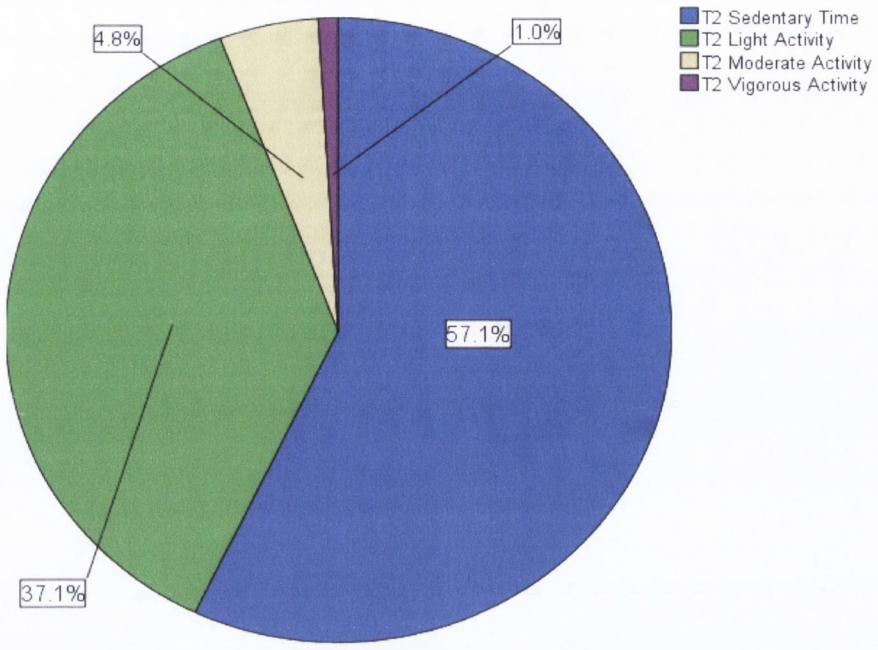
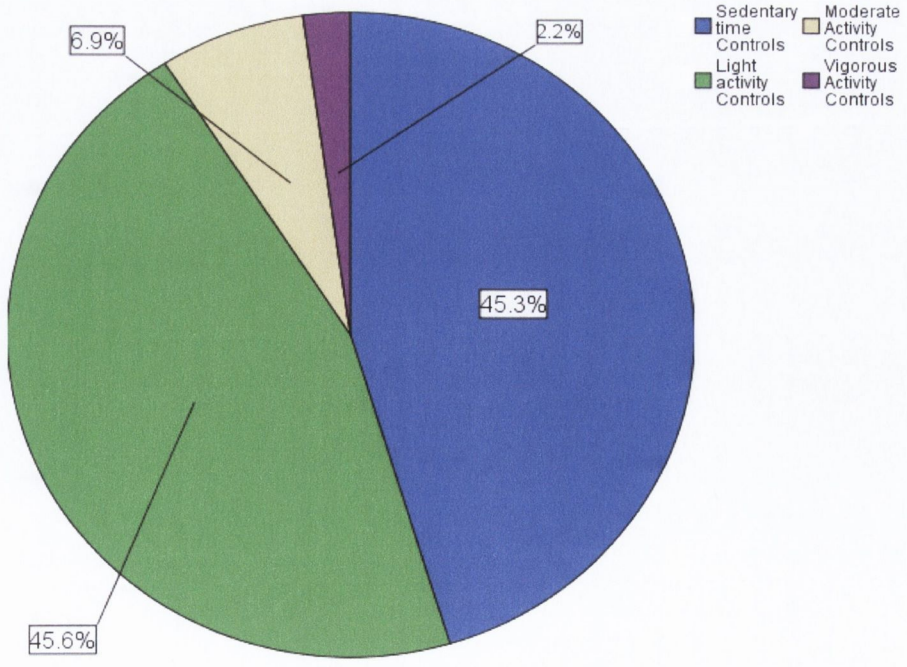


Fig. 4.4b Pie chart of objectively measured time in sedentary, light, moderate and vigorous domains of control data



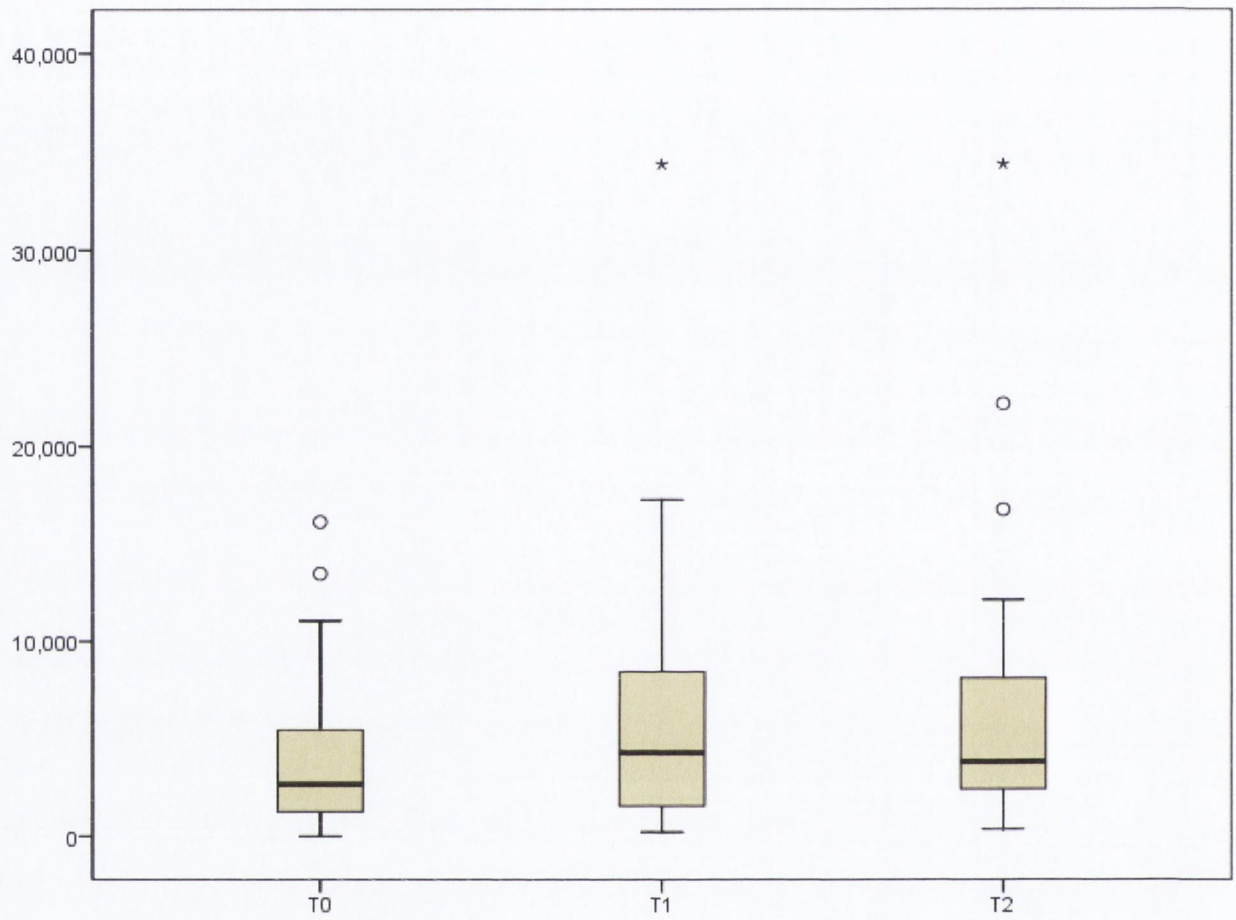
Self-reported PA was measured using the IPAQ questionnaire. As IPAQ scores were non- normally distributed, descriptive data was generated as medians and inter-quartile ranges. Table 4.4 displays IPAQ results; although there was a trend towards increased self-reported time in activity, no significant change was noted in variables over time.

Table 4.4 IPAQ results of participants at T0 (6 week), T1 (6 month) and T2 (1 year) time-points and Control Data (MET-mins refers to weekly activity).

	T0	**T1**	**T2**	**Control Data**	**p**
Total Walking	693.0	1039.5	1633.5	544.5	0.239
(MET-mins)	(198 – 1485.0)	(251.6 – 2326.5)	(519.8 – 3262.4)	(206.3-3368.5)	
Total Moderate	1785.0	2287	1905.0	2910	0.579
(MET-mins)	(427.5 – 3630.0)	(592.5 – 5730.0)	(1042.5 – 5760.0)	(1147.5-9112.5)	
Total Vigorous	0 (0 – 0)	0 (0 – 0)	0 (0 – 8.25)	0 (0-18)	0.218
Total PA	2655.0	4282.5	3823.5	3865.5	0.166
(MET-mins)	(1219.5 – 5467.5)	(1351.1 – 8709.8)	(2266.5 – 8292.3)	(2348.3-11578.5)	
Total Sit weekday (hrs)	5 (4.0 – 6.5)	4.5 (3.5 – 6.4)	4.9 (4.0 – 6.4)	4 (2 -7)	0.492
Total Sit weekend (hrs)	6.0 (4.0 – 7.0)	5.0 (3.6 – 6.9)	5.0 (3.3 – 6.4)	4.5 (2.3-5.9)	0.344
Reported mins walking/week	300 (60-570)	315 (76.3-775.0)	400 (157.0-802.5)	165 (62.5-787.5)	0.375
Reported mins in mod & vigorous activity/day	60.0(20.4-136.1)	94.7 (27.9-234.3)	82.2(36.4-233.6)	145.7 (40.7-2452.5)	0.163

Abbreviations: mins=minutes, hrs=hours, p refers to comparison between T0,T1,T2 and control data

Fig. 4.5 Box-plot of total physical activity (measured by IPAQ) at T0 (6 weeks), T1 (6 months) and T2 (12 month) time-points (* and ° denote outliers)



Using minutes spent walking (across leisure, transport, occupational and household domains), 70.4% (n=19) of cancer participants, met PA guidelines (>150 minutes per week), at T1 this was 64.3% (n=18) and at T2 this was 88.9% (n=24). Mean (SD) minutes in moderate and vigorous domains of activity were 103.1 (128.8) at T0, 138.3 (128.8) at T1, and 143.2(140.5)[20] at T3. Using minutes spent in moderate and vigorous domains of activity (across leisure, transport, occupational and household domains), 85.2% (n=23) adhered to PA guidelines (>150 minutes per week) at T0, this was 96.3%

[20] Although data were non-normally distributed, mean (SD) were generated to enable comparison with objective data and other studies.

(n=26) at T1, and 96.3% (n=26) at T2. Using only reported leisure-time PA, 25% were meeting PA guidelines at T0, 28.6% at T1 and 47% at T2.

Using objective PA data, 14% (n=4) met PA guidelines at T0, no participants met guidelines at T1, and 4% (n=1) met guidelines at T2.

There was a poor correlation between total PA from IPAQ and total time spent in PA from the RT3 at each of the three time-points (T0: r=-0.27, p=0.17, T1: r=0.02, p=0.94, T2: r=-0.06, p=0.78).

4.3.3.2 Body weight

There was a mean increase of 2.9kgs from cancer diagnosis to T2[21] corresponding to a significant difference in weight (F (48, 2) = 6.1, p=0.005, effect size =0.20) with the difference lying between weight at diagnosis and T2 (p=0.006). There was a mean increase in weight from T0 to T2 of 1.9kg corresponding to a marginally significant difference between weight at T0 and T2 (p=0.05). There was no weight difference by age with a median split at 50 years; weight gain (mean (SD)) in those <50 years (n=8) was 3.0(1.4) kgs and in those ≥50 years (n=17) was 2.9(5.9) kgs. There was a mean increase in weight of 2.6(4.9) kgs in the breast cancer cohort (n=23), and an increase of 6.6(2.8) kgs in the colo-rectal cancer cohort (n=2).

4.3.3.3 Quality-of-life

Quality of life was measured using the EORTC-QLQ C30 V3 questionnaire. Combined results as well as changes over time are shown in Table 4.5. A high score for a functional scale represents a high level of functioning, but a high score for a symptom scale/item represents a high level of symptomology/problems. Significant changes over time were shown for physical functioning, cognitive function, fatigue and sleep disturbance, although associated effect sizes were small. At T1 there was a small

[21] Based on full data set of n=25 (missing values for weight in n=4 of subjects) for T2.

clinically relevant (a change of between 5-10 points) decline in physical functioning, emotional functioning, financial impact and pain and improvements were noted in cognitive functioning, diarrhoea and nausea and vomiting as compared to T0. At T2 there were small clinically relevant improvements in role functioning, cognitive functioning, social functioning, fatigue, appetite loss, and financial impact compared to T0, and declines in physical functioning, as well as dyspnoea and diarrhoea symptoms. From T1 to T2, there were small improvements in role-functioning, social functioning and pain, and declines in diarrhoea symptoms. Symptoms of sleep disturbance improved moderately from T0 to T2, and financial impact improved moderately from T1 to T2 (decrease of 10-20 points).

Table 4.5 Combined Mean (SD) EORTC-QLQ C30 scores at 6 weeks after cessation of chemotherapy (T0), 6 months after cessation of chemotherapy (T1) and 12 months after completion of chemotherapy (T2), mean scores subtracted at time-points T1-T0, T2-T0, T1-T2, p values, effect size and time point of statistical difference.

				Adjusted difference in mean change with 95% confidence intervals					
	T0	T1	T2	T1-T0[a]		T2-T0[a]		T2-T1[a]	
				Mean	95% CI	Mean	95% CI	Mean	95% CI
Functioning Scales									
Physical	*84.8 (15.7)*	78.9 (20.1)	80.2 (20.0)	-6.9	-16.3→2.3	-5.0	-13.9→4.7	2.4	-12.7→8.0
Role	*73.6 (26.6)*	73.6 (26.6)	82.2 (26.3)	0	-13.7→13.7	8.6	-4.9→22.2	8.6	-22.2→-4.9
Cognitive	*73.3 (26.7)*	82.2 (25.6)	78.7 (29.5)	8.9	-4.5→22.4	5.5	-9.0→20.0	-3.5	-10.8→17.7
Emotional	*76.7 (23.3)*	70.8 (25.1)	72.1 (28.9)	-5.9	-18.4→6.6	-4.6	-18.1→8.9	1.3	-12.7→15.2
Social	*75.9(23.8)*	75.3 (30.0)	82.8 (24.2)	-0.6	-13.7→12.5	6.8	-5.5→19.3	7.5	-20.1→5.7
Global QOL	*68.4 (17.7)*	69.3 (20.6)	69.6(23.0)	0.9	-9.0→10.8	-1.2	-9.4→11.7	0.3	-11.5→10.9
Symptom scales									
Fatigue	*33.0 (20.0)*	29.1 (19.8)	24.5 (20.0)	-3.8	-14.1→6.4	-8.4	-18.7→1.9	-4.6	-5.7→14.8
Nausea & Vomit.	*7.5 (15.2)*	1.7 (5.2)	4.6 (9.9)	-5.8	0.08→11.6	-2.9	-9.5→3.7	2.9	-6.9→1.2
Pain	*20.7 (23.4)*	27.0 (26.5)	20.1 (27.2)	6.3	-6.6→19.2	-0.6	-13.7→12.5	-6.9	-6.9→20.7
Dyspnoea	*15.0 (26.1)*	15.0 (22.9)	20.7 (27.3)	0	-12.6→12.6	5.8	-8.0→19.5	5.8	-18.7→7.2
Sleep disturbance	*35.6(32.0)*	34.5 (28.9)	21.8(25.6)	-1.1	-9.8→21.7	-13.8	-28.8→1.1	-12.7	-1.5→26.7
Appetite loss	*9.2 (17.6)*	4.6 (19.4)	3.5 (10.3)	-4.6	-14.1→4.9	-5.8	-13.2→1.7	-1.2	-6.9→9.2
Constipation	*9.2 (15.2)*	13.8 (22.8)	9.2 (15.2)	4.6	-5.4→14.6	0	-7.8→7.8	-4.6	-0.5→9.7
Diarrhoea	*12.7 (22.6)*	6.9(16.4)	20.7(33.8)	-5.8	-15.9→4.5	8.1	-6.8→22.9	13.8	-27.5→0.1
Financial impact	*26.5 (32.6)*	32.2 (37.3)	20.7 (33.8)	5.8	-12.3→23.8	-5.8	-22.9→11.3	-11.5	-6.8→29.8

Abbreviations:vomit:vomiting

Table 4.6 Changes over time in QOL domains (General linear models used with normally distributed data, Friedman test for non-normally distributed data-no effect size or F score generated).

	F Value	P value	Effect size	Difference
Functioning scales				
Physical functioning	F(1.6, 56)=3.3	0.04*	0.11	T0 & T1 (p=0.03)
Role functioning	F(2,56)= 1.6	0.22	0.05	
Cognitive functioning	F(1.6,56)=3.5	0.05*	0.11	T0 & T1 (p=0.01)
Emotional functioning	F(2,56)=0.939	0.40	0.03	
Social functioning	F(2,56)=1.6	0.21	0.06	
Global quality-of-life	F(2, 56)=0.54	0.09	0.91	
Symptom scores				
Fatigue	F(2,56)=3.8	0.03*	0.12	T0 & T2 (p=0.02)
Nausea & vomit.		0.15		
Pain	F(2,56)=1.4	0.26	0.05	
Dyspnoea		0.20		
Sleep disturbance	F(2,56)=3.5	0.04	0.11	T0&T2 (p=0.37)
Appetite loss		0.10		
Constipation		0.30		
Diarrhoea		0.13		
Financial Impact	F(2,56)=2.3	0.11	0.08	

Abbreviations: Vomit: vomiting

QOL results were also expressed separately by disease location in Table 4.7a and 4.7b as different reference values pertain to each. Even though a large number of the functional and symptom scales were non-normally distributed (nausea and vomiting, dyspnoea, appetite loss, cognitive function, diarrhoea, financial impact, insomnia, social functioning and pain), means and SD were reported to enable comparison with the EORTC reference

values. There were no differences between the breast cancer cohort and the colo-rectal cohort at T0. At T1, fatigue (p=0.05) and dyspnoea (p=<0.001) symptoms were higher in the breast cancer cohort, and diarrhoea (p=0.05) symptoms were worse in the colo-rectal cohort. At T2, physical functioning (p=0.04), cognitive functioning (p=0.02) and fatigue (p=0.04) were higher in the breast cancer cohort than the colo-rectal cohort.

When compared to reference values Table 4.7a and 4.7b, higher mean scores than reference values were reported in the colo-rectal cohort for all functioning scores, lower than reference scores were noted for sleep disturbance (T1) constipation (T0, T1) diarrhoea at T0 and financial impact (T0, T1, T2). A higher functioning and symptom burden was reported in the breast cancer cohort, with higher mean scores than reference values for physical functioning (T1, T2), role functioning (T1, T2), emotional functioning (T0, T1, T2), social functioning (T2), global QOL (T0, T1, T2). Lower scores in the study cohort compared to reference values were noted for fatigue (T1), nausea and vomiting (T1), dyspnoea (T1, T2), sleep disturbance (T0, T1), diarrhoea (T0, T1, T2), and financial impact (T0, T1, T2).

Table 4.7a Mean (SD) EORTC-QLQ C30 Scores 6 weeks after cessation of chemotherapy (T0), 6 months after cessation of chemotherapy (T1) and 12 months after completion of chemotherapy (T2) in breast cancer cohort (n=24).

	T0	**T1**	**T2**	**Ref. Values***
Functioning scales				
Physical	85.8 (14.8)	76.4 (21.0)	79.4 (21.6)	78.4 (21.3)
Role	69.4 (30.2)	71.5 (28.0)	78.5 (28.0)	70.9 (29.9)
Cognitive	66.3 (30.7)	79.9 (26.0)	74.3 (31.1)	81.5 (21.8)
Emotional	73.3 (27.3)	71.4 (26.9)	71.5 (30.6)	68.6 (23.8)
Social	70.8 (27.0)	74.3 (28.2)	79.9 (25.5)	77.0 (27.1)
Global QOL	69.1 (17.1)	69.8 (19.8)	70.5 (23.7)	61.8 (24.6)
Symptom scales				
Fatigue	36.6 (20.3)	30.6 (21.3)	27.3 (20.7)	33.3 (26.2)
Nausea & Vomiting	8.3 (16.3)	1.4 (4.7)	4.9 (10.4)	7.7 (13.3)
Pain	26.4 (28.6)	8.3 (24.6)	22.9 (28.6)	28.7 (28.7)
Dyspnoea	16.7 (27.8)	22.2 (28.9)	23.6 (28.6)	18.1 (26.8)
Sleep disturbance	36.1 (33.9)	36.1 (29.3)	25.0 (26.5)	29.8 (31.6)
Appetite loss	13.9 (25.9)	8.3 (24.6)	4.2 (11.3)	18.5 (28.9)
Constipation	11.1 (23.4)	12.5 (23.7)	9.7 (15.5)	17.4 (27.2)
Diarrhoea	11.1 (21.2)	6.9 (13.8)	25.0 (35.8)	5.9 (15.4)
Financial impact	27.5 (32.8)	30.6 (39.2)	25.0 (35.8)	18.3 (27.8)

* Ref. Values; Reference values from EORTC QLQ-C30 reference values manual.

Table 4.7b Mean (SD) EORTC-QLQ C30 Scores 6 weeks after cessation of chemotherapy (T0), 6 months after cessation of chemotherapy (T1) and 12 months after completion of chemotherapy (T2) in colo-rectal cancer cohort (n=5).

	T0	**T1**	**T2**	**Ref. Values***
Functioning Scales				
Physical	80.0 (21.1)	85.0 (14.3)	84.0 (9.0)	79.2 (21.1)
Role	80.0 (18.3)	83.3 (16.7)	93.3 (9.1)	70.4 (32.8)
Cognitive	86.7 (14.0)	90.0 (22.4)	96.7 (7.5)	85.2 (20.4)
Emotional	76.7 (14.9)	68.3 (16.1)	71.7 (20.9)	68.9 (24.5)
Social	83.3 (16.7)	80.0 (21.7)	90.0 (14.9)	76.0 (28.6)
Global QOL	65.0 (22.4)	66.7 (26.4)	65.0 (20.8)	60.7 (23.4)
Symptom scales				
Fatigue	28.9 (18.6)	22.2 (7.9)	17.8 (9.9)	34.7 (28.4)
Nausea & vomiting	3.3 (7.5)	3.3 (7.5)	3.3 (7.5)	7.3 (17.2)
Pain	13.3 (18.3)	23.3 (19.0)	13.3 (18.3)	24.0 (29.6)
Dyspnoea	6.7 (14.9)	0.0 (0.0)	13.3 (18.3)	17.4 (26.3)
Sleep disturbance	26.7 (27.9)	33.3 (23.6)	13.3(18.3)	30.5 (32.6)
Appetite loss	6.7 (14.9)	0.0 (0.0)	0.0 (0.0)	19.1 (30.2)
Constipation	20.0 (18.3)	20.0 (18.3)	13.3 (18.3)	15.8 (27.9)
Diarrhoea	20.0 (29.8)	13.3 (29.8)	20.0 (44.7)	16.6 (27.6)
Financial impact	46.7 (44.7)	40.0 (27.9)	20.0 (44.7)	13.6 (26.3)

** Ref. Values; Reference values from EORTC QLQ-C30 reference values manual.

4.3.3.4 Fatigue

Fatigue across the three time points was measured using the Brief Fatigue Inventory (BFI) (Table 8). At T0 40.7% (n=11) reported 'severe fatigue' as per the BFI measure (Section 2.2.4.2 page 92), at T1 this was 44.4% (n=12) and at T2 this was 33% (n=10). Separated by disease location, the breast cancer cohort 38.1% reported severe fatigue at T0, this was 48% at T1 and 38.1% at T2. For the colo-rectal cohort, this was 50% at T0 and T1, and 25% at T2.

Table 4.8 Brief Fatigue Inventory results across T0 (6 weeks), T1 (6 months) & T2 (12 months after cessation of chemotherapy (n=28).

Mean (SD)	**T0**	**T1**	**T2**
GFS*	3.4(2.3)	3.5(2.4)	2.8(2.4)
Interference Score	3.2 (2.5)	2.8(2.6)	2.3(2.5)
Mean fatigue Score	4.1(2.6)	4.4(2.5)	3.4(2.7)

*GFS; Global fatigue score

Comparing the Global fatigue score across the 3 time-points, no difference was found across time-points ($p = 0.182$). A moderately strong inverse correlation was found between global fatigue score and global QOL for T0 ($r=-0.57$, $p=<0.001$), T1 ($r=-0.78$, $p< 0.001$) and for T2 ($r=-0.64$, $p<0.001$). Comparing the Global fatigue score to time spent in moderate and vigorous domains of activity , measured objectively; there was a moderately strong relationship observed at T0 ($r=0.47$, $p=0.01$). This was not significant at T1 or T2 ($r=-0.32$, $p=0.03$, and $r=0.17$, $p=0.40$ respectively). There was a significant association between the Global fatigue score (From the BFI) and BMI at T0 ($r=0.49$, $p=0.01$), and at T2 ($r=0.57$, $p=<0.001$).

4.4 Discussion

The main aim of this study was to evaluate PA patterns of breast and colo-rectal cancer patients during the first year after completion of adjuvant chemotherapy. As pre-diagnosis PA levels are very difficult to assess, the approach taken in this study was to compare levels to those of age, gender and educationally matched normal control subjects. A number of studies have explored PA longitudinally after a cancer diagnosis; however, a limitation of these studies was that subjective methods were used to evaluate PA. This is the first longitudinal study which assessed objective PA patterns within a cancer cohort during the first year after cessation of chemotherapy.

Contrary to expectations, PA levels remained the same during the first year after cessation of chemotherapy. A trend was shown of decreasing objective PA, however these values did not reach statistical significance. Self-report PA showed the opposite trend of increasing PA over the time course of the study. It was found that the cancer cohort was no less active that the matched control group with regard to both objectively measured and self-report PA, which infers that PA levels may have been similar to pre-diagnosis levels reflecting low societal levels of PA.

Other studies have compared cancer survivors to non-cancer controls and similarly, little difference was found in activity levels between the cancer cohort and the non-cancer controls (Grimmett et al., 2009, Eakin et al., 2007, Courneya et al., 2008a). However, varying results have been reported as another study reported greater PA levels among cancer survivors (Bellizzi et al., 2005), and a further study reported the same or lower PA levels among cancer survivors (Coups and Ostroff, 2005).

Another approach taken by many studies is to recall pre-diagnosis PA retrospectively. Some studies report that pre-diagnosis PA levels reflect post diagnosis activity (Friedenreich et al., 2009, Courneya and Friedenreich, 1997a) and others have found that

many cancer survivors do not return to their pre-diagnosis PA levels (Courneya and Friedenreich, 1997b, Irwin et al., 2003, Blanchard et al., 2003), however, retrospectively recalled PA is prone to recall bias.

Objective data from the present study showed that approximately 50% of waking hours were spent sedentary, equivalent to approximately 7 hours per day, and similar levels were found in the control group. Although seemingly high, these values compare favourably with reported findings by Lynch et al., (2010) in a cancer cohort in which 66% of time was spent sedentary, although absolute values were not quantified. It is not known if the cancer cohort in this study were genuinely more active or if was related to discrete cut-off points for domains of activity pertaining to different accelerometers, as the Actigraph accelerometer was used in the study by Lynch et al., (2010) as opposed to the RT3 accelerometer used in the present study. Similar levels of sedentary time (8.4 hours), corresponding to 56.6% of the day, was reported in a 'healthy' Australian population (n=173) (Healy et al., 2008b). Of note, time spent in moderate and vigorous domains in the present study was similar to reported levels of 4.4% in the study by Healy et al., (2007) and higher than levels reported by Lynch et al., (2010) of just 1%.

There may be many reasons why objective PA levels remained the same during the time course of the study; it may simply be that patients were well-intentioned at the 6-week time-point as the acute effects of chemotherapy would be expected to lessen at this time, corresponding with an increase in energy levels. This could also reflect the return to work as 6 weeks post completion of chemotherapy, 7% had returned to paid employment outside the home, and by 1 year after completion of chemotherapy this figure had increased to 48%. Most occupations are sedentary, and the return to work may have left little time for recreational activity. The vast majority of participants underwent radiotherapy treatment, which in many cases would have over-lapped with the 6-week time-point after cessation of chemotherapy in which most activity was registered. It is possible that walking related to getting to and from daily radiotherapy treatment may have elevated activity readings beyond normal levels. The wash-out period of

chemotherapy regimens and latent treatment effects (Courneya and Friedenreich, 1997b) are not fully known which may have metabolic consequences as by 1 year post cessation of chemotherapy, one third still complained of 'severe fatigue'. PA counselling/advice is not part of the survivorship care plan or standard recommendations (Irwin, 2009) after a cancer diagnosis, so patients may not be fully aware of the importance of resuming PA after cessation of treatment.

This study showed a divergence between objective and self-report PA. Comparing these different PA quantification methods, participants over-estimated time spent in moderate and vigorous PA levels by approximately two-fold, which highlights the difference in perception between PA actually performed and self-report PA. There was also a considerable difference when comparing adherence levels to exercise guidelines from self-reported and objective methods. This may be related to the suggestions for domains of activity in the IPAQ which may lead to confusion in terms of its wording – it may be debatable whether gardening or 'yard work' is performed at a sufficiently high intensity to be considered truly high intensity. Also 'carrying light loads, sweeping, washing windows and raking in the garden or yard' as well as 'washing windows, scrubbing floors and sweeping' are all included under 'moderate' PA. The difficulty is that individuals may carry out these activities at a low intensity level or pace, thereby not reaching the threshold of moderate activity measured using accelerometer cut-off points. In addition, the self-report measure of PA used in this study may have falsely elevated time in activity as domains of transport, occupational, household and leisure time activity are included in this questionnaire, whereas many self-report questionnaires do not include domains such as transport or occupation. Thus, MET-minute values in this study were noted to be exceptionally high and time spent in activity was overestimated by about 30% compared to objective measurement.

The majority of studies in the literature examine PA and cancer employed self-report methods. This study highlights the difficulty of comparing self-report methods to PA guidelines. Including self-reported time spent walking across leisure, transport,

occupational and household domains, a much higher percentage of participants met PA guidelines of >150 minutes per week than leisure-time walking only. To enable comparison to many of these studies, only reported leisure-time activity was extracted from the IPAQ questionnaire, revealing that 25% were meeting PA guidelines at T0, 28.6% at T1 and 47% at T2 which is comparable to many studies quoted (Andrykowski et al., 2007, Pinto et al., 2002b, Milne et al., 2007, Blanchard et al., 2008, Lynch et al., 2007a, Eakin et al., 2007). This highlights the low levels of planned PA - most of activity generated by participants was non-planned household or occupational activity, although incidental PA may be more important in terms of overall energy expenditure balance.

The pattern of self-reported PA increasing over time replicates results reported by Emery et al., (2009), where it was found that PA gradually increased in the first 18 months to a peak level then declined steadily over the subsequent 18 months. Many other studies found a decline in PA after a cancer diagnosis (Irwin et al., 2003, Courneya and Friedenreich, 1997a) with the largest decreases for recreational activity (Irwin et al., 2003). Declines in PA after a cancer diagnosis were also reported by Littman et al., (2010), who reported that PA levels decreased by 50% in the 12 months after diagnosis (from 18.8 to 9.2 MET-hours/wk). PA levels increased by the time period 19-30 months post-diagnosis, but remained about 3 MET-hours/wk lower than before diagnosis. As PA was not measured beyond the 1-year time point in the present study, it is not known whether the same pattern of increasing PA levels after this time-point would be replicated. Other studies showed a lack of change in average PA levels at the time-point of 6-18 months post diagnosis (Harrison et al., 2009).

The relationship between decreased PA levels, weight gain and QOL after cancer treatment is complex as many factors influence PA. In a 5-year follow-up study it was found that physical health status, HRQOL, depressive symptoms and social support influenced PA (Emery et al., 2009). It is thought that lower PA levels and weight gain may increase fatigue and other symptoms such as constipation and dyspnoea thereby negatively influencing QOL (Voskuil et al., 2010). A moderately strong inverse association

was shown between BMI and time in moderate and vigorous domains of activity. This mirrors findings by Lynch et al., (2010) and highlights the importance of PA as a weight control strategy.

Although a moderate correlation emerged between BMI and time spent in activity at the six-week time-point, no correlation was noted at the six month or 1-year time-point. This study showed a worrying trend of increasing BMI from diagnosis to the first year after cessation of chemotherapy, with only just over 10% displaying a healthy BMI by the 1-year time-point. Although the non-cancer control group was matched by age, gender and education, large differences in terms of BMI between the groups were noted with 61% of the control group exhibiting a normal BMI. Of note, this is higher than the value of 43% of Irish people reported to have a normal body weight (Report of the National Taskforce on Obesity, 2005). A significant weight gain in a breast cancer cohort has previously been defined as a weight gain of >2.5kg (Ingram and Brown, 2004). The mean change observed in this study was 2.6kg from diagnosis to one year after cessation of chemotherapy. This increase in weight represents a worrying trend as increased weight gain after a breast cancer diagnosis is associated with an increased risk for recurrence and death (Doyle et al., 2006, Kroenke et al., 2005). Adjuvant chemotherapy treatment has been linked to progressive weight gain (Vance et al., 2010). A longitudinal study which reviewed 185 women diagnosed with Stage I-III breast cancer, reported a mean weight change of 1.5kgs at year one, 2.7kgs at year two and 2.8kgs at year three (Makari-Judson et al., 2007). Similarly, a study of (n=53) pre-menopausal women with breast cancer reported a mean weight gain of 2.5 kg at 6 months and 2.1 kg at 1 year post cessation of adjuvant treatment (Demark-Wahnefried et al., 2001). In the study by Voskuil et al (2010), BMI did not change over the time from pre-diagnosis to 1 year and 2 years after the start of endocrine therapy-but only one third were treated with chemotherapy. There is a suggestion that higher weight gain may occur in premenopausal women which corresponds with treatment-induced menopause (Vance et al., 2010). In this study it was not recorded whether patients were pre-menopausal or post-menopausal, however using a conservative age cut-off of age 50 years, there was no difference observed in this study

between the weight gain of those age <50 years versus those > 50 years. In the Health, Eating, Activity, and Lifestyle (HEAL) study, women who were obese at baseline (4-12 months post diagnosis) had larger decreases in recreational PA and vigorous intensity activity compared to normal weight women (Irwin et al., 2003). These relationships did not hold true in this study as no clear relationship emerged between high BMI and either objectively measured or self-report PA. This study may have been too small to show relationships clearly. It is not known whether an increase in PA or a decrease in BMI is a more beneficial therapeutic target, but they are inextricably linked; a PA intervention which targets both which would be the ideal.

In this study lean body mass was not measured. BMI was measured which has limitations as outlined in Section 2.2.6.1 (page 98). Literature in this area using more advanced testing methods suggests a pattern of 'sacropenic obesity' (Rock and Demark-Wahnefried, 2002), which is an increase in adipose tissue, without an associated increase in lean tissue, as opposed to 'normal' weight gain which results in increases in adipose tissue as well as lean tissue.

Weight gain after a breast cancer diagnosis has been associated with earlier recurrence and shorter survival (Chlebowski et al., 2002), with most explanations focusing on adiposity rather than body weight per se (Irwin et al., 2005). Thus, the worrying rate of overweight and obesity among the cancer cohort reported in the present study is likely to predispose subjects to other chronic diseases and even possibly a higher rate of recurrence. Even though PA levels were similar between the cancer cohort and matched control group -a higher overall volume of PA or less time sedentary may be required to reverse the trend towards weight gain in the cancer cohort.

Overall, QOL levels in this study were generally higher than reference values from the EORTC manual. However, reference values are based on a mixed population of patients from diagnosis to many years after treatment as well as metastatic patients. Despite this, no ceiling effect was observed as a number of QOL measures changed positively over the time-course of this study. Of note, physical functioning was highest at the 6-week time-

point and decreased significantly by 6 months. This may have mirrored the downward trajectory in objectively measured PA. Physical functioning increased slightly by 1 year post cessation of chemotherapy but did not return to 6-week levels.

The EORTC QOL questionnaire was also used by Voskuil et al., (2010). Functional values were generally higher in the present study, although some of the symptom scores in were higher in this study (pain, dyspnoea, diarrhoea, and financial impact), possibly indicating a higher symptom burden of patients in the present study. However, the population in the study by Voskuil et al., (2010) were breast cancer patients, 1 and 2 years after the start of endocrine therapy and only one third were treated with chemotherapy, so the cohort may not have been directly comparable to the sample used in this study. A striking finding in this study was the large number reporting financial problems. This may be related to the fact that a number of participants couldn't work due to disease or treatment related restrictions, it could also mirror more widespread financial difficulties associated with the economic recession in Ireland. It did decrease over the time course of the study however, presumably as more participants returned to work, easing the financial burden.

Of note, QOL was lower in the breast cancer group than the colo-rectal cancer group, this seems surprising as larger surgery and more dose-dense chemotherapy regimens were endured by the colo-rectal cohort. It may be that colo-rectal cancer patients may have anticipated a higher disease burden at the outset than breast cancer patients, and then post-treatment reported a more optimistic self-assessment, or simply that patients with colo-rectal cancer in this study had a good QOL.

Fatigue decreased by 1 year post cessation of chemotherapy and closely linked to this, 'sleep disturbance' (from the EORTC questionnaire) improved by 1 year post cessation of chemotherapy. Cognitive function improved by 6 months post cessation of chemotherapy. It is possible this may be related to the phenomenon of 'chemo-brain'. Chemo-brain has been described as 'foggy thinking' following chemotherapy treatment. The notion of chemo-brain has often been derided, as there can be many confounding variables such as co-existing depression and fatigue which may also influence cognition

(Hede, 2008). Therefore, it is difficult to speculate on the cause of the increase in cognitive function in this study, whether it may be an improvement in 'chemo-brain' per se; or related to a complex interaction of improvements of variables such as fatigue and depression.

Many studies have shown that PA is associated with an increased QOL (Blanchard et al., 2008, Lynch et al., 2007b, Grimmett et al., 2009) through its effects on cardiovascular fitness, muscular strength, fatigue and patient-related functioning in terms of daily living (Courneya et al., 2003b). Some moderate associations were noted between QOL domains and objective as well as self-reported PA in this study. It is not known whether increased PA levels mediate higher QOL levels or vice-versa. It is also possible that with higher QOL levels, individuals may have been feeling better generally, therefore perceive themselves to be carrying out higher levels of PA at the 1-year time-point.

Strengths of this study included the non-cancer comparison group matched for age, gender and education and the longitudinal, prospective design of this study. An objective measure of PA was used in this study is more robust than self-report methods which are likely to over-estimate PA. This study had comprehensive data on all variables related to diagnosis, and treatment verified from patients' medical records; in many studies cancer stage and grade is self-reported which can be problematic. Participants self-selected in to this study and despite its small sample size, this study included participants of differing educational attainment, and a large age-range so may be generalised to the breast and colo-rectal population. This study also had excellent cohort maintenance (91%).

The main limitation of this study was the small sample size, although a sample size of 25 was the original intention, so recruiting 29 subjects to this study clearly exceeded this number. Further limitations of this study were that variables were only investigated up to the first year after cessation of treatment. Longer term activity patterns of this cohort would have enhanced comparability to longer-term survivorship studies in the area and would have also permitted relating these variables to mortality and recurrence. Again though, the original aim was to follow participants over a 1-year time period.

Despite these limitations, this study revealed important information relating to PA and other variables during the first year after cessation of chemotherapy. We believe this is the first study which investigated objective PA levels of this cohort during this time-period. Physical inactivity is a risk factor for cancer recurrence, yet results showed that by 1 year after cessation of chemotherapy, PA levels had not changed since completing chemotherapy but were similar to a matched cohort. Rates of overweight and obesity were higher than expected and increased over the time-course of the study, despite the fact that participants reported reasonable QOL levels and over-estimated their PA.

These findings highlight the need for more comprehensive data about PA and BMI in follow-up. This research also underlines the need to explore intervention methods to increase PA and maintain a healthy body weight in this population. There is clearly a need to apply the rehabilitation model to increase exercise tolerance so that PA levels can be increased. The challenge however is not just to increase PA levels to population norms as these are clearly low, but to rehabilitate PA to levels in excess of this.

Chapter 5

5.1 Introduction

The results from Study I demonstrated that PA levels were low at the time of cancer diagnosis. Following on from this, the results from Study II indicated that PA levels remained low, and did not change during the first year after cessation of chemotherapy, highlighting the need for intervention.

Although a recently published consensus document (Schmitz et al., 2010) provided guidance in terms of exercise prescription within cancer populations; the frequency, time and type of exercise which positively effects change in parameters such as PA and fitness are not fully known. A number of meta-analyses have pooled information from available intervention studies in cancer and exercise (Fong et al., 2012, Knols et al., 2005, Oldervoll et al., 2004a, Stevinson et al., 2004, Schmitz et al., 2005, Galvao and Newton, 2005, Conn et al., 2006a, Speck et al., 2010, Spence et al., 2010, Jones et al., 2011, McNeely et al., 2006a, Duijts et al., 2011, Ferrer et al., 2011) as outlined in Section 1.5.1 (page 47). The majority of interventions were performed either during treatment, or many years into survivorship. Only a small number of studies have evaluated the effect of a short, clinically transferable intervention programme which takes place in the first year after cessation of therapy. It could be argued that such a time period would be the most opportune time for an intervention to take place (Spence et al., 2010, Courneya and Friedenreich, 2001). The majority of exercise intervention studies have included patients with breast cancer, which limits the applicability of results to heterogeneous cancer populations.

The overall aim of this study was to examine the effects of a supervised exercise program commenced within 2-6 months after completion of chemotherapy in a heterogeneous cancer population on cardio-respiratory fitness, PA and a number of other outcomes.

The objectives of this study were as follows;

1. To compare outcomes of an 8-week exercise intervention to a usual care control group in terms of fitness, objective and self-reported PA, QOL, fatigue and morphological outcomes
2. To assess the feasibility of this trial in terms of adherence and retention rates as well as participant feedback

5.2 Methods

5.2.1 Study design and subjects

This study was a single-blind two arm pragmatic randomised controlled trial of individually prescribed exercise in a class setting versus usual care. Participants were sourced from the institutional cancer database, and from the medical oncology and multidisciplinary team in St. James's Hospital and St. Luke's Hospital[22]. This study was termed the 'PEACH trial' Prescribed Exercise after Chemotherapy. Eligible patients were invited to participate by the study coordinator at clinics in St. James's Hospital and St. Luke's Hospital. To ensure all suitable patients were informed of this study, additional patients not approached in clinics were posted a colour summary leaflet of the study (Appendix XIV). Ethical approval was gained from St. James's Hospital and from St. Luke's Hospital ethical committee (Appendix XI).

[22] Radiotherapy treatment is delivered in St. Luke's Hospital. Ethical approval (Appendix XI) was sought to recruit patients in St. Luke's Hospital meeting eligibility criteria who originated from St. James's Hospital.

5.2.2 Eligibility Criteria

The inclusion criteria were as follows;

1. Diagnosis of solid tumour or lymphoma (Hodgkin's or non-Hodgkin's disease) and completion of chemotherapy and/or radiotherapy with curative intent within the preceding 2-6 months. Patients who received neo-adjuvant chemotherapy or chemo-radiotherapy followed by surgery were also eligible as well as patients continuing onto adjuvant hormone therapy and anti-Her2 directed therapy
2. Able to understand English
3. Willing to be randomised
4. Medical clearance to exercise
5. Age 21-69
6. Modified Bruce Fitness test result: Fitness level average, fair or poor according to pre-determined cut-off points for age and gender (Fletcher et al., 2001) (Appendix IV)
7. Willing and able to attend supervised exercise sessions twice weekly for a period of 8 weeks, with an intention of achieving > 90% attendance
8. Left ventricular ejection fraction (LVEF) (Appendix XV) of > 50% and not < 20% worse than baseline in applicable patients

The exclusion criteria were as follows;

1. Evidence of active cancer

2. Chronic medical and orthopaedic conditions that would preclude exercise (e.g. uncontrolled congestive heart failure or angina, recent MI, breathing difficulties requiring oxygen use or hospitalization)

3. On beta-blocker medication

4. Prior history of another cancer in previous 5 years (exception: non-melanoma skin cancer and non-invasive cancer of the cervix)

5. Confirmed pregnancy

6. Dementia or psychiatric illness that would preclude ability to participate in study

7. Incomplete haematological recovery after chemotherapy (WCC< 3, Hb < 10 or Platelets < 100)

8. Body Mass Index > 35

9. Left ventricular ejection fraction (LVEF) (Appendix XV) post chemotherapy < 50% or > 20% deterioration of baseline pre-systemic treatment (LVEF criteria are applicable in patients who have received chemotherapy 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)

5.2.3 Study Measures

Assessment by a 'blind' tester as outlined in Section 2.1 page 66 was completed at week 0 (T0)[23], on completion of the 8-week programme (T1) and 3 months after the exercise programme (T2). Cancer grade, stage, surgical management, treatment regimen (chemotherapy, radiation therapy, hormonal therapy) and previous medical history were recorded by accessing medical charts. Socio-demographic variables recorded were age,

[23] The assessment at T0 was scheduled in the week preceding the exercise intervention start date

gender, ethnicity, employment status, smoking, and alcohol habits. These were accessed from medical charts and/or subjective interview.

Protocol deviations such as switching or contamination, subjects dropping-out or adhering non-perfectly were also recorded. Safety was paramount and any adverse events were recorded. An exercise programme adherence rate of > 90% was anticipated.

5.2.3.1 Primary Outcome measure

Physical fitness was the primary outcome measure. This was assessed using the Modified Bruce Protocol. A sub-maximal test was selected over a maximal test for this population because of safety and motivational concerns (Noonan and Dean, 2000). A full description of the Modified Bruce Protocol is described in Appendix IV. Contraindications and precautions to exercise testing as per the American College of Sports Medicine Guidelines were determined before testing. Verbal encouragement during the exercise test was standardised.

5.2.3.2 Secondary outcomes

Secondary outcome measures were body composition, quality-of-life, self reported PA, objectively measured PA and fatigue. An evaluation of the programme was also carried out. These secondary outcomes are described in more detail in Table 5.1.

Table 5.1 Secondary outcome measures

Body Composition	Body weight and lean body mass was measured to the nearest gram (g) using a standardised digital scales (Tanita MC 180 MA Multi-Frequency Body Composition Anaylzer) (Section 2.2.6.2 page 99). Waist circumference was measured at the mid-point between the top of the iliac crest and the 12th rib (Section 2.2.6.3 page 99). Measures were taken in duplicate and averaged for data entry (Appendix X). Standing height was measured, without shoes, to the nearest millimetre (mm) using a stadiometer. BMI was calculated by dividing weight in kilograms by height in metres squared.
Quality-of-life	The FACT-G scale (general, version 4) (Section 2.2.5.3, page 96, Appendix VI), and the physical functional measure of the SF-36 were used to measure quality-of-life (QOL) (Section 2.2.5.4, page 97, Appendix VIII).
Self-reported PA	The modified version of the Godin Leisure Time Exercise Questionnaire was used (Section 2.2.2.3.3, page 84, Appendix III) which has been shown to be a reliable and valid self-report measure of physical activity (Godin and Shephard, 1985) (Chapter 2, X.X).
Objectively measured PA	The RT3 accelerometer (Section 2.2.2.2.1 page 79, Appendix I) was used to monitor 7 days of activity at Week 0, Week 8 (immediately post intervention) & 3 months post intervention.
Cancer-related fatigue	The 13-item Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue) (Section 2.2.4.3 page 92, Appendix VI) of the Functional Assessment of Chronic Illness Therapy measurement system was used which has been developed specifically for the cancer population (Cella, 1997b, Cella et al., 1993).
Programme Evaluation	A self-administered questionnaire was filled out by participants on completion of programme. Participants were asked to highlight what they liked about the programme, what they didn't like, and suggestions for change (Appendix XVI).

5.2.3.3 Exercise Training Intervention

The class was supervised by a physiotherapist and a research assistant. There was a maximum of 10 participants in each class, giving a ratio of 1:5, instructor: patient ratio.
A warm-up preceded each exercise class which consisted of progressive aerobic exercises such as marching on the spot and side-stepping. The duration of the warm-up was 7-10 minutes (at initial stage of training the warm-up was longer to allow time for extra accommodation).

The duration of each class was one hour class in total, with the aerobic component increasing on a weekly basis (Table 5.2).

The type of exercise performed during each class consisted of aerobic continuous rhythmic exercise using large muscle groups. Stations included treadmills, cycle ergometers, and a rowing machine/stepper/other aerobic exercise such as marching on the spot deemed suitable by the class instructor.

The frequency of classes was twice per week for a total of 8 weeks. In addition, participants were requested to exercise in the home environment, starting with at least one day per week and building up to at least 3 other days per week (Appendix XVII). Participants were instructed that exercise at home could be carried out in multiple sessions (but no less than 10 minutes each time) and a polar watch (FT4) was worn during these exercise sessions to monitor intensity. Exercise diaries were filled out for the home exercise programme.

Table 5.2: Progression of the intensity & duration of the exercise class

Intensity	Poor	Fair	Average
Week 1	35-55% HRR	40-60% HRR	45-65% HRR
	21 mins aerobic	21 mins aerobic	21mins aerobic
Week 2	35-55% HRR	40-60% HRR	45-65% HRR
	24 mins aerobic	24 mins aerobic	24 mins aerobic
Week 3	40-60% HRR	45-65% HRR	50-70% HRR
	24 mins aerobic	24 mins aerobic	24 mins aerobic
Week 4	40-60% HRR	45-65% HRR	50-70% HRR
	27 mins aerobic	27 mins aerobic	27 mins aerobic
Week 5	45-60% HRR	50-65% HRR	55-70% HRR
	27 mins aerobic	27 mins aerobic	27 mins aerobic
Week 6	45-60% HRR	50-65% HRR	55-70% HRR
	30-33 mins aerobic	30-33 mins aerobic	30-33 mins aerobic
Week 7	50-60% HRR	55-70% HRR	65-75% HRR
	30-33 mins aerobic	30-33 mins aerobic	30-33 mins aerobic
Week 8	50-60% HRR	55-70% HRR	65-75% aerobic
	33-36 mins aerobic	33-36 mins aerobic	33-39 mins aerobic

HRR: Heart rate reserve

The intensity was based on the result of the Modified Bruce Fitness test. Participants falling into 'poor', 'fair' or 'average' fitness classifications (Appendix IV) exercised during the aerobic element of the class to heart rate reserve (HRR) levels detailed in Table 5.2. As there were no suitable recommendations for cancer populations, HRR and time progression was based on ACSM recommendations (2009b).

5.2.3.4 Measurement of Cardiovascular Parameters and Additional Safety Considerations

Resting heart rate (Appendix XVII) was measured after a five minute rest period in a seated position. Heart rate reserve was calculated by subtracting the resting heart rate from peak heart rate during exercise.

Blood pressure (Appendix XIX) was measured before each exercise class, during the aerobic component of the class, and after the exercise class. If resting blood pressure was > 144/94 at the start of the class, then physician consent was sought to allow exercise (Canadian Society for Exercise Physiology Guidelines)[24]. Blood pressure (BP) during assessments (was measured using the auscultatory method in accordance with the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines (Appendix XIX)). Blood pressure was measured by the manual method or electronic BP monitor using the Omron HEM-79IT.

As well as wearing polar monitors, participants were instructed in how to use the 'Ratings of perceived exertion scale' (Table 5.3). This scale was also used by participants during their home exercise programme to monitor exertion levels. Participants were instructed to stay within the descriptors of 11-13 of this scale. A polar monitor (FT4) was set up individually for each patient based on their age, height and weight. The prescribed heart rate range (Table 5.2) was programmed into the watch to assess adherence to the prescribed regimen during the exercise class. Participants also recorded their own home exercise programme using the polar monitor and an exercise diary supplied (Appendix XVII). The contra-indications to exercise testing for patients with cancer (ACSM 2009 were adhered to (Appendix XX).

[24] In practice, this did not occur as blood pressure levels did not exceed this value

Table 5.3 Ratings of Perceived Exertion Scale

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

5.2.4 Statistical analysis

Randomization was by a computer-generated random numbers list (www.randomization.com). Baseline descriptive statistics were compared using independent t-tests for continuous data and as the total sample size was <50 and one or more cell counts were low, Fishers exact test was used for categorical data.

The primary outcome measure of this feasibility study was fitness. Assuming a difference of 5mL.kg^{-1}.min^{-1}, with a SD of 6.5, and a 5% significance (two-sided) and 80% power, 28 participants were required per group, with no adjustment for multiple testing. However, the original goal was to accrue 32 subjects per group to allow for a 15% drop out rate and

subgroup analyses. One year was allowed for accrual of participants, however a slower than expected recruitment rate meant 43 participants were recruited in total, 23 participants randomized to the exercise group (EG) and 20 to the usual care (UC) control group.

Missing data was dealt with using the last observation carried forward and intention-to-treat was utilised as the primary analysis, and for the secondary analysis, per-protocol analysis. Per-protocol analysis was based on 90% attendance for the exercise group participants (n=11) and completing all assessments for the control group (n=17) participants. Repeated measures of variance (ANOVA) was employed with T0 (baseline), T1 (8 week data), and T2 (20 week data) as outcomes and any appropriate baseline measures (age, marital status (married, other), BMI, working (currently working or not), cancer type (breast cancer, other), radiotherapy (radiotherapy treatment or none)) as covariates to test for the main effects of study grouping (usual care versus exercise group) on outcomes. General linear models were used to compare values across time when data were normally distributed. F values were reported where appropriate and refer to the test statistic, which is variance of the group means/mean of the within group variances. Effect sizes were calculated with 0.2-0.3 a 'small' effect size, 0.5-a 'medium' effect and 0.8 or higher a 'large' effect (Cohen, 1988). Friedmans' test was used when data were non-normally distributed. All statistical tests were two-sided with a significance level set at 0.05. SPSS for Windows (16.0) was used for statistical analysis (SPSS Inc., Chicago, IL).

5.3 Results

5.3.1 Demographic details

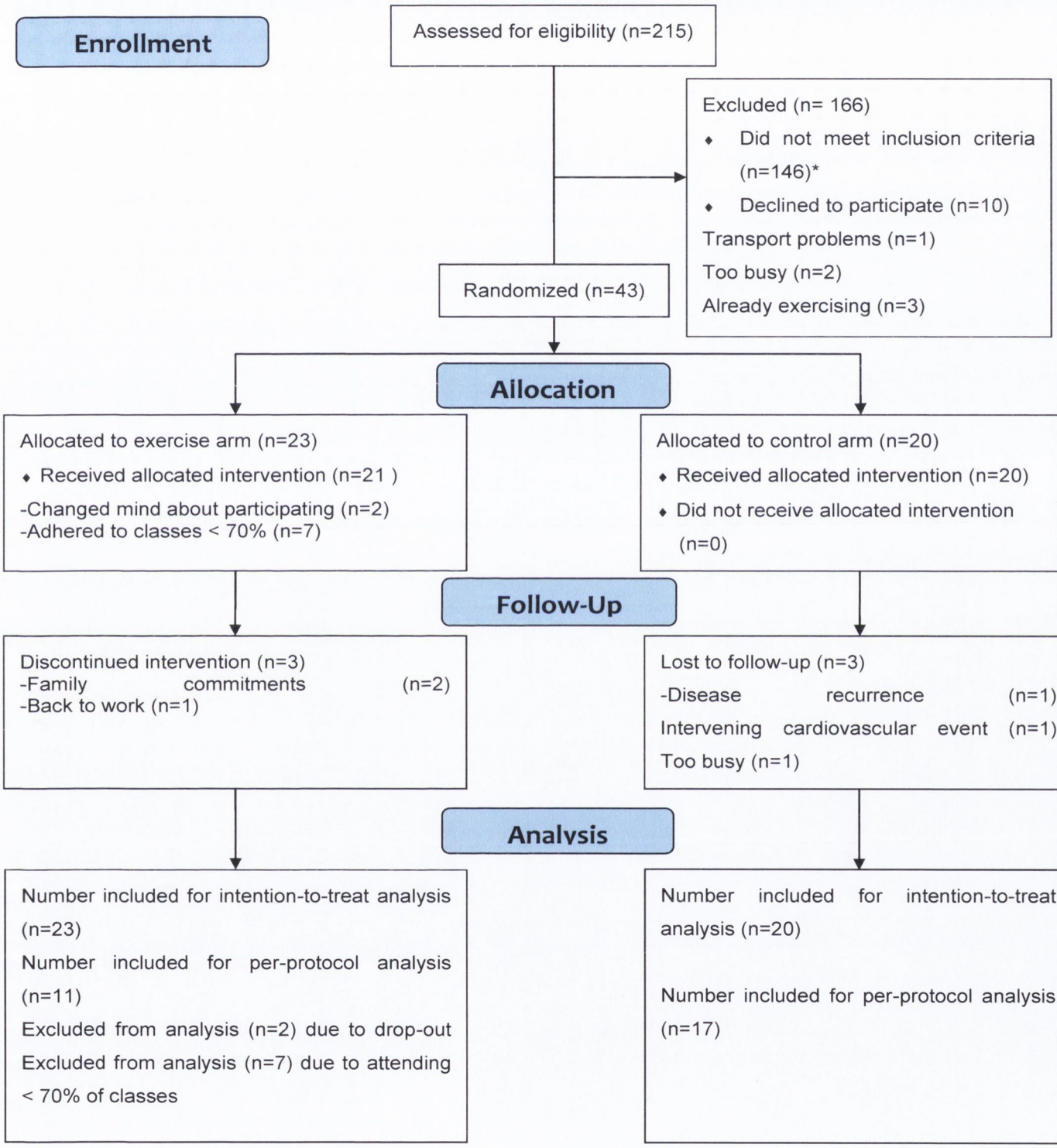
Study recruitment took place from February 2010 - February 2011. Two-hundred and fifteen subjects were screened, of these 20% (43/215) participants gave full informed consent and were enrolled for study participation; 23 were randomized to the exercise group (EG) and 20 to the control arm which consisted of usual care (UC). The flow of participants through the study is shown in Fig.5.1. The mean (SD) age of participants was 51.8 (9.2) years, and the male: female ratio was 6:37.

The most common cancer type of participants was breast cancer (72.1% of total (n=31)), comprising 80.1% of total females recruited. Other cancer types of participants are reported in Table 5.5. There was an 8.7% (n=2) attrition rate in the exercise group. This was related to participants (n=2) realising the time commitment was too great to participate in the exercise group, and subsequently dropping out of the programme after the initial assessment, as well as non-attendance at follow-up assessments. There was a 5% (n=1) attrition rate in the control group, due to one subject being unable to attend the study centre to complete the final assessment due to family commitments. Of the 43 participants enrolled, 88% (n=38) completed assessments at 8 weeks (due to drop-outs (n=2), disease recurrence (n=1), intervening sickness (n=1), and unable to make it to study centre for assessment due to family commitments (n=1)) and 86% (n=37) at 20 weeks (due to drop-outs (n=2), disease recurrence (n=1), an intervening cardiovascular event (n=1), and unable to make it to the study centre for assessment due to being back at work and family commitments (n=2)). There were no serious adverse effects associated with

the exercise intervention. One participant complained of anterior knee pain, and another of calf pain, these symptoms settled and did not affect adherence.

Table 5.4 details demographic characteristics of participants. The only statistical differences between the groups were more breast cancer participants ($p<0.05$) and an increased number of participants who underwent radiotherapy treatment ($p<0.05$) randomized to the exercise group. As both of these variables were closely related, breast cancer diagnosis was the only variable entered as a covariate for repeated measures analysis. There was no difference in baseline characteristics between those who attended >90% of the programme, and those who attended < 90% of the programme. Cancer-related information is shown in Table 5.5.

Fig. 5.1 CONSORT Flow Diagram



*Did not meet inclusion criteria due to the following reasons; cancer within the previous 5 years (n=7), participation in another trial which may have affected outcomes (n=18), completion of chemotherapy < 2 or > 6 months previously (n=29), living too far from study site (n=29), BMI > 35 (n=12), did not complete >80% chemotherapy prescribed (n=3), co-morbidities (n=24), age > 70 years (n=3), on beta-blocker medication (n=5), poor English (n=3), ejection fraction (n=3) and progressive disease/high risk of relapse (n=10).

Table 5.4 Baseline demographic details

	Overall (n=43)	Usual care (n=20)	Exercise Group (n=23)	P
Demographic details				
Age, years				
Mean (SD)	51.8 (9.2)	51.2 (10.3)	52.3 (8.3)	0.70
Range	25.5-69.2	25.5-68.5	34.9-69.2	
Ethnicity				
Caucasian				
No. (%)	42 (97.7)	21 (100)	21 (95.5)	1.0
Asian				
No. (%)	1 (2.3)	0 (0)	1 (4.5%)	
BMI				
Mean (SD)	26.7 (3.7)	26.7 (3.6)	26.6 (4.0)	0.92
Range	18.0-34.9	21.1-33.0	18.1-34.9	
Married				
Number (%)	25 (58.1)	12 (60)	13 (56.5)	1.0
Gender				
M/F	6/37	5/15	1/22	0.08
Currently Workingł				
	16 (37.2)	6 (30)	10 (43.5)	0.36
Occupation (before diagnosis)				
Professional	10 (23.3)	5(25)	5(21.7)	
Management/Clerical	8(18.6)	3 (15)	5 (21.7)	
Manual/non-skilled	13 (30.2)	8 (40)	5 (21.7)	
Not working/retired	12 (27.9)	4 (20)	8 (34.8)	

ł Currently working: includes participants who were working at trial entry and those who returned to work during the trial time period

Table 5.5 Cancer related variables

	Overall (n=43)	Usual care (n=20)	Exercise group (n=23)	P
Cancer type				
Number (%)				
Breast	31 (72.1)	11 (55)	20 (87)	0.04*ł
Colo-rectal	5 (11.6)	5 (25)	0 (0)	
Lymphoma	3 (7.0)	2 (10)	1 (4.3)	
Oesophageal	2 (4.7)	1(5)	1(4.3)	
Gynaecological	2 (4.7)	1(5)	1(4.3)	
Cancer Stage				
I	10 (23.3)	6(30)	4 (17.4)	
II	15 (34.9)	4 (20)	11 (47.8)	
III	8 (18.6)	3 (15)	5 (21.7)	
Missing/non applicable	10 (23.3)	7(35)	3 (13.0)	
Months since diagnosis				
Mean (SD)	9.1 (1.57)	8.91 (2.04)	9.13 (1.0)	0.66
Range	5.72-13.31	5.72-13.31	7.82-11.47	
Surgery				
Number (%)				
Wide local excision	17 (39.5)	5 (25.0)	12 (52.2)	
Mastectomy	14 (32.6)	6 (30.0)	8 (34.8)	
Anterior resection	4(9.3)	4(20.0)	0	
Hemi-colectomy	1 (2.3)	1 (5.0)	0	
Radical gastrectomy	2 (4.7)	1 (5.0)	1 (4.3)	
Gynaecological Surgery	2 (4.6)	2 (10.0)	1 (4.3)	
No surgery	3 (7)	2 (10)	1 (4.3)	
Chemotherapy regimen				
AC	2(4.7)	0	2(8.7)	
AC followed by Paclitaxel	13 (30.2)	7 (35.0)	6 (26.1)	
Docetaxol and Cyclophosphamide	14(32.6)	3 (15)	11 (47.8)	
Paclitaxel and Carboplatin	2(4.7)	0	2 (8.7)	
Carboplatin, Docetaxel and Trastuzumab	1 (2.3)	1 (5)	0	
m-FOLFOX 6	4 (9.3)	4 (20)	0	
R-CHOP	2 (4.7)	1 (5)	1 (4.3)	
R-EPOCH	1 (2.3)	1 (5)	0	
EOX (dose adjusted)	2 (4.7)	1 (5)	1 (4.3)	
Missing	0 (0)	1(5)	1 (2.3)	
Hormonal therapy				0.45łł

Number (%)				
Tamoxifen	15 (34.9))	8 (40.0)	6 (26.1)	
Letrozole	7 (16.3)	1(5.0)	6 (26.1)	
Anastrazole	1 (2.3)	0	1 (4.3)	
Not prescribed	20 (46.5)	11 (55)	9 (4.3)	
Ongoing maintenance therapy				
Number (%)				
Trastuzumab	6 (14)	2(10)	4 (17.4)	0.67ŧŧŧ
Bevaczumab	1 (4.3)	0	1 (4.3%)	
Rituximab	1 (4.3)	0	1 (4.3%)	
Months since completed chemotherapy				
Mean (SD)	3.7(1.2)	3.3(1.2)	3.9(1.2)	0.08
Range	1.4-6.6	1.4-6.6	2.1-6.0	
Radiation therapy				
Number (%)	31 (72.1)	12 (57.1)	19 (86.4)	0.05*

Ł Refers to comparison of percentage of participants with a breast cancer diagnosis versus non-breast cancer diagnosis participant

ŧŧ Refers to hormonal treatment versus no-hormonal treatment

ŧŧŧ Refers to ongoing maintenance therapy versus none

Abbreviations; AC=cyclophosphamide and doxorubicin, m-FOLFOX 6=Folinic acid, fluorouracil, oxilaplatin, R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone . R-EPOCH=rituximab, etoposide, doxorubicin, vincristine, cyclophosphamide, prednisolone. EOX=epirubicin, oxaliplatin, capecitabin

5.3.2 Physical measures of participants

Fitness (VO_2 max) was the primary outcome measure which was estimated using the Modified Bruce Protocol. Table 5.6 presents the predicted VO_2 max scores achieved and time to end of treadmill test (seconds). BMI and waist circumference measures are also shown in Table 5.6.

Table 5.6 Fitness test (Mean (SD) and body composition measures at T0 (Baseline), T1 (8 week time-point), T2(20 week time-point))

	Intention-to-treat data		Per-protocol data	
	Usual Care (n=20)	Exercise Group (n=23)	Usual Care (n=17)	Exercise Group (n=14)
Predicted VO_2max ($mL.kg^{-1}.min^{-1}$)				
T0	19.4(5.6)	20.1(5.0)	19.2 (5.5)	20.5(5.0)
T1	20.4 (6.2)	22.9 (7.4)	20.9(6.2)	25.0(8.1)
T2	20.4(6.2)	22.6(6.7)	19.9(6.2)	25.8(7.6)
Time to end of test (seconds)				
T0	628.1(151.5)	655.8(111.1)	623.6(149.0)	651.7(104.1)
T1	661.1 (144.0)	712.4 (144.1)	668.6(137.9)	674.1(264.8)
T2	664.7 (137.1)	688.8 (147.3)	658.7(132.2)	716.7(172.5)
BMI($kg.m^{-2}$)				
T0	26.6(3.5)	26.6(4.1)	26.1(3.8)	27.6(3.5)
T1	26.7(3.7)	26.1(5.2)	26.8(4.0)	27.3(3.5)
T2	26.9(3.9)	26.6(4.0)	26.8(4.0)	27.3(3.5)
Waist Circumference (cm)				
T0	87.5(9.9)	87.5(10.4)	88.2(11.3)	92.3(8.8)
T1	87.0(11.5)	85.7(11.0)	87.6(13.4)	89.7(8.2)
T2	87.4(12.1)	86.4(10.8)	87.5(13.2)	88.5(8.7)
Fat-free Mass (%)				
T0	47.8(8.8)	44.5(6.5)	46.8(8.1)	46.9(7.0)
T1	47.8(8.6)	44.6(6.7)	47.0(7.9)	47.1(7.7)
T2	48.1(8.4)	44.8(6.7)	47.3(7.9)	44.1(10.9)

Objective physical activity was measured using an RT3 accelerometer, and self-report physical activity was measured using the Godin Leisure Time Index. Intention-to-treat and per-protocol data is shown in Table 5.7.

Table 5.7 Objective and subjective physical activity measures: Intention-to-treat and per-protocol data

	Intention-to-treat data		Per-protocol data	
	Usual Care (n=20)	Exercise Group (n=23)	Usual Care (n=17)	Exercise Group (n=14)
Objective Physical Activity: RT3 Accelerometer Results				
Time spent in Moderate and Vigorous Domains of activity (Minutes per day)				
T0	52.6(44.8)	52.6(32.2)	49.2(25.8)	55.0(26.3)
T1	44.9(26.9)	52.7(30.5)	51.4(26.5)	56.1(25.4)
T2	60.2(43.2)	65.1(55.6)	64.4(58.3)	73.5(46.7)
Time spent Sedentary (Minutes per day)				
T0	413.5(134.1)	452.0(120.5)	428.6(128.2)	413.6(133.1)
T1	418.9(110.7)	439.9 (128.0)	386.6(92.1)	420.7(110.7)
T2	399.9(106.8)	395.4(124.4)	381.5(108.5)	398.1(95.1)
Subjective Physical Activity: Godin Activity Score (Units Arbitrary)				
T0	28.3(20.1)	20.7(17.9)	24.7(17.8)	16.5(10.4)
T1	22.4(22.4)	31.0(25.4)	24.0(23.4)	45.5(22.7)
T2	26.3(23.1)	25.4(20.0)	26.6(23.1)	39.0(28.1)

5.3.3 Analysis of Study Outcomes

5.3.3.1 Changes in physical outcome measures

The intention-to-treat analysis revealed a significant time related effect for total time on the treadmill[25] ($p=0.001$). No group related effects were noted using intention-to-treat analysis. The per-protocol analysis revealed significant time related changes for waist circumference ($p<0.001$) and subjectively measured PA ($p=0.001$). The only group related effect was noted for subjectively measured PA ($p=0.001$). Complete details of physical outcomes are shown in Table 5.8a, 5.8b and 5.8c.

[25] Element of the Modified Bruce Protocol

Table 5.8a Effect of Study Outcomes: Intention-to treat and per-protocol analysis; fitness and body mass measures (significant values p<0.05 highlighted in bold)

	Intention-to-treat analysis		**Per-protocol analysis**		
	Time effect	**Time * Group effect**		**Time effect**	**Time * Group effect**
Total time on treadmill (seconds)					
F (2,80)	7.50	0.74	F(2,52)	11.97	1.27
P	**0.001**	0.48	**P**	**<0.001**	0.29
Effect size	0.16	0.02	Effect size	0.32	0.05
Waist Circumference (cm)					
F (1.71, 80)	1.03	1.12	F(1.1,52)	1911.9	0.62
P	0.36	0.33	**P**	**<0.001**	0.54
Effect size	0.03	0.03	Effect size	0.99	0.02
Body Mass Index ($kg.m^{-2}$)					
F (1.57, 80)	0.84	0.59	F(1.28,52)	0.41	1.18
P	0.41	0.52	P	0.58	0.30
Effect size	0.02	0.02	Effect size	0.02	0.43
Fat-free Mass (%)					
F (2, 80)	0.22	0.12	F(2,52)	1.06	0.6
P	0.80	0.89	P	0.35	0.55
Effect size	0.01	0.00	Effect size	0.04	0.02

P-values for repeated measures ANOVA with diagnosis as a covariate and T0, T1 and T2 as outcomes.

Table 5.8b Predicted VO_2 max (p-values generated)

	Intention-to-treat data*			**Per-protocol data***		
	T0 →T1	**T1→T2**	**T0→T2**	**T0→T1**	**T1→T2**	**T0→T2**
Predicted VO_2 max ($mL.kg.min^{-1}$)	0.31	0.18	0.61	0.56	0.18	0.61

*Mann-Whitney U test performed as data non-normally distributed

Table 5.8c Effect of Study Outcomes: Intention-to treat and per-protocol analysis; objective and subjective physical activity measures

	Intention-to-treat analysis		**Per-protocol analysis**		
	Time effect	**Time * Group effect**		**Time effect**	**Time * Group effect**
Objective Physical Activity Assessment					
RT3 Accelerometer: Moderate and Vigorous Domains of Activity (mins)					
F (1.51,78)	1.40	0.13	F(1.22,52)	1.75	0.03
p[†]	0.35	0.82	P	0.20	0.92
Effect size	0.04	0.00	Effect size	0.06	0.00
RT3 Accelerometer: Time spent sedentary (mins)					
F (1.30,78)	0.02	0.37	F(1.31, 52)	0.84	0.53
P	0.95	0.60	P	0.50	0.52
Effect size	0.00	0.01	Effect size	0.03	0.02
Subjective Physical Activity Assessment (units arbitrary)					
Godin Leisure Time Index					
F (1.69, 80)	1.56	2.73	F(2,56)	7.86	7.92
P	0.22	0.08	**P**	**0.001*[26]**	**0.001***
Effect size	0.04	0.07	Effect size	0.23	0.23

†P-values for repeated measures ANOVA with diagnosis as a covariate and T0, T1 and T2 as outcomes.

5.3.3.2 Quality-of-life and Fatigue Analysis

The Fact-G questionnaire and physical functioning measure of the SF-36 were used to measure quality-of-life. The FACIT-F was used to measure fatigue. Quality-of-life and fatigue scores at each time-point and the main effects of the exercise intervention are shown in Table 5.9. The mean total FACT-G score was (SD) 88.4(12.0) for the combined group at T0. As higher scores indicate better quality-of-life, QOL values reported in this study were higher than reference values for all subscales and the total score of a normative population and a mixed cancer population (score of 80.1 (18.1) from a 2002 sample of the US general

[26] Post hoc testing revealed differences between T0 and T1 for time effect (p=0.012), and Time*Group effect (p=0.002), and T1 to T2 (p=0.01)

population, scores from a mixed cancer diagnosis sample of 80.4 (15.9) (Brucker et al., 2005)). Overall high internal consistency for the FACT-G was found in this study with a Chronbach's alpha of 0.92.

A 2-3 point difference on the FACT-G subscale scores and a 3-7 point difference on the FACT-G total score is associated with a meaningful difference on clinical and subjective indicators (Brucker et al., 2005, Webster et al., 2003). Clinically meaningful differences were found in the exercise group from T0-T1 for the physical well-being score of the FACT-G and the FACT-G total score.

The physical functioning measure of the SF-36 was used to evaluate physical aspects of QOL. Good internal consistency for this measure was shown with a Chronbach's alpha of 0.87.

The FACIT-F was used to evaluate fatigue levels. Lower scores indicate greater fatigue and a minimal clinically important difference of 3 points has been established for this measure (Cella et al., 1993). The mean (SD) reference value for the fatigue subscale was 40.1 (10.4) (Cella et al., 2002c). Chronbach's alpha for the fatigue subscale was good at 0.86. A number of fatigue variables improved significantly over time, but clinically meaningful differences were found in the exercise group from T0-T1 for the fatigue subscale.

Repeated measures ANOVA revealed a significant time effect using intention-to-treat analysis for the physical composite of the SF-36 ($p=0.02$). The per-protocol analysis revealed a significant group effect for the Physical Well-being (PWB) composite of the FACT-G ($p=0.018$), and time related effects for the PWB component, the FACT-G total score ($p=0.002$), the fatigue subscale of the FACIT-F ($p=0.002$) and the Facit-F total score ($p < 0.001$). Full details of all values are shown in Table 5.11.

Table 5.9 Fact-G and Physical Functioning Mean measure of the SF-36, mean (SD) scores and main effects on quality-of-life

	T0	T1	T2	Adjusted difference in mean change[a] with 95% confidence intervals					
				T1-T0		T2-T0		T1-T2	
				Mean	95% CI	Mean	95% CI	Mean	95% CI
Fact-G Subscale									
Physical well being									
Usual care	23.4(2.5)	24.3(2.7)	23.9(3.2)	1.0	-1.2→3.2	0.5	-1.8→3.0*	0.4	-1.8→2.6*
Exercise Group	21.3(4.8)	24.5(3.3)	23.5(4.0)	3.1	1.0→5.1	2.2	-0.9→5.3*	0.9	-1.1→2.9*
Social/family well-being									
Usual Care	25.1(2.6)	26.6(7.7)	25.5(2.6)	1.7	-1.5→4.8*	0.2	-1.8→2.2*	1.5	-1.7→4.6*
Exercise Group	24.3(3.7)	23.9(4.1)	24.9(4.0)	-0.6	-3.5→2.4*	0.8	-0.7→3.3*	-1.4	-4.3→1.6*
Emotional well-being									
Usual Care	20.4(3.2)	20.7(2.4)	20.6(2.9)	0.5	-1.7→2.7*	0.2	-4.3→4.8*	0.3	-1.9→2.4*
Exercise Group	18.4(4.4)	19.1(3.6)	19.0(4.1)	0.6	-1.5→2.6*	0.6	-1.6→2.8*	-0.1	-1.0→1.9*
Functional well-being									
Usual care	22.7(2.7)	24.2(3.0)	23.9(3.4)	1.0	-1.3→4.4*	1.0	-1.7→4.0*	1.0	-2.4→3.1*
Exercise Group	21.7(5.7)	22.0(5.4)	23.0(5.2)	1.0	-2.3→3.0*	1.0	-1.2→4.0*	0.9	-3.7→1.5*
FACT-G total									
Usual Care	91.5 (7.8)	95.7 (10.8)	93.8 (9.6)	2.6	-3.8→11.1*	2.8	-5.3→9.5*	2.7	-5.0→10.1*
Exercise Group	85.6 (14.3)	89.4 (12.9)	90.5 (13.9)	3.4	-4.5→9.4*	2.6	-1.9→11.8*	0.8	-8.6→5.4*
Physical functioning Measure (SF-36)									
Usual Care	47.0(6.7)	49.5(6.7)	50.7(6.0)	2.0	-2.5→6.4*	3.2	-1.2→7.7*	-1.3	-5.1→2.5*
Exercise Group	46.6(8.3)	49.8(5.2)	49.4(5.8)	3.6	-0.5→7.7*	3.2	-0.9→7.3*	0.4	-3.1→3.9*

[a=] Calculated based on adjusted mean change from generalized linear model, Usual care group (n=20), Exercise group (n=23).

*Confidence Intervals encompassing zero denote significant changes.

Table 5.10 FACIT-F scores

	T0	T1	T2	Adjusted difference in mean change[a] with 95% confidence intervals					
				T1-T0[a]		T2-T0[a]		T1-T2[a]	
				Mean	95% CI	Mean	95% CI	Mean	95% CI
Fatigue Subscale									
Usual Care	40.8(9.5)	42.9(8.9)	42.5(10.0)	2.4	-3.6→8.4*	0.1	-6.2→6.3*	2.3	-3.5→8.1*
Exercise Group	40.8(9.5)	42.9(8.9)	42.5(10.1)	5.2	-5.2→10.8*	6.2	0.4→12.0	-1.0	-6.4→4.4*
FACIT-F total score									
Usual Care	132.3(15.9)	138.6(17.2)	137.6(18.9)	0.1	-12.3→12.4*	0.02	-12.5→12.6	0.1	-12.2→12.3*
Exercise Group	121.1(23.7)	130.3(20.6)	129(23.6)	0.9	-11.4→11.5*	0.1	-11.7→11.8*	-0.03	-11.4→11.4*

[a=] Calculated based on adjusted mean change from generalized linear model

*Confidence Intervals encompassing zero denote significant changes.

Table 5.11 Effects of the Exercise intervention on QOL; SF-36 (Physical Functioning Measure) and FACIT-F, Intention-to treat analysis and per protocol analysis (significant values p<0.05 highlighted in bold)

	Intention-to treat analysis			Per protocol analysis		
	Time effect	Time * Group effect		Time effect	Time * Group effect	
Physical well-being						
F (2,80)	1.20	2.31	F (2,52)	13.36	4.49	
P	0.31	0.11	P	**<0.001**	**0.018**[27]	
Effect size	0.03	0.06	Effect size	0.34	0.15	
Social well being						
F (1.347,80)	0.79	2.02	F (1.3,52)	1.61	0.21	
P	0.42	0.15	P	0.22	0.71	
Effect size	0.02	0.05	Effect size	0.06	0.008	
Emotional well being						
F (2,80)	0.08	0.09	F (2,52)	0.76	0.35	
P	0.92	0.92	P	0.47	0.71	
Effect size	0.00	0.00	Effect size	0.03	0.01	
Functional well being						
F (2,80)	0.97	1.04	F (2,52)	1.75	0.53	
P	0.39	0.36	P	0.19	0.59	
Effect size	0.03	0.03	Effect size	0.06	0.20	
FACT-G total						
F (2,80)	1.37	1.22	F (2,52)	6.74	0.08	
p[†]	0.26	0.30	p[†]	**0.002**	0.92	
Effect size	0.03	0.03	Effect size	0.21	0.003	
Fatigue subscale						
F (2,80)	0.96	2.97	F (1.39,52)	7.15	1.27	
P	0.39	0.06	P	**0.002**	0.29	
Effect size	0.02	0.07	Effect size	0.22	0.05	
FACIT-F total score						
F (2,80)	1.4-	2.19	F (1.63,52)	10.17	0.35	
P	0.26	0.12	P	**<0.001**	0.67	
Effect size	0.04	0.05	Effect size	0.28	0.01	
Physical composite measure (SF-36)						
F (1.512,80)	4.50	0.44	F (1.51,52)	5.51	0.34	
P	**0.02**	0.59	P	0.07	0.66	
Effect size	0.10	0.01	Effect size	0.97	0.01	

[†]P-value for repeated measures ANOVA with diagnosis as a covariate and T0, T1 and T2 as outcomes

[27] Post-hoc testing revealed differences to be between T0 and T1 (p=0.02)

5.3.3.3 Process Evaluation and Participant feedback

In the scheduled exercise classes, the prescribed exercise duration and intensity (i.e. time spent in prescribed target heart rate range in class, (Table 5.2) was met by 105% - that is time spent in prescribed exercise duration and intensity was exceeded by 5%. Excluding participants (n=2) who dropped out after the initial assessment, and did not attend any exercise classes or follow-up assessments, the attendance rate was 78.3% for the exercise group (EG). Almost one third 31.6% (n=6) of those randomized to the exercise EG attended all exercise classes, and 60.9% (n=14) attended >70% of classes and completed all elements of their home exercise programme. Information of compliance with the exercise classes and home exercise programme are detailed in Appendix XVII.

Over two-thirds (77.3%) of participants met the home exercise programme (HEP) guidelines. Participants who met the HEP guidelines (Appendix XVI) carried out almost three-times the minimum recommended exercise duration advised (296.2%), carrying out a mean (SD) of 186.8 (63.6) minutes of non-protocol related exercise per week (brisk walking) measured using the polar heart rate monitor.

Using the RT3 data to compare compliance with PA guidelines (150 minutes of moderate/vigorous intensity exercise, accumulated over 5 days per week, with exercise bouts of no less than 10 minutes), overall 15.0% met these guidelines, this was equivalent to 17.1% at T0, 11.1% at T1, and 16.7% at T2.

The percentage of subjects categorised as 'physically active'[28] using the Godin Leisure Time Index was 39.7% overall. This corresponded to 32.6% (n=29) at T0, 40.5% (n=22) at T2 and 45.9% (n=20) at T3.

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[28] As the Godin Leisure Time Index (Appendix III) assess the number of exercise bouts per week >15 minutes, rather than the absolute amount of time per day, it was not possible to compare results to exercise guidelines. As per the method used by Grimmett et al. (2011), subjects were considered 'physically active' if they performed ≥ 5 bouts of moderate or strenuous activity per week.

The feedback from participants assigned to the intervention component indicated that the intervention was positively received (Feedback is detailed in Appendix XV). Overall, most would have a liked a larger group, more variety of equipment available and the programme to be offered on a routine basis to cancer survivors within the hospital.

5.4 Discussion

This study investigated whether an intervention initiated during the first six months after completion of chemotherapy could increase outcomes including fitness and activity levels. The primary analysis revealed no difference between the exercise and control groups, which may not be too unexpected as this was an underpowered trial. In both groups, there were time related improvements- irrespective of group assignment, in subjectively assessed physical well-being and "time on treadmill" during the fitness test. The secondary analysis revealed increases in self-reported PA, and physical well-being in the exercise group compared to the control group in those who adhered well to the programme. There were time related improvements on treadmill time during the fitness test, waist circumference, subjectively measured PA, physical well-being, total quality-of-life and fatigue, which were irrespective of group assignment. Thus, mirroring results of Study II, a number of variables increased naturally over time after cessation of treatment. The current study demonstrated that implementing a short, physically intensive programme in the initial time period after cessation of treatment did not accelerate these changes, as the primary analysis showed no difference between the exercise and control groups.

5.4.1 Participation rates

In the present study 62% of eligible participants took part. No comparable values were available for similar studies performed soon after treatment in heterogeneous populations. This participation rate was considerably higher than studies in the breast cancer literature of 17-20% (Pinto et al., 2005b, Mutrie et al., 2007) and 33% (Courneya et al., 2007). Thus, among eligible patients this study displayed high acceptability levels. Of the total number of potential participants screened, 68% were ineligible, and the reasons were mainly due to completing chemotherapy outside the

2-6 month timeline specified in this study, and living too far from the study site. Other reasons included co-morbidities precluding participation, age and BMI outside specified limits, beta-blocker medication and low ejection fraction.

Factors such as transport difficulties and living too far from the study site were expected barriers to participation, as the intervention was delivered in an acute hospital site. Approximately 40% of patients with cancer treated in St. James's hospital are from outside the local hospital catchment area, thus travelling to a twice weekly programme presented difficulties for a number of patients. Home-based settings have been reported to be preferential in breast cancer survivors (Rogers et al., 2009b), however the same degree of control over the exercise intervention would not have been permitted in such a programme.

A number of potential patients were deemed ineligible due to a body mass index of over 35. A cut-off point of 35 was chosen due to safety considerations in terms of injury risk and calculating heart rate response to exercise (Kim et al., 2005). It has also been suggested that obese individuals have a lower maximum heart rate which would suggest the 220-age formula for deriving maximum heart rate used in this study would not have been appropriate (Miller et al., 1993). However a cut-off point of 35 may have been too restrictive and meant that patients who potentially had a greater need for exercise intervention were denied access to this programme.

A number of potentially eligible patients were excluded due to co-morbidities limiting participation, which is understandable with an exercise intervention such as this. A high risk of relapse deemed a number of patients ineligible for study participation, and most of these were patients with gynaecological cancer. Risk of relapse was also identified as a factor in patient ineligibility in a recent study carried out in a mixed gynaecological cancer population (Donnelly et al., 2011). A further exclusion criterion was patients on prescribed beta-blocker medication, due to lower heart rate values and potentially altered heart rate responses to exercise associated with taking this medication. Patients with low ejection faction (< 50%) associated with taxane based chemotherapy and continuing treatment such as trastuzamab were also excluded from participation. As ECG monitoring was not utilised in the submaximal fitness test

or during the exercise intervention, caution was therefore exercised in case of potential cardiovascular problems associated with the physical aspect of the exercise programme.

A cut-off of age over 70 years was chosen in this study, as different factors with respect to heart rate may pertain to the elderly, and they may also be at an increased risk of arrhythmias during exercise and display variability in maximum heart rate (ACSM, 2000).

Although this was termed a 'pragmatic' trial, in retrospect some of the eligibility criteria chosen particularly with regard to the 2-6 month time-frame post cessation of chemotherapy and BMI >35 may have been too restrictive. However, although the ineligibility rate identified in this study was high, this was comparable to a 66% rate in a gynaecological cancer population (Donnelly et al., 2011).

Excluding participants (n=2) who dropped out after the initial assessment, the attendance rate was 78.3% for the exercise group. Almost one third 31.6% (n=6) of those randomized to the exercise group attended all exercise classes, and 60.9% (n=14) attended >70% of classes and completed all elements of their home exercise programme. This is comparable to compliance rates of 70% which have been quoted in other studies (Stevinson et al., 2004) and 61% for a 12-week combined aerobic and resistance programme (Milne et al., 2008).

5.4.2 Effect on Study Outcomes

The lack of a treatment effect observed in this study may have been related to a number of reasons. The main reason is likely to be due to the study being underpowered, meaning statistical relationships would be more difficult to achieve, unless very large changes in study parameters occurred as a result of the intervention.

There are a number of other factors which may have contributed to the lack of a treatment effect. It is possible that the time-frame chosen for this study was not appropriate. Results of Study II identified that PA levels did not increase in the first year after completion of chemotherapy therefore his time period was felt to be an

important 'window' in which patients may be receptive to an intervention aiming to increase fitness and PA levels. It was also felt this time–point may coincide with the time period before returning to work thereby enabling participation. Although relatively soon after completion of chemotherapy - a two-month window was felt to be appropriate to allow for recovery of haematological and immunological parameters possibly altered by treatment. The time frame of this study also coincided with the 'rehabilitation period' (Courneya and Friedenreich, 2001) of 3-6 months identified to be the most opportune time for an exercise intervention to take place (Courneya and Friedenreich, 2007, Spence et al., 2010).

However, in practice, the time frame was found to be a very narrow window for patients to avail of the intervention, as a large proportion of eligible patients received radiotherapy, which overlapped with the 2-6 month window post cessation of chemotherapy. Also a number of patients remained on regimes such as anti-HER 2 directed therapy during this time period, requiring further hospital appointments making participation difficult. Thus, if the time-frame had been wider, it would have enabled access to more potential study participants.

Contrary to the study hypothesis, the fitness level of the exercise group did not increase significantly, although a trend towards an increase was shown in the exercise group. The secondary analysis revealed a time related improvement in time-to-end of fitness test. This may have been related to factors such as a natural improvement in fitness over time irrespective of group assignment and may also have been reflective of familiarisation with the exercise test protocol.

This study overcame one of the methodological flaws of previous studies in patients with cancer by only including participants who scored average or below average in terms of fitness levels for their age and gender (Fletcher et al., 2001). Those with high levels of fitness at baseline presumably do not need an intervention designed to increase this variable, and would need higher exercise loads for improvements in this factor to occur. A downward trajectory in cardio-respiratory fitness is associated with chemotherapy treatment (Haykowsky et al., 2009) as outlined in Section 2.2.3.1 (page

87) . Therefore, not-surprisingly, no participants tested at baseline scored above 'average' fitness levels for their age and gender.

The pooled results of 3 studies in breast cancer participants at various stages of treatment and recovery (Courneya et al., 2003b, Crowley, 2003, Drouin, 2002) reported in a systematic review and meta-analysis (Mc Neely et al., 2006) reported a significant improvement in peak oxygen consumption with exercise of 3.39 mL.kg.min^{-1}. In a heterogeneous population of young and middle aged adults with cancer (lymphoma, breast, gynaecologic and testicular), a 14 week intervention carried out 1 month after cessation of curative chemotherapy resulted in an increase in VO_2 max of 6.4mL.kg.min^{-1} in the intervention group and 3.16 mL.kg.min^{-1} in the control group (Thorsen et al., 2005). In the present study, we reported an improvement of 2.8mL.kg.min^{-1} in the exercise group and 1 mL.kg.min^{-1} in the control group. Although, in those who complied with >90% of the exercise classes there was an increase of 4.3 mL.kg.min^{-1} in the exercise class and an improvement of 3.5 mL.kg.min^{-1} from baseline to the 3 month follow-up. There is no established minimally important difference for fitness in the oncology population. A 3.5 mL.kg.min^{-1} is equivalent to a one metabolic equivalent (MET) improvement in fitness which has been found to correspond to a 12% improvement in survival in men (Myers et al., 2002) which was based on a large population of > 6,000 men, including those with cardiovascular disease and 'healthy' subjects. So, although the improvement in fitness did not reach significance, a 1 MET improvement in fitness may have important survival implications, if this level of improvement is maintained.

The present study was powered based on an increase in fitness of 5mL.kg.min^{-1}. Due to a slower than anticipated recruitment rate, this study was underpowered and increases in fitness did not exceed 5mL.kg.min^{-1} therefore, not surprisingly fitness levels did not increase significantly. It is possible that an expected 5mL.kg.min^{-1} increase in fitness may have been overly ambitious with an 8-week intervention. However, as fitness levels were below age and gender expected norms presumably these individuals were de-conditioned and higher increases in fitness could be expected as a result. The failure of our exercise intervention to improve fitness

sufficiently to achieve significant results may have been due to many reasons. The 8-week (X2 weekly) exercise duration in this study may not have been a sufficiently long enough period for physiological changes to occur translating into a detectable increase in fitness.

Perhaps also the exercise programme was under-prescribed and should have been set at a higher intensity to effect greater physiological changes. Is not known whether there is a threshold intensity effect for fitness improvements specific to the cancer population (Courneya et al., 2009) and in the absence of guidelines recommending specific exercise training levels for oncology patients, heart rate ranges for this exercise intervention were based on the baseline fitness test and were individualised for each participant using heart rate reserve.

Heart rate reserve (HRR) takes into account both the maximum and the resting heart rates which is useful as resting heart rate can vary considerably from person to person, therefore it is deemed appropriate to prescribe levels of exercise intensity according to a HRR (Warburton et al., 2006). However, there may have been inherent problems in using the HRR method in this study. Firstly, the maximum heart rate was based on the 220-age method which is so generic and can be prone to inaccuracies (Fleg et al., 2000) and its use in patients with cancer has not been examined. Also, although resting heart rate was measured after a five minute rest period in a seated position, heart rate variability can be a latent effect of chemotherapy treatment due to autonomic dysfunction (Pujol et al., 2009).

As de-conditioned individuals after anti-HER 2 therapy and/or chemotherapy may demonstrate increases in their cardio-respiratory fitness with exercise intensities at the lower end of the intensity continuum, and fitter individuals need to work at the higher end of the intensity continuum to improve fitness (ACSM, 2000), a table was devised for this study (Table 5.2) with training ranges for individuals falling into 'poor', 'fair' and 'average' fitness classifications based on the baseline fitness test. The training intensity of this study was commenced at 35-55% HRR for those falling into the 'poor' fitness category for their age and gender. This was based on the minimal training intensity deemed to be 30% - 40% HRR for unfit healthy people (Swain and

Franklin, 2002, Pollock et al., 1998). An initial training range of 40-60% HRR was devised for those falling into the 'fair' category as 'more' active individuals are proposed to require an intensity in the order of 45 - 50% of HRR (Pollock et al., 1998, Swain and Franklin, 2002). Similarly, an initial training range of 45 – 65% of HRR was devised for those with an 'average' baseline fitness test. These values were also based on the ACSM's Resource Manual for Guidelines for Exercise Testing & Prescription which recommends training to commence at 30% - 45% HRR for sedentary individuals, 40% for other 'beginners', to more than 50% HRR for individuals with higher aerobic capacities. These values were the minimum level of intensity needed to increase cardio-respiratory fitness; as intensities above these thresholds are more effective in increasing fitness, the intensity increased over the duration of the exercise regimen. In defence of the training heart rate ranges devised, patients subjectively perceived their exercise to be at a moderate intensity level using the rating of perceived exertion scale and no adverse effects were noted-so it would appear that exercise was delivered at an appropriate level for participants.

This study was carried out relatively close to the completion of chemotherapy. The effects of on-treatment exercise trials show a blunted cardio-respiratory response and lack of effect (Speck et al., 2010) which may be due to the latent effect of chemotherapy. The wash-out period of chemotherapy drug regimens is not known and some patients remained on ongoing maintenance therapy. The negative effects of chemotherapy depend on the type and dosage of drugs prescribed. As a heterogeneous population participated in this study, patients had been on a range of different chemotherapy regimes, each with potentially varied side effects as detailed in Section 1.1.2 (page 4). Physiological changes associated with cancer treatment occur due to a complex interaction with pre-existing conditions and surgery (Schmitz and Speck, 2010). Thus, lower fitness levels in this population may be related to central or peripheral systems or a combination of both.

Sub-maximal tests are frequently used in the cancer population. Ideally, a maximum cardio-pulmonary exercise test should be performed; however this was not feasible due to a lack of resources. In a systematic review of cardio-respiratory exercise testing

in clinical oncology research; it was reported that 45% of intervention studies used sub-maximum exercise testing (Jones et al., 2008), although no gold standard sub-maximal test exists in this population. The Modified Bruce Treadmill test was chosen over the Bruce Protocol for use in this study, as it starts at a lower workload and is deemed more suitable for sedentary individuals. It was found to be safe and utilised walking which was a familiar activity to participants. To improve standardisation of testing, the same study personnel carried out all tests on the same treadmill.

The failure of our intervention to significantly increase fitness may have been related to the testing protocol of the Modified Bruce test. This protocol may have diluted the effects of the intervention due to not being sensitive or specific enough to pick up subtle changes in fitness due to the cut-off points of the 3-minute stages being too wide. Time-to end-of-treadmill test is potentially a more sensitive measure and showed a significant time effect however didn't yield results for a group effect, in those who adhered well to the intervention.

There was a trend towards a decrease in waist circumference noted in the exercise group among those who adhered >90%, with no changes in body mass index or fat-free mass. Of note waist circumference at baseline was 94.6cm for males and 86.4cm for females at baseline. This is higher than recommended values for females of 80cm and at the upper end of recommended levels for males of 94cm. Converse to the results of the present study, a systematic review of 14 exercise interventions in breast cancer patients/survivors concluded that there were few changes in body weight but some improvements in body composition (Ingram et al., 2006), although many of these programs were longer in duration than the present study. A study which compared dual-energy X-ray absorptiometry-based (DXA) analysis of fat and fat-free mass to bioelectrical impedance analysis and to regional computed tomography (CT) images in 50 patients with cancer found that bioelectrical impedance overestimated or underestimated fat-free mass substantially compared with DXA as the method of reference (up to 9.3 kg difference) (Mourtzakis et al., 2008). Thus, bioelectrical impedance as a measure of fat-free mass may not be sensitive enough to measure

small changes, however neither CT nor DXA were available for the purposes of this study.

Participants were asked not to change their diet, but there was no dietary intervention incorporated in this study. This may have been required in combination with exercise to accelerate body mass measures, given the relatively short time period of the intervention. However, this would have contaminated the exercise effects, so therefore was not incorporated in the design of this program.

In those who adhered >90% to the exercise programme, self-reported PA improved significantly from baseline to completion of the programme, and was maintained after completion of the programme showing evidence of behavioural change. This highlights the discrepancy between self-reported and objective PA, which mirrors results from Studies I and II already described in this thesis.

A small number of cancer intervention studies incorporated accelerometers as objective measures (Pinto et al., 2005b) of PA. The study by Pinto compared 12 weeks of PA counselling (based on the Transtheoretical Model) delivered via telephone, as well as weekly exercise tip sheets to patients with stage 0 to II breast cancer. A Caltrac accelerometer was used to objective measure physical activity and the 7-day physical activity recall study to assess self-reported PA. Consistent with our study results, greater increases in self-reported PA were shown without comparable increases in objective measurement (Sloane et al., 2009, Pinto et al., 2005b). Conversely, another study evaluated a 12-week home-based walking intervention among breast cancer survivors (n=36) (Matthews et al., 2007). Physical activity was assessed by self-report using the Community Health Activities Model Program for Seniors Physical Activity Questionnaire (CHAMPS) and the Actigraph accelerometer (MTI, Fort Walton Beach, FL, USA) was used in a subsample (n=23). A significant increase in self-reported and accelerometer-monitored PA was reported.

The QOL and fatigue measures used in this study have been well established as psychometrically sound, and high internal consistency values were found. Baseline QOL values were higher than reference values, which were based on mixed cancer

populations including those many years after a cancer diagnosis, so may not be directly comparable. Although some significant clinically significant changes were shown, small effect sizes were generated, which could have been due to the ceiling effect. The physical well-being subscale of the FACT-G questionnaire was the only QOL variable which showed a group effect (although this was based on secondary analysis) which mirrors the change in self-reported PA. Thus, even though fitness and objective PA did not change, patients perceived themselves to have higher levels of physical well-being and to be more physically active. A significant time effect for fatigue and the physical composite measure of the SF-36 was found which suggests this measure may improve naturally over time, irrespective of group assignment. Similarly, a 14-week intervention carried out in a mixed cancer population, reported that fatigue scores decreased in intervention group (Thorsen et al., 2005).

5.4.3 Strengths and weaknesses of this study

This exercise trial addressed some of the methodological considerations of previous RCTs in the oncology population. Namely it included a heterogeneous population, acutely post cessation of treatment, likely to be the most optimal time for an exercise intervention to take place, a high quality objective observation of PA (accelerometer) and high quality assessment of effort (polar monitor and Modified Borg Scale). The aim was to capture data from patients in a real clinical setting. Although the eligibility criteria of this study were tight, and in retrospective were not very 'pragmatic' as was our original premise, nonetheless among eligible patients, this study displayed acceptability levels. Feedback received was very positive and the recruitment rate was high among eligible patients. Adherence and tolerability of the programme was good.

Other strengths of this study were its strictly supervised nature which afforded a great deal of control over the exercise load imposed in the intervention. Many studies are biased towards the healthiest survivors whereas this study recruited participants with lower than average fitness levels and focussed the intervention on those most at need of increasing exercise capacity. There was a blind assessor and also minimal loss-to-follow up and intention-to-treat as well as per-protocol analysis was incorporated.

However, this study also highlights the challenges of intervention delivery in the cancer setting. Recruitment to this programme was quite difficult. The lower than anticipated accrual rate was not due to a lack of interest, but instead due to many other factors such as the momentum necessary to establish a routine referral pattern and the tight time-line after cessation of chemotherapy excluded considerable numbers of otherwise suitable candidates.

As a result of the slower than expected recruitment rates, this study was underpowered, meaning it was less likely to detect significant changes in outcome measures. Also, given the large number of tests, modest statistical changes reported in this study may not have reached significance if adjusted for multiple testing, which increases the possibility of false positive findings.

Due to time restrictions, there was a short follow-up period for this study of three months after completion of the intervention. This time-period was potentially not sufficiently long to assess maintenance of longer-term behavioural change, although this study endeavoured to assess the shorter-term effects of an intervention.

There was no resistance exercise element in this study. It was felt that a programme of this duration and frequency was not sufficient for changes in muscle physiology to occur; only adaptive changes would occur by this time. Many studies are multi-modal in their design-including resistance and aerobic elements as well as multi-disciplinary components, therefore the independent contribution of any one of these components can be difficult to establish.

5.4.4 Conclusion

This short exercise intervention was demonstrated to be feasible and participant feedback received was very positive. However, this programme did not accelerate recovery from treatment and did not increase fitness or objective PA levels. Despite the original premise of being a pragmatic trial, high ineligibility rates and slower than expected recruitment rates, culminated in this trial being underpowered, limiting the ability to evaluate outcomes fully. Despite this, there were some small changes in QOL

parameters and self-reported PA among those who displayed high adherence rates. This demonstrates the challenges of achieving physiological changes in fitness and embedding behavioural change within this population, meaning other delivery methods may warrant further exploration.

Chapter 6

6.1 Introduction

Cancer screening and management has progressed to such an extent that fortunately in many cases, a cancer diagnosis does not carry grave connotations of a poor life expectancy and impending death. This more positive prognosis has extended the direction of cancer research from purely treatment-focussed to a newer area of 'survivorship' research and has raised questions about the longer-term health and well-being of this growing population.

This thesis is the first to explore PA levels objectively from the point of cancer diagnosis to one year into cancer 'survivorship'. PA levels are important at all stages of the cancer trajectory. PA levels were low at the point of cancer diagnosis as outlined in the first study of this thesis (Chapter 3), and remained low even after treatment for cancer ceased as described in the second study (Chapter 4). This led to the implementation of an intervention to increase PA levels in the third study (Chapter 5), but results demonstrated no difference between the control and experimental arms, indicating that alternative methods need to be considered to increase PA in this population.

6.2 PA as an outcome measure and its quantification method

A limitation of PA studies within the cancer literature has been the pervasive use of self-report measures, which lack precision and are prone to inaccuracies which may lead to 'faulty conclusions' (Colbert and Schoeller, 2011). Self-report measures have been adequate to answer epidemiological questions which require broad information about PA exposure, and their ease of use facilitates the measurement of large population-based studies. However, in order to answer the next generation of questions pertaining to more precise dose-response relationships, more robust PA measurement tools are needed (Colbert and Schoeller, 2011). One such method is

accelerometry, and the three studies described in this research support its feasibility and clinical utility within cancer populations.

Only a small number of studies within the cancer literature have incorporated accelerometers as a measure of PA (Demark-Wahnefried et al., 2008, Matthews et al., 2007, Maddocks et al., 2010, Dahele et al., 2007, Sloane et al., 2009, Nikander et al., 2007, Rogers et al., 2009a, Lynch et al., 2010, Pinto et al., 2005b, Vallance et al., 2007). The research presented in this thesis was unique in that no previous study incorporated accelerometer measurement when assessing PS in a heterogeneous cancer population at the time of cancer diagnosis, in patients assessed longitudinally in the first year after cessation of chemotherapy, or as part of an intervention study during the first year after cessation of chemotherapy.

Results of Study III showed an increase in self-reported PA without a comparable change in objectively measured PA. A divergence between objective and self-reported PA was also noted in Studies I and II which mirrors results from a number of other studies within the cancer literature (Vallance et al., 2007, Sloane et al., 2009, Rogers et al., 2009a, Pinto et al., 2005b). The anomaly between objective measures and self-report has also been highlighted within 'normal' populations. The NHANES study (2003–2004) and (2005–2006) incorporated self-reported and objective measures of PA in a large population of U.S. adults (Troiano et al., 2008, Tucker et al., 2011). Results indicated that the proportion of adults self-reporting sufficient PA to meet guidelines was 6- to 10- fold higher than that measured by accelerometers. Similarly, obese patients undergoing bariatric surgery self-reported five-fold increases in time in moderate-vigorous activity post-surgery, while accelerometer-determined measures indicated a net decrease (Bond et al., 2010). This discrepancy between self-report and more objective measures is worth considering when reviewing PA literature within the cancer area, and highlights the need for incorporation of more robust tools such as accelerometers in future research.

Considering PA more broadly, its measurement has been considered an 'underutilised tool' within the cancer and exercise literature (Rogers, 2010). This has also been borne

out in the most recent meta-analysis published by Fong et al. 2012, in which PA was used as an outcome measure in less than half of the trials included (15 out of 34 trials). When used, it tended to be a secondary outcome measure, and only three studies incorporated objective measures (two used accelerometers and one a pedometer). As highlighted throughout this thesis, PA is an important outcome measure and failing to include it may be a missed opportunity. Indeed, measuring PA objectively could be considered a proxy measure of overall health incorporating QOL, fatigue and physical functioning dimensions. Objective PA may also have great potential to be used as measure of the functional consequences of the disease and its treatment, and more generally as a measure of global functioning within cancer clinical trials (Maddocks et al., 2010). Physical activity may serve as a useful barometer of 'recovery' within survivorship research, although prospective trials would be needed to evaluate these relationships.

As further evidence of the potential usefulness of incorporating PA measures, in a malignant glioma population, Ruden et al. (2011) reported that the six-minute walk test was not predictive of survival, but was found to be a subjective measure of exercise behaviour. However, the Godin Leisure Time Index was predictive of survival, indicating that habitual exercise levels rather than physical capacity may be more important to measure. It is not known whether results are transferable to more heterogeneous cancer populations, and it can only be speculated as to whether accelerometry as a more accurate measure of exercise behaviour, may be an even more accurate prognostic indicator. Should this be the case, objectively measured PA – a relatively straightforward measure, could aid in more accurate prognostication along with traditional measures such as PS scales.

Future work should also focus on how 'fitness' for cancer therapy is assessed in a sedentary society and should tease out the complex relationship between 'fitness' and 'fit' for therapy. Work from this thesis naturally leads to further questions such as how much does cardiovascular 'fitness' predict ability to tolerate treatment, or is a global measure of real-time PA such as accelerometry in fact a better method of predicting 'fitness' for therapy?

Greater consistency in terms of PA measures within the cancer literature is needed. Previously, accelerometers were purely used in research settings due to the technical expertise required for their use. Due to the incorporation of accelerometer technology into iPhones for example, incorporating low-tech versions of these tools may be feasible in the clinical setting and may require further investigation. Newer accelerometer technology is continually being developed and can be integrated into GPS, HR monitors and skin temperature sensors-although some of these may be too burdensome for clinical uses. The future may be the integration of modified accelerometers in iPhones to advance the feasibility of these tools.

6.3 Low PA levels throughout the cancer trajectory

The low PA levels of participants' throughout this study was one of the most striking findings. Mean (SD) time spent sedentary at cancer diagnosis (Study I) was 8.1 (2.1) hours (which corresponded to 61.6% of waking hours spent sedentary), during the first year after cessation of chemotherapy (Study II) was 7.2 (2.1) (54.6% of waking hours sedentary) hours, and the combined average for all participants 2-6 months after cessation of treatment (Study III) was 6.7 (1.9) hours (51.1% of waking hours sedentary).

It may be important to put results of this research in context with available literature. In fact, the majority of studies which incorporated accelerometer measures did not specify time spent sedentary which limits comparison between studies. In a U.S. breast cancer cohort approximately ten years after diagnosis, Lynch et al. (2010) reported that the cancer survivor cohort spent a mean (SD) of 9.3 (1.7) hours sedentary per day (66% of time spent sedentary) while the corresponding value for the non-cancer cohort was 8.2 (1.7) hours. Values in the study by Lynch et al. (2010) were noted to be higher than the present research. However, non-wear time was estimated in the study by Lynch et al. (2010), as opposed to an exercise diary which was incorporated in our research, which is likely to lead to more accurate results. Also, the study by Lynch et al. (2010) assessed long term cancer survivors (mean of 10 years post diagnosis) and the average age of the study population in the study by Lynch et al. (2010) (70 years) was

considerably older than the present study of 52 years. Different societal activity norms may have also accounted for the difference between studies. The study time scale of the work presented in this thesis was similar to the study by Matthews et al. (2007). However, this US based study included a relatively small number of breast cancer participants only, and absolute time spent sedentary was not specified. Percentage time sedentary was reported to be 77.2% and 73.6% in the usual care and intervention groups at baseline. Again, societal factors may have accounted for the difference between Matthews study and the present research. Thus, even considering studies which specified this variable, no good comparisons exist.

It may be helpful to consider sedentary time of 'normal' populations to put results of cancer survivors in context. Most data comes from a longitudinal US based study The National Health and Nutrition Examination Survey (NHANES) – one of the largest studies which has incorporated PA measured by accelerometer. Average number of hours sedentary from 2003-2004 data (>6,000 participants) was 7.7 hours/day (Matthews et al., 2008), and using accelerometer results, less than 5% complied with PA guidelines (Troiano et al., 2008). A more recently published study (Tucker et al., 2011) using NHANES data from 2005-2006 (almost 5,000 participants) reported that the proportion of adults meeting guidelines was 62% for self-report and 9.6% for accelerometry. A smaller Australian sample (n=153), reported that adults spent 57% of time sedentary, although the absolute number of hours was not qualified (Healy et al., 2008b).

Similar sedentary hours therefore were noted in the cancer participants throughout this thesis and the 'normal' population outlined above. However, objective data from Study III indicated that overall 17% of participants at baseline met PA guidelines. This value was lower at 6% on average for Study II, which is similar to the 5% value quoted by Troriano et al. (2008) described above. One can only speculate that the difference in values found in this thesis between Study II and III was related to participants being signed up for an exercise trial. Nonetheless, even the value of 17% compliance with activity guidelines in Study III participants is still low. Of course, it is important to be cognisant that PA guidelines are based on data from studies which employed self-

reported PA methods, so potentially less objectively measured PA is sufficient for health benefits-but exact volumes have not been elucidated to this point.

As PA levels are low in cancer survivors, the challenge is not just to rehabilitate PA levels to 'normal' or pre-diagnosis levels as these are low – but bearing the health benefits in mind, to exceed these levels where possible, so that PA guidelines are met as much as possible.

It may be helpful to consider reasons why PA levels are low throughout the cancer trajectory. Firstly, although the evidence in favour of exercise within the cancer literature is convincing, there seems to be a gap in translation of the evidence base to the observed clinical reality. Potentially, a lack of dissemination of this research 'from bench to bedside' per se is related to a knowledge gap among cancer survivors of the benefits of PA. Following on from this, there is no intuitive link between PA and cancer, and PA has not traditionally been viewed as a modifiable risk factor within this area. It is possible that many health care professionals are not fully aware of the benefits of PA in this population, or are not familiar with validated methods for increasing it. Cancer survivors may have 'other priorities' and be primarily focussed on the cancer itself and the fear of its recurrence (Llewellyn et al., 2008) which is something which was noted anecdotally among study cohorts in Study II and III. Treatment can also make PA more difficult to adopt into daily life (Irwin, 2008) due to the side-effects of treatment such as fatigue.

6.4 Possible strategies to increase PA levels within this population

As highlighted above, PA levels did not change over the time course of this study and were no higher than matched controls, thus, the 'teachable moment' premise (Demark-Wahnefried et al., 2005) was not borne out. In light of the benefits of PA, it is not sufficient just to rehabilitate levels back to 'normal', as these are low. For instance, the latest Irish population based estimates of PA levels of the 'normal' population indicate that 84% are insufficiently active (Morgan et al., 2008). Therefore, there is a

need to encourage participants to adopt a higher level of PA than before diagnosis, or than their peers. This of course is a difficult challenge as PA, like other behaviours, is to a certain extent constrained by 'social norms' (Rose, 1985), and it can be difficult or inconvenient to flout these norms.

A seminal paper published by the epidemiologist Geoffrey Rose 'Sick individuals and sick populations' in 1985 may be useful to consider in this context. In this paper, two approaches to public health were outlined. One consisted of the 'individual strategy' where high risk or susceptible individuals are identified and offered individual 'protection' i.e. advice or intervention. In this context, this would mean identifying cancer survivors with low PA levels and intervening on an individual basis. While individual advantages pertain to this approach, disadvantages are that individuals who need 'help' are identified, but a larger number of borderline cases are not identified. On the other hand, the 'population strategy' attempts to control the determinants of incidence at a public health level and aims to positively influence the whole distribution of exposure of a particular risk or variable. This more radical approach has led to successes such as the wearing of seat-belts and mass immunisations. In this context, increased PA levels would become a 'social norm' which would ultimately reap great rewards not only in the cancer context but would also result in wider health benefits. However, this approach may yield little individual benefit. It is likely that integrating both approaches would be the optimum. While promoting PA is important to the population as a whole, it may be also important to promote at an individual level, incorporating PA programmes/advice as an integral component of survivorship care.

At an individual level, one possible option to increase PA levels is the rehabilitation model. For many decades, modifiable risk factors have been targets for intervention in other areas of clinical medicine such as cardiology, and cardiac rehabilitation with a focus on risk factor reduction is a well established element of the standard treatment regimen. It is likely that a similar model could work within the cancer area, as research has also attested to the role of PA as a risk factor in the recurrence of certain cancers, namely colo-rectal and breast cancer (Meyerhardt et al., 2006a, Irwin et al., 2008b).

Perhaps more importantly, an exercise-based rehabilitation model could address the debilitating side-effects of cancer and its treatment. Naturally, there are other cancer-related risk factors such as smoking and poor diet. Ideally, a multi-modal integrated education element could also address these other risk factors with PA at its core. Study II indicated a high prevalence of overweight and obese patients, so it may be especially important to incorporate a dietary element as well as a modified exercise element with higher levels of energy expenditure to effect change. This is an important therapeutic target as obesity in breast cancer survivors is associated with a higher rate of recurrence (Chlebowski et al., 2002, Carmichael, 2006).

It took many years for cardiac rehabilitation to become accepted as a mainstream treatment; exercise rehabilitation after cancer on the other hand is at a much earlier stage of evolution, and is likely to become more accepted as the evidence base builds (Stevinson and Fox, 2006). Instead, physical rehabilitation tends to consist of physiotherapy treatment offered on an individual basis for a specific treatment-related impairment such as lymphoedema or reduced shoulder movement. No figure exists for Ireland, but in the UK, fewer than 9% of centres routinely include exercise within the rehabilitation service for patients with cancer (Stevinson and Fox, 2006).

Even if resources were available, which of course is another factor, developing a generic 'cancer rehabilitation' programme would not be an easy challenge. With the advent of personalised medicine and individually prescribed multi-model regimens, there is considerable heterogeneity among cancer populations with varying combinations of surgical, chemotherapeutic, nuclear, biological, and hormonal treatments prescribed. The physical side-effects, wash-out period of chemotherapy regimens and latent treatment effects (Courneya and Friedenreich, 1997b) are not fully known. This may have metabolic consequences as in Study II it was found that by 1 year post cessation of chemotherapy, one third still complained of 'severe fatigue'. This is also a continually changing area, and for example the impact of newer targeted treatments like trastuzumab and its effect on ejection fraction would need to be considered in screening and exercise prescription. Among patients with advanced disease-a resistance programme may be more efficacious for addressing cachexia and

maintaining the ability to carry out activities of daily living (Maddocks et al., 2011, Oldervoll et al., 2004a). It is also not fully known if the exercise prescription should vary to target specific symptoms such as fatigue. Also the timing of a rehabilitation programme should be considered. Programmes which take place during treatment for cancer generally exhibit a dampened-down physiological response (Speck et al., 2010) compared to 'off-treatment' programmes. The most opportune time to carry out an intervention may be during the rehabilitation phase when patients are recovering from cancer (Spence et al., 2010). Home based programmes have been shown to be feasible, convenient and accessible (Rogers et al., 2007, Mock et al., 2005, Pinto et al., 2005b, Segal et al., 2001, Donnelly et al., 2010) and deserve further exploration within this area.

The new ACSM guidelines (Schmitz et al., 2010) provide some much needed guidance in this area but clearly, no 'one size fits all' rehabilitation protocol exists within the cancer area. It is imperative that the "right type of exercise is delivered at the right time to optimise efficacy and safety " (Jones and Peppercorn, 2010). However, many questions remain as to the optimum intervention time, rehabilitation model, programme type and length and precise dose-response relationships are not known.

One possible intervention model was explored in this study. Study III took place within a hospital setting-which is important when initially testing the safety and efficacy of such a programme. Overcoming many of the shortcomings of exercise trials in this area which exclusively focussed on the breast cancer population, during the 'on-treatment' phase or else many years into survivorship - this study was designed to be pragmatic and included a heterogeneous cancer population in the acute phase after cessation of chemotherapy, when the need for intervention was perceived to be greatest. In practice, the eligibility criteria still eliminated many cancer survivors. The 2-6 month time period after cessation of chemotherapy-designed to reflect the so called "teachable moment" (Demark-Wahnefried et al., 2005) resulted in slow recruitment, and ultimately an underpowered study. The lack of a treatment effect on the majority of outcomes highlights the difficulty of designing a short, clinically

transferable intervention to effect change among mixed cancer populations and underlines the need to explore other models.

A pragmatic 'individual approach' to be considered is PA counselling which is generally not incorporated into survivorship care planning (Irwin, 2009). Indeed, providers' of and survivors' have reported favourable opinions regarding survivorship care plans, and the institute of Medicine in the US has recommended their widespread use, therefore incorporation of physical activity advice into this document may be feasible (Salz et al., 2012). However, it is not known whether education alone as part of survivorship care planning would be sufficient to raise awareness to such as level that behavioural change would occur, and there is no strong evidence to support it. Although, Rose (1985) suggested that 'once only advice is a waste of time', and that considerable follow-up time is necessary to effect change. It has been shown that an oncologist's recommendation to participate in PA makes a positive impact in terms of uptake (Jones et al., 2004, Segar et al., 1998). This approach is clearly underutilised, as a postal questionnaire sent to oncologists and surgeons in the United Kingdom to investigate whether PA was discussed with their patients reported that 55.9% did not routinely discuss PA in consultations (Daley et al., 2008).

The sedentary behaviour of patients with cancer has been highlighted throughout this thesis. Breaking up sedentary time and substituting it with light activity has been shown to have beneficial associations with adiposity and metabolic biomarkers in healthy populations (Healy et al., 2008a, Healy et al., 2011) and has been suggested as a strategy to reduce the risk of Type II diabetes and cardiovascular disease (Healy et al., 2007a). A very recently published (Dunstan et al., 2012) randomised trial compared the effects of uninterrupted sitting, seated with 2-min bouts of light-intensity walking every 20 min, and seated with 2-min bouts of moderate-intensity walking every 20 min on postprandial glucose and insulin levels in overweight and obese subjects. Results indicated that interrupting sitting time with light or moderate intensity walking may improve glucose metabolism as postprandial glucose and insulin levels were reduced in this population of overweight/obese adults. As the insulin pathway has been proposed as a factor in cancer aetiology, breaking up sedentary activity may show

promise as a therapeutic target in patients with cancer. This has not yet been explored in the cancer area. Results of this research may indicate the necessity of a paradigm shift within the cancer survivorship area which focuses on reducing sedentary instead of an exclusive focus on promoting increased engagement in moderate and vigorous activity domains. Indeed, the optimum may be to encourage activity at both ends of the activity continuum to maximise overall energy expenditure.

At a population level, strategies are not designed with the cancer population specifically in mind. It would seem that PA has been on the public health agenda in recent years with the publication of National Guidelines on PA recently published by the Department of Health and Children (2009) and two further policy documents were also published by the Department of Transport in 2009 which mainly addressed cycling and walking policies as well as guidelines for group based exercise. The influence of these generic policies on cancer survivors specifically is not known. Although no doubt of benefit, it is likely that these initiatives alone would not be sufficient to result in changes in PA levels.

Future research should also explore what will maximise adherence, and facilitate longer-term maintenance of therapeutic benefits in this population. Newer technologies may be worth exploring further in this regard such as dedicated websites and harnessing the support of on-line communities and PA apps on android phones.

Correlates of PA should also be considered within this area. Correlates of PA generally consist of physical, environmental, demographic, biological, emotional, and cognitive factors as well as behavioural attributes and skills (Trost et al., 2002). Out of all these factors, self-efficacy is considered the strongest correlate of PA, across a variety of populations (Trost et al., 2002). Therefore, promoting self-efficacy may deserve further consideration as part of a strategy to promote PA among cancer populations. Allied to this, future research should also incorporate models of behavioural change into approaches to increase PA, such as the Health Belief Model (Champion and Skinner, 2008), the theory of planned behaviour (Azjen, 1991), and the Social Cognitive Theory (Mc Alister et al., 2008).

The health economic cost of implementing strategies to increase PA levels in cancer survivors is not known. This would have to be weighed up with the cost of inactivity, which can lead to considerable costs, both direct and indirect to governments, employers and society at large. A recent 2008 report termed the 'Physical Activity and the Environment Costing Report' published by the National Institute for Health and Clinical Excellence (NICE) stated that increases in PA can lead to long term improvements in health and decreases in expenditure for health services and economies as a whole. It has been estimated that 'well designed' interventions to instigate sufficient activity in inactive adults could be carried for as little as €800 per person per year (Muller-Riemenschneider et al., 2008). Health economic 'proof' is needed to make a case for PA interventions to become an element of mainstream treatment.

6.5 Critical Evaluation

Limitations pertaining to each study within this thesis were addressed in individual chapters. A number of global limitations pertaining to the three studies within this thesis will be described.

Naturally survival is the outcome measure of utmost importance within the cancer area. The ultimate question is whether more active individuals at diagnosis and throughout the cancer trajectory have better survival prospects. On the other hand, the consequences of inactivity in cancer are not known. There are cellular and metabolic effects of inactivity (Hamilton et al., 2007). It is not known whether these affect tumour progression, regression, as well as treatment toxicity and tolerability. No survival data was available for this study and the effect of longer term activity patterns on mortality and recurrence not evaluated. Prognostic outcomes were not followed up, as this study solely aimed to evaluate the shorter-term effects of PA rather than longer term prognostic markers and survival.

Subject numbers were relatively small within this thesis, although recruitment targets were met for Study I and Study II. In retrospect, the eligibility criteria of Study III were more rigorous than originally envisaged, despite the original premise of being a

pragmatic study. This ultimately led to an underpowered study rendering statistical relations difficult to establish.

The third study in this thesis attempted to overcome the limitations of the majority of studies within the cancer literature which only include breast cancer patients by including heterogeneous cancer populations. Although in practice, the majority of participants had a breast cancer diagnosis due to their suitability, availability and willingness to participate. Little is known about PA patterns in understudied populations such as head and neck cancers, lung cancers and many haematological cancers. All participants within this study were treated with curative intent. Many questions remain about PA levels and their effect in 'on treatment' patients, metastatic and palliative patients.

6.6 Conclusion

The first study in this thesis indicated that at the point of cancer diagnosis, ECOG PS ranked patients appropriately. However, PA levels were lower than verbal descriptors of the scale and fatigue levels were reported to be high, even among patients assigned a "good" PS. Thus, a complex picture was built up of patients at diagnosis generally displaying low objective PA levels, higher levels of self-reported PA, high levels of fatigue, and almost universally assigned a 'good' performance status. The results of this study raised questions about the effect of sedentarism on 'fitness' for therapy and treatment tolerability and naturally led to questions about whether the low PA levels observed at diagnosis were observed throughout the cancer trajectory.

The second study assessed PA levels over the first year after cessation of chemotherapy. There was no difference in activity levels between the cancer cohort and the matched control group, suggesting that PA levels of the cancer cohort after treatment correspond to low societal levels of PA. However, some QOL indices such as cognitive function, and physical function improved throughout the time course of this study. Despite the latter positive effects, the lack of an increase in PA levels and the

increased BMI levels throughout the time course of the study highlight the need to explore interventions to target these variables.

In the third study, an 8 week intervention was implemented soon after completion of adjuvant chemotherapy. Results indicated that while the programme was well received, primary analysis revealed no change in study parameters. However, there were changes in self-reported PA, and physical well-being in those who adhered well to the programme. This study highlighted the challenges of achieving change in fitness and PA behaviour, even with the implementation of an intervention.

Naturally, cancer remains a complex and multi-faceted disease entity. PA represents one small element only of the cancer control strategy and survivorship care planning. Nonetheless, PA is a modifiable factor which can at least help alleviate the medium and long term side effects of treatment, and may affect the risk of cancer recurrence. This thesis highlighted low PA levels through the cancer trajectory from diagnosis into survivorship, and the challenges of reversing this behaviour which clearly merits further attention.

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RT3 ACTIVITY MONITOR INSTRUCTIONS

Thank you for agreeing to wear the RT3 activity monitor. 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 either Julie or Emer on (087) 0679445.

You are required to wear your activity monitor for one week (7 days).

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

RT3 Activity Diary

Day 1: Date:

Time on	Time off	Activities completed when not wearing monitor

Day 2: Date:

Time on	Time off	Activities completed when not wearing monitor

Day 3: Date:

Time on	Time off	Activities completed when not wearing monitor

Day 4: Date:

Time on	Time off	Activities completed when not wearing monitor

Day 5: Date:

Time on	Time off	Activities completed when not wearing monitor

Day 6: Date:

Time on	Time off	Activities completed when not wearing monitor

Day 7: Date:

Time on	Time off	Activities completed when not wearing monitor

Day 8: Date:

Time on	Time off	Activities completed when not wearing monitor

Working out RT3 activity cut-off points

1. Data was downloaded from RT3 accelerometer, exported to excel and saved as a (*.xls) file

2. Combined Vector Magnitude (VM) column was identified from RT3 raw data excel file, and pasted to a separate location within the excel spreadsheet. Calculations were carried out on this column

3. Value corresponding to total number of days accelerometer worn was identified, and data any below this value was deleted (eg if the monitor was worn for 7 days, any values below 10,080 were deleted. The value 10,080 was based on 1440 minutes per day multiplied by 7 days). The RT3 was set up to record data in mode 4, ie a minute-to-minute basis. Therefore every row on the excel sheet corresponded to 1 minute of wearing time. The number of days that the monitor was worn was selected; the information was based on the accompanying activity diary. Each day contains 1440 minutes and therefore for seven days wearing time 10080 row (minutes) were selected.

4. Combined VM column was re-arranged in order of ascending values

5. Non-wear time (including time spent sleeping) was calculated from activity diary above. This corresponding number of minutes was deleted from zero values in this column

6. Number of minutes in sedentary (VM 0-100), light (VM 101-984), moderate (VM 985-2341) and vigorous (VM >2341)[1] domains of activity was calculated

---

[1] Cut-off points based on :
Rowlands AV, Thomas PWM, Eston RG, Topping R. Validation of the RT3 Triaxial Accelerometer for the Assessment of Physical Activity. *Med. Sci. Sports Exerc.* 2004;36(3):518-24.
Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, Mc Dowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc* 2008;40:181-8.

```
            Else
               intSaveColumn = 7
            End If
         Else
            intSaveColumn = 7
         End If
      Else
         If intCurrentRow > 4320 And intCurrentRow <= 5760 Then
            If intStartCount <= 4316 Then
               If intStartCount - 1 + (intCurrentCount / 2) <= 4320 Then
                  intSaveColumn = 7
               Else
                  intSaveColumn = 8
               End If
            Else
               intSaveColumn = 8
            End If
         Else
            If intCurrentRow > 5760 And intCurrentRow <= 7200 Then
               If intStartCount <= 5756 Then
                  If intStartCount - 1 + (intCurrentCount / 2) <= 5760 Then
                     intSaveColumn = 8
                  Else
                     intSaveColumn = 9
                  End If
```

```
                Else
                    intSaveColumn = 9
                End If
            Else
                If intCurrentRow > 7200 And intCurrentRow <= 8640 Then
                    If intStartCount <= 7196 Then
                        If intStartCount - 1 + (intCurrentCount / 2) <= 7200
Then
                            intSaveColumn = 9
                        Else
                            intSaveColumn = 10
                        End If
                    Else
                        intSaveColumn = 10
                    End If
                Else
                    If intCurrentRow > 8640 And intCurrentRow <= 10080
Then
                        If intStartCount <= 8636 Then
                            If intStartCount - 1 + (intCurrentCount / 2) <= 8640
Then
                                intSaveColumn = 10
                            Else
                                intSaveColumn = 11
                            End If
                        Else
```

```
        intSaveColumn = 6
      End If
    Else
      If intCurrentRow > 2880 And intCurrentRow <= 4320 Then
        If intStartCount <= 2876 Then
          If intStartCount - 1 + (intCurrentCount / 2) <= 2880 Then
            intSaveColumn = 6
          Else
            intSaveColumn = 7
          End If
        Else
          intSaveColumn = 7
        End If
      Else

        If intCurrentRow > 4320 And intCurrentRow <= 5760 Then
          If intStartCount <= 4316 Then
            If intStartCount - 1 + (intCurrentCount / 2) <= 4320 Then
              intSaveColumn = 7
            Else
              intSaveColumn = 8
            End If
          Else
            intSaveColumn = 8
          End If
```

```
Else
    If intCurrentRow > 5760 And intCurrentRow <= 7200 Then
        If intStartCount <= 5756 Then
            If intStartCount - 1 + (intCurrentCount / 2) <= 5760 Then
                intSaveColumn = 8
            Else
                intSaveColumn = 9
            End If
        Else
            intSaveColumn = 9
        End If
    Else
        If intCurrentRow > 7200 And intCurrentRow <= 8640 Then
            If intStartCount <= 7196 Then
                If intStartCount - 1 + (intCurrentCount / 2) <= 7200 Then
                    intSaveColumn = 9
                Else
                    intSaveColumn = 10
                End If
            Else
                intSaveColumn = 10
            End If
        Else
            If intCurrentRow > 8640 And intCurrentRow <= 10080 Then
                If intStartCount <= 8636 Then
```

```
                    If intStartCount - 1 + (intCurrentCount / 2) <= 8640 Then
                        intSaveColumn = 10
                    Else
                        intSaveColumn = 11
                    End If
                Else
                    intSaveColumn = 11
                End If
            Else
                If intCurrentRow > 10080 Then
                    If intStartCount <= 10076 Then
                        If intStartCount - 1 + (intCurrentCount / 2) <= 10080
Then
                            intSaveColumn = 11
                        Else
                            intSaveColumn = 16
                        End If
                    Else
                        intSaveColumn = 16
                    End If
                End If
            End If
        End If
    End If
```

```
            End If
          End If
        End If
        If Cells(2, intSaveColumn) = "" Then
          intSaveRow = 2
        End If
        Cells(intSaveRow, intSaveColumn) = intCurrentCount
      End If
    End If
Wend

blnFound = True
Workbooks.Open Filename:="E:\Excel Work\Record Compl Study II.xlsx"
Sheets(1).Activate

While blnFound
  intCheckRow = intCheckRow + 1
  If Cells(intCheckRow, 34) = "" Then
    blnFound = False
  End If
Wend

Workbooks("Record Compl Study II.xlsx").Close

While intDayCounter < 7
  intDayCounter = intDayCounter + 1
  intColumnSum = Cells(27, intDayCounter + 4)
  intColumnCount = Cells(26, intDayCounter + 4)
  Workbooks.Open Filename:="E:\Excel Work\Record Compl Study II.xlsx"
  Sheets(1).Activate
  Cells(intCheckRow, intDayCounter * 2 + 32) = intColumnSum
  Cells(intCheckRow, intDayCounter * 2 + 33) = intColumnCount
  Workbooks("Record Compl Study II.xlsx").Save
```

7. Time in each domain of activity was divided by total number of days monitored to get average total minutes per day in sedentary, light, moderate and vigorous domains of activity

```
    Workbooks("Record Compl Study II.xlsx").Close

Wend

End Sub
```

APPENDIX II INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

☐ **Yes**

☐ No → ***Skip to PART 2: TRANSPORTATION***

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include travelling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

_____ **days per week**

☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ **days per week**

☐ No moderate job-related physical activity → ***Skip to question 6***

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

_____ **hours per day**
_____ **minutes per day**

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

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

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

_____ **hours per day**
_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

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

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

_____ **days per week**

☐ No travelling in a motor vehicle → ***Skip to question 10***

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

_____ **hours per day**
_____ **minutes per day**

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

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

_____ **days per week**

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**
_____ **minutes per day**

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

_____ **days per week**

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

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

_____ **hours per day**
_____ **minutes per day**

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

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

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

_____ **days per week**

☐ No vigorous activity in garden or yard → ***Skip to question 16***

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

_____ **hours per day**
_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do

moderate activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

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

_____ **hours per day**
_____ **minutes per day**

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

_____ **days per week**

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

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

_____ **hours per day**
_____ **minutes per day**

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

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

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

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

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

_____ **hours per day**

_____ **minutes per day**

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

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

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

_____ **hours per day**
_____ **minutes per day**

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

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

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

PART 5: TIME SPENT SITTING

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

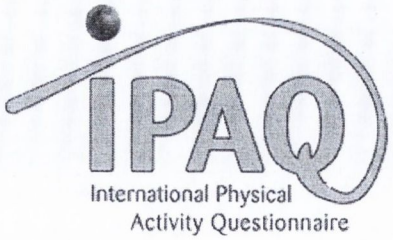
26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**
_____ **minutes per day**

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

_____ **hours per day**
_____ **minutes per day**

This is the end of the questionnaire, thank you for participating.



Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ)

– Short and Long Forms

November 2005

Contents

1. Introduction
2. Uses of IPAQ Instruments
3. Summary Characteristics of Short and Long Forms
4. Overview of Continuous and Categorical Analyses of IPAQ
5. Protocol for Short Form
6. Protocol for Long Form
7. Data Processing Rules
8. Summary Algorithms

Appendix 1. At A Glance IPAQ Scoring Protocol – Short Forms
Appendix 2. At A Glance IPAQ Scoring Protocol – Long Forms

1. Introduction

This document describes recommended methods of scoring the data derived from the telephone / interview administered and self-administered IPAQ short and long form instruments. The methods outlined provide a revision to earlier scoring protocols for the IPAQ short form and provide for the first time a comparable scoring method for IPAQ long form. Latest versions of IPAQ instruments are available from www.ipaq.ki.se.

Although there are many different ways to analyse physical activity data, to date there is no formal consensus on a 'correct' method for defining or describing levels of physical activity based on self–report population surveys. The use of different scoring protocols makes it very difficult to compare within and between countries, even when the same instrument has been used. Use of these scoring methods will enhance the comparability between surveys, provided identical sampling and survey methods have been used.

2. Uses of IPAQ Instruments

IPAQ short form is an instrument designed primarily for population surveillance of physical activity among adults. It has been developed and tested for use in adults (age range of 15-69 years) and until further development and testing is undertaken the use of IPAQ with older and younger age groups is not recommended.

IPAQ short and long forms are sometimes being used as an evaluation tool in intervention studies, but this was not the intended purpose of IPAQ. Users should carefully note the range of domains and types of activities included in IPAQ before using it in this context. Use as an outcome measure in small scale intervention studies is not recommended.

3. Summary Characteristics of IPAQ Short and Long Forms

1. IPAQ assesses physical activity undertaken across a comprehensive set of domains including:
    a. leisure time physical activity
    b. domestic and gardening (yard) activities
    c. work-related physical activity
    d. transport-related physical activity;

2. The IPAQ **short** form asks about three specific types of activity undertaken in the four domains introduced above. The specific types of activity that are assessed are walking, moderate-intensity activities and vigorous-intensity activities.

3. The items in the **short** IPAQ form were structured to provide separate scores on walking, moderate-intensity and vigorous-intensity activity. Computation of the total score for the short form requires summation of the duration (in minutes) and frequency (days) of walking, moderate-intensity and vigorous-intensity activities. Domain specific estimates cannot be estimated.

4. The IPAQ **long** form asks details about the specific types of activities undertaken within each of the four domains. Examples include walking for transportation and moderate-intensity leisure-time activity.

5. The items in the **long** IPAQ form were structured to provide separate domain specific scores for walking, moderate-intensity and vigorous-intensity activity within each of the work, transportation, domestic chores and gardening (yard) and leisure-time domains. Computation of the total scores for the long form requires summation of the duration (in minutes) and frequency (days) for all the types of activities in all domains. Domain specific scores or activity specific sub-scores may be calculated. Domain specific scores require summation of the scores for walking, moderate-intensity and vigorous-intensity activities within the specific domain, whereas activity-specific scores require summation of the scores for the specific type of activity across domains.

4. Overview of Continuous and Categorical Analyses of IPAQ

Both categorical and continuous indicators of physical activity are possible from both IPAQ forms. However, given the non-normal distribution of energy expenditure in many populations, it is suggested that the continuous indicator be presented as median minutes/week or median MET–minutes/week rather than means (such as mean minutes/week or mean MET-minutes/week).

4.1 Continuous Variables

Data collected with IPAQ can be reported as a continuous measure. One measure of the volume of activity can be computed by weighting each type of activity by its energy requirements defined in METs to yield a score in MET–minutes. METs are multiples of the resting metabolic rate and a MET-minute is computed by multiplying the MET score of an activity by the minutes performed. MET-minute scores are equivalent to kilocalories for a 60 kilogram person. Kilocalories may be computed from MET-minutes using the following equation: MET-min x (weight in kilograms/60 kilograms). MET-minutes/day or MET-minutes/week can be presented although the latter is more frequently used and is thus suggested.

Details for the computation for summary variables from IPAQ short and long forms are detailed below. As there are no established thresholds for presenting MET-minutes, the IPAQ Research Committee propose that these data are reported as comparisons of median values and interquartile ranges for different populations.

4.2 Categorical Variable: Rationale for Cut Point Values

There are three levels of physical activity proposed to classify populations:

1. Low
2. Moderate
3. High

The algorithms for the short and long forms are defined in more detail in Sections 5.3 and 6.3, respectively. Rules for data cleaning and processing prior to computing the algorithms appear in Section 7.

Regular participation is a key concept included in current public health guidelines for physical activity.[1] Therefore, both the total volume and the number of days/sessions are included in the IPAQ analysis algorithms.

The criteria for these levels have been set taking into account that IPAQ asks questions in all domains of daily life, resulting in higher median MET-minutes estimates than would have been estimated from leisure-time participation alone. The criteria for these three levels are shown below.

Given that measures such as IPAQ assess total physical activity in all domains, the "leisure time physical activity" based public health recommendation of 30 minutes on most days will be achieved by most adults in a population. Although widely accepted as a goal, in absolute terms 30 minutes of moderate-intensity activity is low and broadly equivalent to the background or basal levels of activity adult individuals would accumulate in a day. Therefore a new, higher cutpoint is needed to describe the levels of physical activity associated with health benefits for measures such as IPAQ, which report on a broad range of domains of physical activity.

'High'

This category was developed to describe higher levels of participation. Although it is known that greater health benefits are associated with increased levels of activity there is no consensus on the exact amount of activity for maximal benefit. In the absence of any established criteria, the IPAQ Research Committee proposes a measure which equates to approximately at least one hour per day or more, of at least moderate-intensity activity above the basal level of physical activity Considering that basal activity may be considered to be equivalent to approximately 5000 steps per day, it is proposed that "high active" category be considered as those who move at least 12,500 steps per day, or the equivalent in moderate and vigorous activities. This represents at least an hour more moderate-intensity activity over and above the basal level of activity, or half an hour of vigorous-intensity activity over and above basal levels daily. These calculations were based on emerging results of pedometers studies.[2]

This category provides a higher threshold of measures of total physical activity and is a useful mechanism to distinguish variation in population groups. Also it could be used to set population targets for health-enhancing physical activity when multi-domain instruments, such as IPAQ are used.

---

[1] Pate RR, Pratt M, Blair SN, Haskell WL , Macera CA, Bouchard C et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *Journal of American Medical Association* 1995; 273(5):402-7. and U.S. Department of Health and Human Services. *Physical Activity and Health: A Report of the Surgeon General.* Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, The Presidents' Council on Physical Fitness and Sports: Atlanta, GA:USA. 1996.

[2] Tudor-Locke C, Bassett DR Jr. How many steps/day are enough? Preliminary pedometer indices for public health. Sports Med. 2004;34(1):1-8.

'Moderate'

This category is defined as doing some activity, more than the low active category. It is proposed that it is a level of activity equivalent to "half an hour of at least moderate-intensity PA on most days", the former leisure time-based physical activity population health recommendation.

'Low'

This category is simply defined as not meeting any of the criteria for either of the previous categories.

5. Protocol for IPAQ Short Form

5.1 Continuous Scores

Median values and interquartile ranges can be computed for walking (W), moderate-intensity activities (M), vigorous-intensity activities (V) and a combined total physical activity score. All continuous scores are expressed in MET-minutes/week as defined below.

5.2 MET Values and Formula for Computation of MET-minutes/week

The selected MET values were derived from work undertaken during the IPAQ Reliability Study undertaken in 2000-2001[3]. Using the Ainsworth et al. Compendium (*Med Sci Sports Med* 2000) an average MET score was derived for each type of activity. For example; all types of walking were included and an average MET value for walking was created. The same procedure was undertaken for moderate-intensity activities and vigorous-intensity activities. The following values continue to be used for the analysis of IPAQ data: Walking = 3.3 METs, Moderate PA = 4.0 METs and Vigorous PA = 8.0 METs. Using these values, four continuous scores are defined:

Walking MET-minutes/week = 3.3 * walking minutes * walking days
Moderate MET-minutes/week = 4.0 * moderate-intensity activity minutes * moderate days
Vigorous MET-minutes/week = 8.0 * vigorous-intensity activity minutes * vigorous-intensity days
Total physical activity MET-minutes/week = sum of Walking + Moderate + Vigorous MET-minutes/week scores.

5.3 Categorical Score

Category 1 Low

This is the lowest level of physical activity. Those individuals who not meet criteria for Categories 2 or 3 are considered to have a 'low' physical activity level.

---

[3] Craig CL,Marshall A , Sjostrom M et al. International Physical Activity Questionnaire: 12 country reliability and validity *Med Sci Sports Exerc* 2003;August

Category 2 Moderate

The pattern of activity to be classified as 'moderate' is either of the following criteria:

a) 3 or more days of vigorous-intensity activity of at least 20 minutes per day
OR
b) 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day
OR
c) 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum Total physical activity of at least 600 MET-minutes/week.

Individuals meeting at least one of the above criteria would be defined as accumulating a minimum level of activity and therefore be classified as 'moderate'. See Section 7.5 for information about combining days across categories.

Category 3 High

A separate category labelled 'high' can be computed to describe higher levels of participation.
The two criteria for classification as 'high' are:

a) vigorous-intensity activity on at least 3 days achieving a minimum Total physical activity of at least 1500 MET-minutes/week
OR
b) 7 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum Total physical activity of at least 3000 MET-minutes/week.

See Section 7.5 for information about combining days across categories.

5.4 Sitting Question in IPAQ Short Form

The IPAQ sitting question is an additional indicator variable of time spent in sedentary activity and is not included as part of any summary score of physical activity. Data on sitting should be reported as median values and interquartile ranges. To-date there are few data on sedentary (sitting) behaviours and no well-accepted thresholds for data presented as categorical levels.

6. Protocol for IPAQ Long Form

The long form of IPAQ asks in detail about walking, moderate-intensity and vigorous-intensity physical activity in each of the four domains. Note: asking more detailed questions regarding physical activity within domains is likely to produce higher prevalence estimates than the more generic IPAQ short form.

6.1 Continuous Score

Data collected with the IPAQ long form can be reported as a continuous measure and reported as median MET-minutes. Median values and interquartile ranges can be computed for walking (W), moderate-intensity activities (M), and vigorous-intensity activities (V) within each domain using the formulas below. Total scores may also be calculated for walking (W), moderate-intensity activities (M), and vigorous-intensity activities (V); for each domain (work, transport, domestic and garden, and leisure) and for an overall grand total.

6.2 MET Values and Formula for Computation of MET-minutes

Work Domain

Walking MET-minutes/week at work = 3.3 * walking minutes * walking days at work

Moderate MET-minutes/week at work= 4.0 * moderate-intensity activity minutes * moderate-intensity days at work

Vigorous MET-minutes/week at work= 8.0 * vigorous-intensity activity minutes * vigorous-intensity days at work

Total Work MET-minutes/week =sum of Walking + Moderate + Vigorous MET-minutes/week scores at work.

Active Transportation Domain

Walking MET-minutes/week for transport = 3.3 * walking minutes * walking days for transportation

Cycle MET-minutes/week for transport= 6.0 * cycling minutes * cycle days for transportation

Total Transport MET-minutes/week = sum of Walking + Cycling MET-minutes/week scores for transportation.

Domestic and Garden [Yard Work] Domain

Vigorous MET-minutes/week yard chores= 5.5 * vigorous-intensity activity minutes * vigorous-intensity days doing yard work (**Note**: the MET value of 5.5 indicates that vigorous garden/yard work should be considered a moderate-intensity activity for scoring and computing total moderate intensity activities.)

Moderate MET-minutes/week yard chores= 4.0 * moderate-intensity activity minutes * moderate-intensity days doing yard work

Moderate MET-minutes/week inside chores= 3.0* moderate-intensity activity minutes * moderate-intensity days doing inside chores.

Total Domestic and Garden MET-minutes/week =sum of Vigorous yard + Moderate yard + Moderate inside chores MET-minutes/week scores.

Leisure-Time Domain

Walking MET-minutes/week leisure = 3.3 * walking minutes * walking days in leisure

Moderate MET-minutes/week leisure = 4.0 * moderate-intensity activity minutes * moderate-intensity days in leisure

Vigorous MET-minutes/week leisure = 8.0 * vigorous-intensity activity minutes * vigorous-intensity days in leisure

Total Leisure-Time MET-minutes/week = sum of Walking + Moderate + Vigorous MET-minutes/week scores in leisure.

Total Scores for all Walking, Moderate and Vigorous Physical Activities

Total Walking MET-minutes/week = Walking MET-minutes/week (at Work + for Transport + in Leisure)

Total Moderate MET-minutes/week total = Moderate MET-minutes/week (at Work + Yard chores + inside chores + in Leisure time) + Cycling Met-minutes/week for Transport + Vigorous Yard chores MET-minutes/week

Total Vigorous MET-minutes/week = Vigorous MET-minutes/week (at Work + in Leisure)

Note: Cycling MET value and Vigorous garden/yard work MET value fall within the coding range of moderate-intensity activities.

Total Physical Activity Scores

An overall total physical activity MET-minutes/week score can be computed as:

Total physical activity MET-minutes/week = sum of Total (Walking + Moderate + Vigorous) MET-minutes/week scores.

This is equivalent to computing:

Total physical activity MET-minutes/week = sum of Total Work + Total Transport + Total Domestic and Garden + Total Leisure-Time MET-minutes/week scores.

As there are no established thresholds for presenting MET-minutes, the IPAQ Research Committee proposes that these data are reported as comparisons of median values and interquartile ranges for different populations.

6.3 Categorical Score

As noted earlier, regular participation is a key concept included in current public health guidelines for physical activity.[4] Therefore, both the total volume and the number of day/sessions are included in the IPAQ analysis algorithms. There are three levels of physical activity proposed to classify populations – 'low', 'moderate', and 'high'. The criteria for these levels are the same as for the IPAQ short [described earlier in Section 4.2]

Category 1 Low

This is the lowest level of physical activity. Those individuals who not meet criteria for Categories 2 or 3 are considered 'low'.

Category 2 Moderate

The pattern of activity to be classified as 'moderate' is either of the following criteria:

d) 3 or more days of vigorous-intensity activity of at least 20 minutes per day
OR
e) 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day
OR

---

[4] Pate RR, Pratt M, Blair SN, Haskell WL , Macera CA, Bouchard C et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *Journal of American Medical Association* 1995; 273(5):402-7. and U.S. Department of Health and Human Services. *Physical Activity and Health: A Report of the Surgeon General.* Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, The Presidents' Council on Physical Fitness and Sports: Atlanta, GA:USA. 1996.

f) 5 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum Total physical activity of at least 600 MET-minutes/week.

Individuals meeting at least one of the above criteria would be defined as accumulating a moderate level of activity. See Section 7.5 for information about combining days across categories.

Category 3 High

A separate category labelled 'high' can be computed to describe higher levels of participation.
The two criteria for classification as 'high' are:

a) vigorous-intensity activity on at least 3 days achieving a minimum Total physical activity of at least 1500 MET-minutes/week

OR

b) 7 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum Total physical activity of at least 3000 MET-minutes/week.

See Section 7.5 for information about combining days across categories.

6.4 IPAQ Sitting Question IPAQ Long Form

The IPAQ sitting question is an additional indicator variable and is not included as part of any summary score of physical activity. To-date there are few data on sedentary (sitting) behaviours and no well-accepted thresholds for data presented as categorical levels. For the sitting question 'Minutes' is used as the indicator to reflect time spent in sitting rather than MET-minutes which would suggest an estimate of energy expenditure.

IPAQ long assesses an estimate of sitting on a typical weekday, weekend day and time spent sitting during travel (see transport domain questions).

Summary sitting variables include

Sitting Total Minutes/week = weekday sitting minutes* 5 weekdays + weekend day sitting minutes* 2 weekend days

Average Sitting Total Minutes/day = (weekday sitting minutes* 5 weekdays + weekend day sitting minutes* 2 weekend days) / 7

Note: The above calculation of 'Sitting Total' excludes time spent sitting during travel because the introduction in IPAQ long directs the responder to NOT include this component as it would have already been captured under the Transport section. If a summary sitting variable including time spent sitting for transport is required, it should be calculated by adding the time reported (travelling in a motor vehicle) under transport to the above formula. Care should be taken in reporting these alternate data to clearly distinguish the 'total sitting' variable from a 'total sitting – including transport' variable.

7. Data Processing Rules

In addition to a standardized approach to computing categorical and continuous measures of physical activity, it is necessary to undertake standard methods for the cleaning and treatment of IPAQ datasets. The use of different approaches and rules would introduce variability and reduce the comparability of data.

There are no established rules for data cleaning and processing on physical activity. Thus, to allow more accurate comparisons across studies IPAQ Research Committee has established and recommends the following guidelines:

7.1 Data Cleaning

I. Any responses to duration (time) provided in the hours and minutes response option should be converted from hours and minutes into minutes.
II. To ensure that responses in 'minutes' were not entered in the 'hours' column by mistake during self-completion or during data entry process, values of '15', '30', '45', '60' and '90' in the 'hours' column should be converted to '15', '30', '45', '60' and '90' minutes, respectively, in the minutes column.
III. In some cases duration (time) will be reported as weekly (not daily) e.g., VWHRS, VWMINS. These data should be converted into an average daily time by dividing by 7.
IV. If 'don't know' or 'refused ' or data are missing for time or days then that case is removed from analysis.

Note: Both the number of days *and* daily time are required for the creation of categorical and continuous summary variables

7.2 Maximum Values for Excluding Outliers

This rule is to exclude data which are unreasonably high; these data are to be considered outliers and thus are excluded from analysis. All cases in which the sum total of all Walking, Moderate and Vigorous time variables is greater than 960 minutes (16 hours) should be excluded from the analysis. This assumes that on average an individual of 8 hours per day is spent sleeping.

The 'days' variables can take the range 0-7 days, or 8, 9 (don't know or refused); values greater than 9 should not be allowed and those cases excluded from analysis.

7.3 Minimum Values for Duration of Activity

Only values of 10 or more minutes of activity should be included in the calculation of summary scores. The rationale being that the scientific evidence indicates that episodes or bouts of at least 10 minutes are required to achieve health benefits. Responses of less than 10 minutes [and their associated days] should be re-coded to 'zero'.

7.4 Truncation of Data Rules

This rule attempts to normalize the distribution of levels of activity which are usually skewed in national or large population data sets.

In IPAQ short - it is recommended that all Walking, Moderate and Vigorous time variables exceeding ' 3 hours' or '180 minutes' are truncated (that is re-coded) to be equal to '180 minutes' in a new variable. This rule permits a maximum of 21 hours of activity in a week to be reported for each category (3 hours * 7 days).

In IPAQ long – the truncation process is more complicated, but to be consistent with the approach for IPAQ short requires that the variables total Walking, total Moderate-intensity and total Vigorous-intensity activity are calculated and then, for each of these summed behaviours, the total value should be truncated to 3 hours (180 minutes).

When analysing the data as categorical variable or presenting median and interquartile ranges of the MET-minute scores, the application of the truncation rule will not affect the results. This rule does have the important effect of preventing misclassification in the 'high' category. For example, an individual who reports walking for 10 minutes on 6 days and 12 hours of moderate activity on one day could be coded as 'high' because this pattern meets the '7 day" and "3000 MET-min" criteria for 'high'. However, this uncommon pattern of activity is unlikely to yield the health benefits that the 'high' category is intended to represent.

Although using median is recommended due to the skewed distribution of scores, if IPAQ data are analysed and presented as a continuous variable using mean values, the application of the truncation rule will produce slightly lower mean values than would otherwise be obtained.

7.5 Calculating MET-minute/week Scores

Data processing rules 7.2, 7.3, and 7.4 deals first with excluding outlier data, then secondly, with recoding minimum values and then finally dealing with high values. These rules will ensure that highly active people remain classified as 'high', while decreasing the chances that less active individuals are misclassified and coded as 'high'.

Using the resulting variables, convert time and days to MET-minute/week scores [see above Sections 5.2 and 6.2; METS x days x daily time].

7.6 Calculating Total Days for Presenting Categorical Data on Moderate and High Levels

Presenting IPAQ data using categorical variables requires the total number of 'days' on which all physical activity was undertaken to be assessed. This is difficult because frequency in 'days' is asked separately for walking, moderate-intensity and vigorous-intensity activities, thus allowing the total number of 'days' to range from a minimum

of 0 to a maximum of 21'days' per week in IPAQ short and higher in IPAQ long. The IPAQ instrument does not record if different types of activity are undertaken on the same day.

In calculating 'moderately active', the primary requirement is to identify those individuals who undertake activity on at least '5 days'/week [see Sections 4.2 and 5.3]. Individuals who meet this criterion should be coded in a new variable called "*at least five days*" and this variable should be used to identify those meeting criterion b) at least 30 minutes of moderate-intensity activity and/or walking; and those meeting criterion c) any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum of 600 MET-minutes/week.

Below are two examples showing this coding in practice:

i) an individual who reports '2 days of moderate-intensity' and '3 days of walking' should be coded as a value indicating "*at least five days*";

ii) an individual reporting '2 days of vigorous-intensity', '2 days of moderate-intensity' and '2 days of walking should be coded as a value to indicate "*at least five days*" [even though the actual total is 6].

The original frequency of 'days' for each type of activity should remain in the data file for use in the other calculations.

The same approach as described above is used to calculate total days for computing the 'high' category. The primary requirement according to the stated criteria is to identify those individuals who undertake a combination of walking, moderate-intensity and or vigorous-intensity activity on at least 7 days/week [See section 4.2]. Individuals who meet this criterion should be coded as a value in a new variable to reflect "*at least 7 days*".

Below are two examples showing this coding in practice:

i) an individual who reports '4 days of moderate-intensity' and '3 days of walking' should be coded as the new variable "*at least 7 days*".

ii) an individual reporting '3 days of vigorous-intensity', '3 days moderate-intensity' and '3 days walking' should be coded as "*at least 7 days*" [even though the total adds to 9] .

8. Summary algorithms

The algorithms in Appendix 1 and Appendix 2 to this document show how these rules work in an analysis plan, to develop the categories 1 [Low], 2 [Moderate], and 3 [High] levels of activity.

IPAQ Research Committee
November 2005

APPENDIX 1

At A Glance
IPAQ Scoring Protocol (Short Forms)

Continuous Score

Expressed as MET-min per week: MET level x minutes of activity/day x days per week

Sample Calculation

MET levels	**MET-minutes/week for 30 min/day, 5 days**
Walking = 3.3 METs	3.3*30*5 = 495 MET-minutes/week
Moderate Intensity = 4.0 METs	4.0*30*5 = 600 MET-minutes/week
Vigorous Intensity = 8.0 METs	8.0*30*5 = 1,200 MET-minutes/week
	TOTAL = 2,295 MET-minutes/week

Total MET-minutes/week = Walk (METs*min*days) + Mod (METs*min*days) + Vig (METs*min*days)

Categorical Score- three levels of physical activity are proposed

1. **Low**

   - No activity is reported **OR**
   - Some activity is reported but not enough to meet Categories 2 or 3.

2. **Moderate**

   Either of the following 3 criteria
   - 3 or more days of vigorous activity of at least 20 minutes per day **OR**
   - 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day **OR**
   - 5 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum of at least 600 MET-minutes/week.

3. **High**

   Any one of the following 2 criteria
   - Vigorous-intensity activity on at least 3 days and accumulating at least 1500 MET-minutes/week **OR**
   - 7 or more days of any combination of walking, moderate- or vigorous-intensity activities accumulating at least 3000 MET-minutes/week

Please review the full document "Guidelines for the data processing and analysis of the International Physical Activity Questionnaire" for more detailed description of IPAQ analysis and recommendations for data cleaning and processing [www.ipaq.ki.se].

APPENDIX 2

At A Glance
IPAQ Scoring Protocol (Long Forms)

Continuous Score

Expressed as MET-minutes per week: MET level x minutes of activity/day x days per week

Sample Calculation

MET levels	**MET-minutes/week for 30 min/day, 5 days**
Walking at work= 3.3 METs	3.3*30*5 = 495 MET-minutes/week
Cycling for transportation= 6.0 METs	6.0*30*5 = 900 MET-minutes/week
Moderate yard work= 4.0 METs	4.0*30*5 = 600 MET-minutes/week
Vigorous intensity in leisure= 8.0 METs	8.0*30*5 = 1,200 MET-minutes/week
	TOTAL = 3,195 MET-minutes/week

Domain Sub Scores
Total MET-minutes/week at **work** = Walk (METs*min*days) + Mod (METs*min*days) + Vig (METs*min*days) at work

Total MET-minutes/week for **transportation** = Walk (METs*min*days) + Cycle (METs*min*days) for transportation

Total MET-minutes/week from **domestic and garden** = Vig (METs*min*days) yard work + Mod (METs*min*days) yard work + Mod (METs*min*days) inside chores

Total MET-minutes/week in **leisure-time** = Walk (METs*min*days) + Mod (METs*min*days) + Vig (METs*min*days) in leisure-time

Walking, Moderate-Intensity and Vigorous-Intensity Sub Scores

Total **Walking** MET-minutes/week = Walk MET-minutes/week (at Work + for Transport + in Leisure)

Total **Moderate** MET-minutes/week = Cycle MET-minutes/week for Transport + Mod MET-minutes/week (Work + Yard chores + Inside chores + Leisure) + Vigorous Yard chores MET-minutes

Note: The above is a total moderate activities only score. If you require a total of all moderate-intensity physical activities you would sum Total Walking and Total Moderate

Total **Vigorous** MET-minutes/week = Vig MET-minutes/week (at Work + in Leisure)

Total Physical Activity Score
Total Physical Activity MET-minutes/week = **Walking** MET-minutes/week + **Moderate** MET-minutes/week + Total **Vigorous** MET-minutes/week

Continued.....

Also

Total Physical Activity MET-minutes/week = Total MET-minutes/week (at Work + for Transport + in Chores + in Leisure)

Categorical Score- three levels of physical activity are proposed

1. **Low**

   No activity is reported **OR**
   a. Some activity is reported but not enough to meet Categories 2 or 3.

2. **Moderate**

   Either of the following 3 criteria
   a. 3 or more days of vigorous-intensity activity of at least 20 minutes per day **OR**
   b. 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day **OR**
   c. 5 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum of at least 600 MET-min/week.

3. **High**

   Any one of the following 2 criteria
   - Vigorous-intensity activity on at least 3 days and accumulating at least 1500 MET-minutes/week **OR**
   - 7 or more days of any combination of walking, moderate- or vigorous- intensity activities accumulating at least 3000 MET-minutes/week

Please review the full document "Guidelines for the data processing and analysis of the International Physical Activity Questionnaire" for more detailed description of IPAQ analysis and recommendations for data cleaning and processing [www.ipaq.ki.se].

Appendix III: Godin Leisure Time Index

Godin Leisure-Time Exercise Questionnaire

INSTRUCTIONS

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

CALCULATIONS

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

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

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

EXAMPLE

Strenuous = 3 times/wk

Moderate = 6 times/wk

Light = 14 times/wk

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

Godin, G., Shephard, R. J.. (1997) Godin Leisure-Time Exercise Questionnaire. Medicine and Science in Sports and Exercise. 29 June Supplement: S36-S38.

Godin Leisure-Time Exercise Questionnaire

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

Times Per Week

a) **STRENUOUS EXERCISE**
(HEART BEATS RAPIDLY) _____
(e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)

b) **MODERATE EXERCISE**
(NOT EXHAUSTING) _____
(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)

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

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

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

APPENDIX IV DOCUMENTATION RELATING TO MODIFIED BRUCE SUBMAXIMAL TEST

INFORMATION LEAFLET
EXERCISE TESTING – Version 1

General instructions to help you prepare for your fitness test

- Wear loose-fitting, comfortable clothes that will allow you to participate easily in the test.
- Avoid food, alcohol and caffeine for at least 3 hours before the test.
- Avoid strenuous activity for 24 before the test.
- Avoid excessive intake of food or drink on the day before the measurement.
- If possible, have 6 to 8 hours the night beforehand.
- Ladies are asked to make the researcher aware if they are menstruating before arriving for the test.
- Scarves or light hats are better than wigs to allow proper heat loss for the fitness test.
- Private changing areas will be provided.

Many thanks for your participation in this study. If you have any further questions please do not hesitate to contact Julie or Emer on 0870679445 or bleep #554.

INFORMATION LEAFLET
EXERCISE TESTING – Version 2

General instructions to help you prepare for your fitness test.

- Wear loose-fitting, comfortable clothes that will allow you to participate easily in the test.
- Avoid food, alcohol and caffeine for at least 3 hours before the test.
- Avoid strenuous activity for 24 before the test.
- Avoid excessive intake of food or drink on the day before the measurement.
- If possible, have 6 to 8 hours sleep the night beforehand.
- Please make the researcher aware if they are menstruating before arriving for the test.
- Scarves or light hats are better than wigs to allow proper heat loss for the fitness test.
- If you wear a breast prosthesis it can become uncomfortable during a fitness test. Wearing your prosthesis for the fitness test is not necessary and please do not feel uncomfortable if you choose to go without it.
- Private changing areas will be provided.
- You will be asked to fill out some questionnaires. Bring reading glasses if you require them.

MODIFIED BRUCE PROTOCOL

Equipment required: Treadmill, Heart rate monitor, Stopwatch

Participants will be allowed a period of time to familiarise themselves with the treadmill.

The participant will use 1-2 fingers for handrail support but not as a means of maintaining balance.

As the test progresses the speed and percentage grade will increase to progress the workload as per table 1.

Stage	Speed (mph)	Grade (%)	Duration (min)
0	1.7	0	3
0.5	1.7	5	3
1	1.7	10	3
2	2.5	12	3
3	3.4	14	3
4	4.2	16	3
5	5.0	18	3
6	5.5	20	3
7	6.0	22	3

Rate of perceived exertion will be recorded at the end of each stage (table 2).

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

Reasons to terminate testing

- When the subjects heart rate reaches 75% of the heart rate reserve.
    - HRR = HR max – HR resting.
    - HR max = 220 – age.

- => Target HR = (HR max – HR resting)(0.75) + HR resting.

If the patient asks to stop due to physical problems such as pain, fatigue, dizziness or difficulty breathing.

Cardiovascular Fitness cut-off levels: Based on VO_2 max ($mL.kg^{-1}.min^{-1}$)

Gender	Age	Poor	Fair	Average	Good	Excellent
Males	< 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
Females	< 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

Taken from 'Essentials of Exercise Physiology', 3rd ed. W. D. Mc Ardle, F. I. Katch, V. L. Katch. *Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Pina IL, Rodney R, Simons-Morton DG, Williams MA, and Bazzarre T.* Exercise Standards for Testing and Training. A Statement for Healthcare Professionals from the American Heart Association. *Circulation* 2001; 104: 1694-740.

APPENDIX V DOCUMENTATION RELATING TO BRIEF FATIGUE INVENTORY

FATIGUE INVENTORY

Study ID #:_____ Hospital #:_____ Time: _____

Name: _____ Date: _____/_____/_____

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right **NOW**.

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your **USUAL** level of fatigue during past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your **WORST** level of fatigue during past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours fatigue has interfered with your:

   A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

   B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

   C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

   D. Normal work (includes both work outside the home and daily chores)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

   E. Relations with other people

Copyright 1999, The University of Texas M.D. Anderson Cancer Center. All rights reserved.

0 1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interferes

F. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interferes

Copyright 1999, The University of Texas M.D. Anderson Cancer Center. All rights reserved.

Calculation of subsets of The Brief Fatigue Inventory (BFI)

Global BFI Score

To calculate this score, each individual item number is summed, then divided by the number of scores. This score is calculated by finding the mean overall score; that is by adding the scores from each individual item and by dividing by the number of items included.

Fatigue Severity Classification (Severe vs. Non-severe)

Based on response to item 3 only (worst level of fatigue in the last 24 hours). Fatigue severity classified as being either 'severe' (a score of 7-10) or non-severe (score 0-6).

Appendix VI: FACIT scales documentation

FACIT-F (Version 4)

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

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACIT-F (Version 4)

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

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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FACIT-F (Version 4)

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

English (Universal)
Copyright 1987, 1997

FACT-G (Version 4)

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

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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FACT-G (Version 4)

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

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

English (Universal)
Copyright 1987, 1997

FACIT Administration and Scoring Guidelines (from www.facit.org)

Administration:

The FACIT scales are designed for patient self-administration, but can also be administered by interview format. For self-administration, patients should be instructed to read the brief directions at the top of the page. After the patient's correct understanding has been confirmed, he/she should be encouraged to complete every item in order without skipping any. Some patients may feel that a given question is not applicable to them and will therefore skip the item altogether. **Patients should be encouraged to circle the response that is most applicable.** If, for example, a patient is not currently receiving any treatment, the patient should circle "not at all" to the question "I am bothered by side effects of treatment."

During interview administration, it is helpful to have the patient hold a card on which the response options have been printed. Interview administration is considered appropriate given adequate training of interviewers so as to elicit non-biased patient responses. One of the aims of a large multi-center study of cancer and HIV patients (N=1227) was to test the psychometric properties and statistical equivalence of the English and Spanish language versions of the FACT subscales across literacy level (low vs. high) and **mode of administration** (self vs. interview). Technical equivalence across mode of administration was demonstrated in the high literacy patients; there were no differences in data quality or in mean QOL scores, after adjustment for performance status rating, socioeconomic status, gender and age. Technical equivalence between modes of administration with the FACT permits unbiased assessment of the impact of chronic illnesses and their treatments on patients from diverse backgrounds.

Scoring the FACT-G:

The FACT-G scoring guide identifies those items that must be reversed before being added to obtain subscale totals. Negatively stated items are reversed by subtracting the response from "4". After reversing proper items, all subscale items are summed to a total, which is the subscale score. **For all FACIT scales and symptom indices, the higher the score the better the QOL.**

Handling missing items. If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. This can be done on the scoring guide or by using the formula below:

Prorated subscale score = [Sum of item scores] **x** [N of items in subscale]□÷ [N of items answered]

When there are missing data, prorating by subscale in this way is acceptable as long as **more than** 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc). The total score is then calculated as the sum of the un-weighted subscale scores. The FACT scale is considered to be an acceptable indicator of patient quality of life as long as **overall item response rate** is greater than 80% (e.g., at least 22 of 27 FACT-G items completed). This is not to be confused with individual subscale item response rate, which allows a subscale score to be prorated for missing items if greater than 50% of items are answered. In addition, a total score should only be calculated if ALL of the component subscales have valid scores.

NOTE: Computer programs written in SPSS and SAS for the FACIT scales and symptom indices are provided on diskette in Section 4 of the manual or can be downloaded from the website at www.facit.org for a nominal fee. Standard raw score scoring templates for all FACIT scales and symptom indices are also provided in Section 4 of the manual or under the "Validity and Interpretation" section of the website.

Scoring the Specific Scales & Symptom Indices:

For the "Additional Concerns" subscale (e.g., cancer-specific questions) and the symptom indices, the procedure for scoring is the same as described above for the FACT-G. Again, **over** 50% of the items (e.g., 5 of 9 items, 7 of 12 items) must be completed in order to consider each subscale score valid.

NOTE: scoring algorithms for the FACIT-TS-G and FACIT-TS-PS are different from other FACIT scales. Please refer to the specific scoring templates for more detail.

Deriving a Total Score:

The total score for the specific FACIT scales is the sum of the FACT-G (the first 4 subscales common to almost all scales) plus the "Additional Concerns" subscale. The symptom indices do not include the FACT-G in the total score. By following this scoring guide and transcribing the FACT-G score, the two totals can be summed to derive the **TOTAL FACT/FACIT SCORE**.

Notes:

1. Multilingual versions can be scored on the English language scoring guides.

2. Several scales have more items listed in the "Additional Concerns" subscale than are currently recommended for scoring. This is usually because additional work on a given subscale has suggested a need for additional items. However, it may take awhile for the new items to be validated so we don't formally recommend they be included in the scoring until we know more about how the item(s) function. We include the items on the scale to encourage investigators who have the time or resources to evaluate their data according to the existing scoring recommendations and to test out the value of the new item(s). As always, we welcome collaborators to share any relevant data of this nature to help further reliability and validity testing of the FACIT questionnaires.

Selecting Scores for Analyses:

These scoring templates allow one to obtain two different total scores in addition to each individual subscale score. The FACT-G total score provides a useful summary of overall quality of life across a diverse group of patients. The disease-specific questionnaire total scores (i.e., FACT-G plus disease-specific subscale score) may further refine the FACT-G summary score. Two alternative approaches are noteworthy, however. One is to separately analyze the FACT-G total score and the specific subscale score. Another is to select subscales of the FACT which are most likely to be changed by an intervention being tested. For example, the Physical, Functional, and Cancer-specific subscales would be most likely to change in a chemotherapy clinical trial. One could also consider

creating a separate a priori index which sums two or three subscales. This has been done with the FACT-L and many other FACIT scales, combining the Physical, Functional and 7-item Lung Cancer Subscales into a 21-item **Trial Outcome Index** (Cella, Bonomi, Lloyd et al, 1994; Brady, Cella, Mo, 1997; Cella, 1997). On the other hand, the Emotional or Social Well-being subscale would be expected to change most when evaluating a psychosocial intervention.

Comparing Version 4 scores to Previously Published (Version 2 & 3) Scores:

Most of the questions from Version 3 remain intact in Version 4 (see item history table in section 3 of the manual for details), although some items have been reworded and a few have changed from being negatively stated to positively stated items. Comparison between scale scores in these two versions is fairly straightforward. Adjustments must be made, however, when comparing the total FACT/FACIT score and when comparing the Emotional Well-Being (EWB) subscale score between the two versions. To compare Version 3 and 4 EWB scales, item GE6 (#25 in Version 3) must be omitted from the scoring of version 4. This can be done by scoring the first 5 items of the EWB subscale, multiplying by 5 (not 6), and dividing by the number of questions answered (not including the sixth question). The Version 4 total FACT-G score has been affected by the dropping of the Relationship with Doctor subscale and the addition in the scoring of item GE6 (#25 in Version 3). One way to compare total scores is to drop item GE6 from the Version 4 scoring and add **6.85** (mean score of the RWD subscale as reported in Cella et al., 1993) to the sum of the four subscales (Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being). This will give you the best estimate for comparison of published FACT/FACIT data.

Appendix VII: EORTC-QLQ C30 V3

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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Scoring the EORTC QLQ-C30 QUESTIONNAIRE

Scoring ranges from 0-100

- Functional scale: high score = high level of function
- Global health status: QoL scale: high score = high QoL
- Symptom scale/ item: high score = high level of problems

Calculating the Score

1. Calculate the **raw score**
   - The average of the items contributing to the scale
   - Raw score (RS) = (Q1 + Q2 +.....+ Q*n*)/*n* *n* = number of items

2. Standardise raw score using **linear transformations**
   - Used so that scores fall in the range of 0-100
   - High and low scores are interpreted as above
   - Linear transformation formulae are as follows:

Functional scales:	$S = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$
Symptom scales / items:	$S = \{(RS-1)/range\} \times 100$
Global health status / QoL:	$S = \{(RS-1)/range\} \times 100$

Fig 1: Linear Transformation Formulae. EORTC QLQ-C30 Scoring Manual

Scoring is summarised in fig 2. This table applies to version 3.0 of the EORTC QLQ-C30. The range in each case refers to the difference between the maximum and minimum possible value for each score, i.e. if an item is scored 1-4 the range is 3.

If using version 2.0 of the questionnaire the scoring for questions 1-5 (or scale PF2) is slightly different. Questions 1-5 are yes/no answers, therefore the range is 1. Refer to fig 3 for details.

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

Fig 2: Scoring the QLQ-C30 version 3.0. EORTC QLQ-C30 Scoring Manual

	Scale	Number of items	Item range*	**Version 2.0** Item numbers	Function scales
Physical functioning (original scale) *Delete PF2*	PF	5	1	1 to 5	F

Fig 3: Scoring the QLQ-C30 version 2.0. EORTC QLQ-C30 Scoring Manual

Missing Items

Multi-item scales

- If at least half the items from each scale has been answered then it can be assumed that the value of the missing items is equal the average of the items that are present.
- Some scales only contain 2 items, i.e. NV (ref to fig 2), therefore only one item needs to be answered.
- Other scales have a greater number of items, i.e. FA which contains 3 items. In this case at least 2 items should be present.
- If less than half the items are missing for a scale then the scale cannot be imputed.

Single-item scales

- If single item scales are missing they cannot be imputed.

Interpretation of Data

There are a number of difference ways to interpret and publish results

Report raw scores and transformed scores

- Raw scores may be more clinically relevant as they provide descriptions such as "very much" or "a little".
- Scores may be reported as distinct groups, i.e. "not at all" vs. "any extent"
- Transformed scores are also reported, i.e. a value between 0-100

Compare against published data

- Published data in EORTC QLQ-C30 Reference Values manual
    - Scores typically seen in different patient groups
    - Identify when scores are higher/lower than normal
    - Size of difference in scores between patients

Changes in scores over time

- Anchor-based interpretations
    - Compare changes in QoL scores to other clinical changes or results
    - Osoba et al1998; King 1996
- Distribution-based interpretations
    - Statistical distribution of results
    - Cohen's effect size
    - Standardised response mean

References

Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomly A. *The EORTC QLQ-C30 Scoring Manual* 3rd ed. Brussels European Organisation for Research and Treatment of Cancer, 2001.

Aaronson NK, Cull AM, Kaasa S, Sprangers MAG. The European Organisation for Research and Treatment of Cancer (EORTC) modular approach to quality of life assessment in oncology: an update. In Spilker E, ed. *Quality of Life and Pharmacoeconomics in Clinical Trials,* 2nd edn. New York, Raven Press, 1996, 179-189

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Takeda F. (1993) The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality of life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 85(5): 365-376***

APPENDIX VIII DOCUMENTATION RELATING TO THE SF-36 PHYSICAL FUNCTIONING COMPONENT

SF – 36 Physical Functioning Component

Study ID #:_____ Hospital #:_____ Time: _____

Name: _____ Date: _____/_____/_____

The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

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

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Scoring the SF-36

Dealing with missing scores

The standard approach for treating missing scores is to impute the missing score with a person-specific estimate derived by calculating the mean response value to the answered items in the same scale when a respondent has answered at 50% of the items in that scale (Ware et al., 2000).

As PF is a hierarchical scale, the item response theory (IRT) was used rather than imputing the missing score with a person-specific estimate derived by calculating the mean response value to the answered items. This method generates an answer based on their responses to previously answered items.

Process for scoring the SF-36

1. Enter item response data
2. Recode item response values
3. Determine health domain raw scores
4. Transform health domain raw scores to 0-100 scores
5. Transform heath domain scale 0-100 to T-scores
6. Score component summary measures
7. Score response consistency index (optional).

The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

Question No.	Variable label	Verbatim items
3a	PF01	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports
3b	PF02	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
3c	PF03	Lifting or carrying groceries
3d	PF04	Climbing <u>several</u> flights of stairs
3e	PF05	Climbing <u>one</u> flight of stairs

3f	PF06	Bending, kneeling, or stooping
3g	PF07	Walking more than a mile
3h	PF08	Walking several hundred yards
3i	PF09	Walking one hundred yards
3j	PF10	Bathing or dressing yourself

Precoded and final values for items 3A-3J

Response choice	**Precoded item value**	**Final item value**
Yes, limited a lot	1	1
Yes, limited a little	2	2
No, not limited at all	3	3

Formula for scoring and transforming scales

Scale	**Sum final item values**	**Lowest and highest possible raw scores**	**Possible raw score range**
Physical functioning	3a+3b+3c+3d+3e+3f+3g+3h+3i+3j	10, 30	20

$$\text{Transformed Scale} = \left[\frac{\text{Actual raw score} - \text{lowest possible raw score}}{\text{Possible raw score range}} \right] * 100$$

Example: A Physical Functioning raw score of 21 would be transformed as follows:

$$\left[\frac{(21-10)}{20} * 100 \right] = 55$$

Where lowest possible score = 10 and possible raw score range =20

Norm-based scoring of scale scores

This involves the norm-based scoring of each 0-100 scale score. A linear z-score transformation is used so all eight SF-36 scales have a mean of 50 and a standard deviation of 10. This allows scale results to be meaningfully compared with the other scales and have a direct interpretation in relation to the distribution of scores in the 1988 general US population. Specifically, all scores above or below 50 are above or below the average, in the 1988 general US population.

Step 1

Formula for z-score standardization of SF-36v2 scales of physical functioning component

PF_Z = (PF – 83.29094)/23.75883

These values are from the 1988 General US population means and SD

Step 2

Involves transforming each SF-36v2 z score to the norm-based (50,10) scoring. This is accomplished by multiplying each z-score from Step 1 by 10 and adding the resulting product to 50.

Norm-based: PF = 50 + (PF_Z*10)

WARE, J. E., KOSINSKI, M. & DEWEY, J. E. 2000. *How to score Version Two of the SF-36 Health Survey,* Lincoln, RI, Quality Metric, Incorporated.

APPENDIX IX DOCUMENTATION RELATING TO BIOIMPEDENCE MEASUREMENT

PROTOCOL FOR USING THE TANITA BODY COMPOSTITION ANALYSER

1. Subjects will be asked to void before measurement.
2. Check position bubble – alter legs if necessary
3. Press clothes – alter if necessary
4. Body Composition Mode 1
5. Before measurement, any dust or dirt will be cleaned form the palms and the feet.
6. Bare feet will be placed correctly on the electrode panel for measurement. Feet will be positioned on the heel and toe electrodes on each side in roughly equal proportions as per the instruction manual.
7. Arms will be placed straight down during measurement.

Points to note

- Do not use equipment near other products that emit electromagnetic waves.
- Avoid contact between the arms and torso and between the inner thighs. If they do come in contact with each other during measurement, a dry towel should be used as a barrier.
- Measurements should be carried out under the same conditions each day.

Reference

Multi-Frequency Body Composition Analyzer MC-180MA Instruction Manual.

APPENDIX X MEASUREMENT OF WAIST CIRCUMFERENCE

GUIDELINES FOR MEASURING WAIST CIRCUMFERENCE

Waist Circumference

- Measurement will be taken at the smallest area of the waist, typically 1 inch (2.54 cm) above the umbilicus.
- Patient will leave on one layer of clothes.
- Patient will find the half way point between the lowest point of the ribs and the iliac crest.
- Patient holds tape and turns.
- Two measurements will be taken and the average calculated.

	Waist Circumference (cm)	
Risk Category	**Women**	**Men**
Very Low	<70	<80
Low	70-89	80-99
High	90-109	100-120
Very High	>110	>120

Table 1: Criteria for Waist Circumference in Adults

References

AMERICAN COLLEGE OF SPORTS MEDICINE. (2009) *ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription.* 6th ed. Philadelphia: Lippincott Williams & Wilkins.

APPENDIX XI: ETHICAL APPROVAL

NOTEPAPER MUST NOT BE USED FOR
RIPTIONS OR INVOICING PURPOSES

AMNCH Research Ethics Committee Secretariat
Lynch Ph: 4142860 email: Dan.Lynch@amnch.ie
a Ryan Ph: 4142342 email: Ursula.Ryan@amnch.ie
tariat Fax 4142371

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND

TELEPHONE +353 1 4142000

Julie Walsh
cipline of Physiotherapy
ity Centre for Health Sciences
James's Hospital
es Street
blin 8

July 22nd 2008

Novel Methods of Measuring Physical Activity in Patients with Cancer and the Role of Exercise Interventions

se quote this reference in any follow up to this letter: 2008/07/01 Chairman's Action.

Julie,

nk you for your recent submission of the above proposal to the SJH/AMNCH
earch Ethics Committee.
Vice-Chair, having reviewed the proposal, has given ethical approval on behalf of
Committee.

rs sincerely,

iel R. Lynch,
etary,
/AMNCH Research Ethics Committee

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

SJH/AMNCH Research Ethics Committee Secretariat
Ursula Ryan Ph: 4142342 email: Ursula.Ryan@amnch.ie
Secretariat Fax 4142371

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

May 4th. 2011

Ms. Julie Walsh
Department of Physiotherapy
Trinity Centre for Health Sciences
St. James's Hospital
Dublin 8

Re: Novel methods of measuring physical Activity in Cancer patients and the role of exercise interventions.

Please quote this reference in any follow up to this letter: 2011/13/09

Dear Dr. Walsh,

Thank you for your Amendment submitted March 2011.

The Chairman, on behalf of the Research Ethics Committee, has given full ethical approval to this amendment.

Yours sincerely

Ms. Ursula Ryan
Secretary,
SJH/AMNCH Research Ethics Committee

SAINT LUKE'S
HOSPITAL

Ms. Julie Walsh,
Discipline of Physiotherapy,
Trinity Centre for Health Sciences,
St. James's Hospital,
DUBLIN 8.

6th July 2010..

Re: PEACH Trial – Prescribed Exercise after Chemotherapy.

Dear Ms. Walsh,

I am pleased to inform you that the above referenced proposal has been reviewed, noted and approved by the Research Management Committee, St. Luke's Hospital.

With kind regards,
Yours sincerely,

Ann Broekhoven

Ann Broekhoven,
Chairperson,
Research Management Committee.

c.c. Prof. Donal Hollywood, Consultant Radiation Oncologist.

St. Luke's Hospital

Highfield Road, Rathgar, Dublin 6
Tel: 01 406 5000, Fax: 01 497 2941

SAINT LUKE'S
HOSPITAL

Ms. Julie Walsh,
Discipline of Physiotherapy,
Trinity Centre for Health Sciences,
St. James's Hospital,
DUBLIN 8.

7th July 2010.

Re: PEACH Trial – Prescribed Exercise after Chemotherapy.

Dear Ms. Walsh,

I am pleased to inform you that the above referenced proposal has been reviewed, noted and approved by the Research Ethics Committee, St. Luke's Hospital.

With kind regards,
Yours sincerely,

p.p. V. Barnes.

Dr. Sheelah Ryan,
Chairperson,
Research Ethics Committee.

c.c. Prof. Donal Hollywood, Consultant Radiation Oncologist.

St. Luke's Hospital

Highfield Road, Rathgar, Dublin 6
Tel: 01 406 5000, Fax: 01 497 2941

APPENDIX XII STUDY I PATIENT INFORMATION LEAFLET AND CONSENT FORM

Patient Information Leaflet (Study I)

Study name: 'Novel methods of measuring physical activity and the role of exercise interventions in patients with cancer'

What is this study about?
A study investigating the activity levels of patients after admission to hospital is being conducted by the Trinity College Department of Physiotherapy and the Department of Medical Oncology in St James's Hospital. Before deciding the most appropriate next step in your treatment plan your doctor will need to know how you are physically coping in your home environment. From discussion with you, your doctor will score your level of daily activity on a scale known as a performance status scale. This is widely used as a guide to how patients may tolerate future treatments.

Until now it was not possible to compare this scale to patients' actual physical activity levels. Therefore, it is unknown whether an interview between a doctor and a patient about how well a patient is managing at home, gives the doctor an accurate impression of how active/inactive the patient really is. The availability of new technology permits the accurate measurement of physical activity.

Using physical activity monitors, this study aims to measure your activity levels while at home for a number of days after you are discharged from hospital. Your doctor will have no access to the information recorded by the activity monitors in this study. Participation in this study will therefore not affect your treatment options in any way.

If you choose to participate in this study you will be required to wear an activity monitor for approximately 7 days. You will also be given two short questionnaires about your activities and fatigue levels while at home.

Who is being asked to participate?
All patients over the age of 18 who are being discharged home or to convalescence following an admission for a procedure related to the treatment or investigation of a confirmed solid tumour or lymphoma being considered for further treatment will be asked to participate in this study.

What do I have to do?
If you choose to participate you will have your age, height and weight recorded by an investigator who will also explain to you about the activity monitor and instruct you on its use. Your activity monitor will be given to you or posted so that you can wear it for the week leading up to your appointment. You should carry on activity as normal while wearing the activity monitors.

At your follow up appointment you will have a medical assessment. As is usual, among the many things your doctor will do after seeing you is to record a score based on his/her impression of your physical activity. On this day you will be asked to return both activity monitors and questionnaires to the investigator.

Activity Monitor

RT3 Accelerometer: This small device is attached to the waistband using a belt clip (Figure 1). It will measure your physical activity for the days that you are at home. It records when, how much and for how long you are active each day. The device must be removed for bathing, swimming and sleeping. You will be given a simple diary for the days that you are to wear this monitor. On this diary you should note the times when you put the monitor on and off and also note any activities completed while you were not wearing the monitor (e.g. showering)

Fig. 1 RT3 Accelerometer

Questionnaire

The International Physical Activity Questionnaire contains questions about the type of activity you do and for how long you do each activity every day for 7days. It includes questions about activities you do at work, as part of your house and yard work, to get from place to place and in your spare time for recreation, exercise or sport.

The Brief Fatigue Inventory is a questionnaire used to assess the severity of fatigue on activities of daily living over the previous 24 hours.

What are the benefits to me?

There are no direct benefits to you for participating in this study, but the results may benefit future patients.

Are there any risks to me?

There is no risk to you that we can think of, in participating in this study. The practitioners involved in this study have current medical indemnity cover.

Who can not participate in this study?

You may not participate in this study if you are unable to give informed consent or if you are currently using external equipment e.g. NG feed or IV drips or if you have a confirmed pregnancy. Also, if you have significant cardiovascular or respiratory disease which restricts your mobility of if you rely on a wheelchair to get about most of the day you will not be asked to participate in this study.

Will my information be confidential?

Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone outside the hospital.

Compensation

Your doctors are covered by standard medical indemnity insurance. 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 quit at any time. If you decide not to participate, or if you quit, you will not be penalised and will not give up any benefits which you had before entering

the study. Your doctor will have no access to the information recorded by the activity monitors in this study. Participation in this study will therefore not affect your treatment options in any way.

Stopping the study
You understand that 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?

You can get more information or answers to your questions about the study, your participation in the study, and your rights, from Julie Walsh (Physiotherapist) who can be telephoned at 01 896 2110 or (01) 413000 bleep 544 or mobile number (087) 0679445 (9am to 5 pm Monday to Friday)

PATIENT CONSENT FORM (Study I)

'Novel methods of measuring Physical Activity and the role of exercise interventions in Cancer patients'

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 wear a small activity monitor on my waistband and for some of the period that I am at home/or in convalescence after being discharged from hospital, until I attend my follow-up out-patient appointment with my doctor. After this appointment, I will return the monitor and completed questionnaires. The information recorded by the monitor will be used to test the accuracy of a scale currently used in many hospitals to rate patient's activity levels.

If I have breast or colon cancer, I may also be asked to participate also at a later stage when my cancer treatment is completed. This would involve wearing one activity monitor for a duration of up to 7 days and completion of questionnaires which would be explained to me at that time.

I agree to allow the investigator in this study to access my medical chart in order to record my doctor's activity score and information relating to the type of illness I have, the treatment/procedures I received and other medical conditions that might affect my activity levels. I consent to the publication of data from this study and understand that my identity will remain confidential. I aggress 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. I have received a copy of this agreement and I understand that, if there is a sponsoring company, a signed copy will be sent to that sponsor.
Name of sponsor:

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.

Investigator's signature:
Date:

APPENDIX XIII STUDY II PATIENT INFORMATION LEAFLET AND CONSENT FORM

'Patient Information Leaflet (Study IIi)

'Novel methods of measuring physical activity and the role of exercise interventions in patients with cancer'

What is this study about?
A study investigating the activity levels of patients post cessation of their cancer treatment is being carried out in the Trinity College Department of Physiotherapy and St James's Hospital.

Very little information is currently available in terms of activity levels and well-being after treatment for cancer has ceased. The availability of new technology permits the accurate measurement of physical activity. This study will investigate physical activity at time-points of 6 weeks, 6 months, and/or 1 year after your treatment for cancer has finished.

Your doctor will have no access to the information recorded by the activity monitors in this study. Participation in this study will therefore not affect your treatment options in any way.

Using a physical activity monitor, this study aims to measure your activity levels while at home for a number of days. You should carry on activity as normal while wearing the activity monitors.

If you choose to participate in this study you will be required to wear an activity monitor for up to 7 days. The monitor can be returned using a stamped-addressed envelope provided. Alternatively, the chief investigator may make arrangements to meet you to remove the monitor. You will also be given a short questionnaire about your activities and movements while at home, as well as a Quality-of Life, Fatigue and Exercise questionnaire which will also be returned with your monitor.

Who is being asked to participate?
All patients over the age of 18 who have completed their treatment for breast or colon cancer.

What do I have to do?
If you choose to participate you will have your age, height and weight recorded by an investigator. An investigator will also show you the activity monitor and instruct you on how to use it. The monitor is small, light and discreet. You should carry on activity as normal while wearing the activity monitors.

As arranged, either by post or in person, the monitor and 3 short questionnaires will be returned to the chief investigator.

Activity Monitor
RT3 Accelerometer: This small device is attached to the waistband using a belt clip. It will measure your physical activity for the days that you are at home. It records when, how much and for how long you are active each day. The device must be removed for bathing, swimming and sleeping. You will be given a simple diary for the days that you are to wear this monitor. On this diary you should note the times when you put the monitor on and off and also note any activities completed while you were not wearing the monitor (e.g. showering)

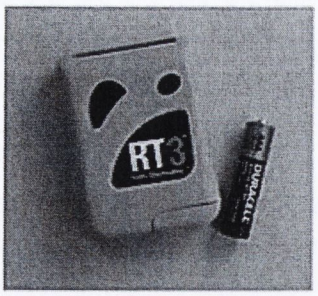


Fig 1: The RT3 activity monitor to be worn on the waistband

Questionnaire

The International Physical Activity Questionnaire contains questions about the type of activity you do and for how long you do each activity every day for 7days. It includes questions about activities you do at work, as part of your house and yard work, to get from place to place and in your spare time for recreation, exercise or sport. You are asked to complete it the evening before you attend for your follow-up outpatient appointment.

The Quality-of-Life questionnaire is the 30-item questionnaire (QLQ-C30 Version 3) of the European Organization for Research and Treatment of Cancer (EORTC). This is a short cancer-specific questionnaire. It evaluates areas such as physical, emotional, cognitive, and social functioning and there are also questions concerning fatigue, pain and nausea.

There is also a short questionnaire on your fatigue levels (Brief Fatigue Inventory).

What are the benefits to me?

There are no direct benefits to you for participating in this study, but the results may benefit future patients.

Are there any risks to me?

There is no risk to you that we can think of, in participating in this study. The practitioners involved in this study have current medical indemnity cover.

Who can not participate in this study?

You may not participate in this study if you are unable to give informed consent or if you are currently using external equipment e.g. NG feed or IV drips. Also, if you have a confirmed pregnancy, have significant disease that restricts your mobility or if you rely on a wheelchair to get about most of the day you will not be asked to participate in this study.

Will my information be confidential?

Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone outside the hospital.

Compensation

Your doctors are covered by standard medical indemnity insurance. 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 quit at any time. If you decide not to participate, or if you quit, you will not be penalised and will not give up any benefits which you had before entering the study. Your doctor will have no access to the information recorded by the activity monitors in this study. Participation in this study will therefore not affect your treatment options in any way.

Stopping the study
You understand that 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?
You can get more information or answers to your questions about the study, your participation in the study, and your rights, from Julie Walsh (Physiotherapists) who can be telephoned at (087) 0679445 or 01 896 2110 bleep 544

PATIENT CONSENT FORM (Study IIi)

Novel methods of measuring Physical Activity and the role of exercise interventions in Cancer patients

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 wear a small activity monitor for a period of up to 7 days. The information recorded by these monitors will be used to evaluate activity levels of patients after their treatment for cancer has ceased.

I will also be asked to complete three short questionnaires.

I agree to allow the investigator in this study to access my medical chart in order to record my doctor's activity score and information relating to the type of illness I have, the treatment/procedures I received and other medical conditions that might affect my activity levels. I consent to the publication of data from this study and understand that my identity will remain confidential. I aggress 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. I have received a copy of this agreement and I understand that, if there is a sponsoring company, a signed copy will be sent to that sponsor.
Name of sponsor:

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:

'Subject Information Leaflet (Study II.ii)

What is this study about?
A study investigating the activity levels of patients post cessation of their cancer treatment is being carried out in the Trinity College Department of Physiotherapy and St James's Hospital.

Very little information is currently available in terms of activity levels and well-being after treatment for cancer has ceased. Research to-date informs us that activity levels often do not return to pre-diagnosis levels. However, we do not have information on pre-diagnosis levels of patients, therefore our approach is to compare levels to those of the healthy population.

Using physical activity monitors, this study aims to measure your activity levels while at home for a number of days. You should carry on activity as normal while wearing the activity monitors. Your doctor will have no access to the information recorded by the activity monitors in this study.

If you choose to participate in this study you will be required to wear an activity monitor for up to 7 days. The monitor can be returned using a stamped-addressed envelope provided. Alternatively, the chief investigator may make arrangements to meet you to remove the monitor. You will also be given a short questionnaire about your activities and movements while at home, as well as a brief questionnaire with demographic details.

Who is being asked to participate?
All patients over the age of 18 who are considered healthy

What do I have to do?
If you choose to participate you will have your age, height and weight recorded by an investigator. An investigator will also show you the activity monitor and instruct you on how to use it. The monitor is small, light and discreet. You should carry on activity as normal while wearing the activity monitors.

As arranged, either by post or in person, the monitor and the short questionnaires will be returned to the chief investigator.

Activity Monitor
RT3 Accelerometer: This small device is attached to the waistband using a belt clip. It will measure your physical activity for the days that you are at home. It records when, how much and for how long you are active each day. The device must be removed for bathing, swimming and sleeping. You will be given a simple diary for the days that you are to wear this monitor. On this diary you should note the times when you put the monitor on and off and also note any activities completed while you were not wearing the monitor (e.g. showering)

Questionnaire
There is also a brief questionnaire on your some of your demographic details.

What are the benefits to me?
There are no direct benefits to you for participating in this study, but the results may benefit future patients.

Are there any risks to me?
There is no risk to you that we can think of, in participating in this study. The practitioners involved in this study have current medical indemnity cover.

16/01/2009

Who can not participate in this study?
You may not participate in this study if you are unable to give informed consent or if you have had a confirmed cancer diagnosis other than non-melanoma skin Cancer or pre-invasive cancer of the Cervix in the last 5 years. Also, if you have a confirmed pregnancy, have significant disease that restricts your mobility or if you rely on a wheelchair to get about most of the day you will not be asked to participate in this study.

Will my information be confidential?
Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone outside the university/hospital.

Compensation
Trinity College Dublin is covered by standard indemnity insurance. 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 quit at any time.

Stopping the study
You understand that 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?
You can get more information or answers to your questions about the study, your participation in the study, and your rights, from Julie Walsh (Physiotherapists) who can be telephoned at (087) 0679445 and is contactable at bleep 544 (01 4103000) (9am to 5 pm Monday to Friday)'

SUBJECT CONSENT FORM (Study II.ii)

Study title: 'Novel methods of measuring Physical Activity and the role of exercise interventions in patients with Cancer'

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 wear a small activity monitor for a period of up to 7 days.

I will also be asked to complete a short questionnaire on some of my demographic details.

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. I have received a copy of this agreement and I understand that, if there is a sponsoring company, a signed copy will be sent to that sponsor.
Name of sponsor:

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:

APPENDIX XIV PATIENT INFORMATION LEAFLET AND CONSENT FORM STUDY III

Title of study: 'Novel methods of measuring physical activity in patients with cancer and the role of exercise interventions'

Principal investigator: Dr. Dearbhaile O' Donnell
Name of researcher: Ms. Julie Walsh
Funding body: Health Research Board

Patient Information Leaflet

What is this study about?
We know that many cancer survivors are unfit or are not as active as is recommended for good general health. However, the best level of exercise for cancer survivors and how they should try to get back to a level of activity recommended for general fitness remains unclear. We are investigating whether an exercise programme in the first few months after chemotherapy or radiotherapy could increase fitness in cancer survivors. At the moment, patients recovering from chemotherapy and radiotherapy are free to undertake physical activity when they feel able to do or wish to do, with general informal advice from their doctors and nurses.

If you decide to participate in the study, you will either be offered a structured exercise class or to be part of a control group. A control group means that you will not be offered a structured exercise programme at that time. You will still be able to carry out physical activity as you feel able to do or wish to do, as advised by your doctors and nurses in your recovery period from chemotherapy, which is what we normally do. If you are in the control group, after the study period we will offer you an individualised exercise programme and advise you of other exercise options available.

Your doctor will have no access to the questionnaire information or any other data received as part of this study.

Who is being asked to participate?
If you have cancer and you have completed your cancer therapy, you may be asked to participate in this study. You will have been cleared by your doctor as suitable to participate in this study.

How is it decided whether I am allocated to the exercise programme or usual care?
You will be randomly assigned to either the exercise programme or usual care. You or your doctor cannot decide whether you are assigned to the structured exercise class or to usual care (also called "the control group"). This is standard practice in scientific studies

such as this, so that the true effect of being assigned to the programme or not can be assessed.

What do I have to do?
Taking part in this study involves, first, a fitness assessment, questionnaires and activity monitoring. You may then be asked to participate in a control group (receiving usual care) or in a structured exercise class. Whichever group you are allocated to, you will be asked to take the fitness test, questionnaires and activity monitoring after 9-10 weeks, and again 3 months after that. Your fitness is measured each time by a walking test. The questionnaires ask you about various aspects of your daily activity including physical activity and quality of life. Your activity levels are measured by wearing a small, unobtrusive monitor on your waist during waking hours for a week (it is described in more detail below).

What if I am allocated to the control group?
If you are part of the control group, you will be asked to carry on activities as normal. You will get an opportunity to get an individualised exercise assessment and programme as well as advice on exercise options available to you on completion of your assessments.

What if I am allocated to the exercise programme?
If you are carrying out the structured exercise class, this will consist of a short warm-up with gentle exercises and stretches and a number of exercises in a circuit-style system in a class setting. Your exercise intensity will be adjusted to suit you individually. The exercise component will last up to 40 minutes and there will be a cool-down consisting of gentle exercises and stretched for approximately 10 minutes at the end.

What does the assessment involve?
The assessment is a fitness (walking) test on a treadmill and the completion of short questionnaires on fatigue levels, quality-of-life and activity.

<u>Quality-of life Questionnaire</u>
We will use the FACT-G scale (general) and the physical functional measure of the SF-36. These will give us an overall measure of how you are functioning from a physical and emotional point of view.

<u>Fatigue Questionnaire</u>
We will also assess your fatigue levels by using a questionnaire called the FACT-F. This questionnaire relates to your fatigue and energy levels.

<u>Activity Questionnaire</u>
We will use the modified version of the Godin Leisure Time Exercise Questionnaire. The questionnaire contains three questions that assess the average frequency and duration of mild, moderate, and strenuous exercise carried out during a typical week.

<u>Activity Monitor</u>
RT3 Accelerometer: This small device is attached to the waistband using a belt clip. This monitor will measure your level of activity, you should carry on as normal while wearing the monitor. It records when, how much and for how long you are active each day. The device must be removed for bathing, swimming and sleeping. You will be given a simple diary for the days that you are to wear this monitor. The accelerometer will be used to

monitor 7 days of activity at three different time points, corresponding to before the programme, after the programme has been completed, and three months afterwards.

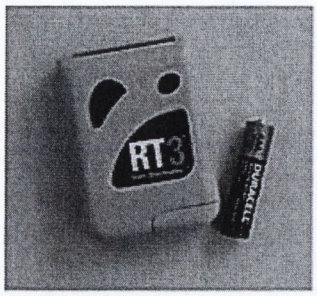


Fig 1: The RT3 activity monitor to be worn on the waistband

What are the benefits to me?
It is possible that there may be some benefits if you participate in the exercise element of the study. However, we do not know if they are over and above the improvements that tend to occur in fitness and activity once treatment has been completed (that is the purpose of the study).

Is the programme dangerous- Are there any risks to me?
We do not anticipate adverse effects for the exercise programme other than the minor short-term side-effects associated with usually starting a routine exercise programme eg. mild, short-duration muscle soreness. Occasionally, people can feel dizzy or breathless when doing unaccustomed exercise. However, because the exercise program is carefully graded, the risks of this happening are minimal. The exercise class will be conducted by two qualified physiotherapists with experience in conducting exercise programmes such as this. The exercise class will start very gradually, only progressing as you feel able based on your symptoms and heart rate. Your level of exertion will also be carefully monitored throughout the programme by using a polar heart rate monitor as well as a scale of exertion. 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.

Who can not participate in this study?
You may not participate in this study if any of the following hold;

- you are unable to give informed consent or
- if you have evidence of active cancer or a history of previous cancer (not the one for which you have been recently treated) in the past 5 years
- if you have any conditions which may affect your ability to exercise or if you are on beta-blocker medication.
- if you are pregnant
- if your blood counts have not recovered fully after chemotherapy
- if you have a body mass index of > 35
- if you have been on treatment that can affect the heart and your heart test shows a low left ventricular ejection fraction (the measure of the pumping ability of your heart)
- if your fitness test already shows your fitness level is good or excellent. If it is, it is likely that you are exercising regularly to appropriate levels, and therefore you would not benefit to a great extent from this exercise programme.

Therefore, if your score is above average levels, when you carry out the fitness assessment, the physiotherapist carrying out the test will be able give you feedback on your score and answer any questions you may have on the continuation of your own exercise programme.

Will my information be confidential?
Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone outside the hospital.

Compensation
Your doctors are covered by standard medical indemnity insurance, the postgraduate students who are conducting the assessment and exercise classes are physiotherapists and are 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
You understand that 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?
You can get more information or answers to your questions about the study, your participation in the study, and your rights, from Julie Walsh (Study Investigator & Physiotherapist) who can be telephoned at (01) 896 211) or (087) 0679445 (9am to 5 pm Monday to Friday).

PATIENT CONSENT FORM

Title of study: 'Novel methods of measuring physical activity in patients with cancer and the role of exercise interventions'

Principal investigator: Dr. Dearbhaile O' Donnell
Name of researcher: Ms. Julie Walsh
Funding body: Health Research Board

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 a fitness test prior to study enrolment. This will consist of a walking test. I will be randomly allocated to a control group or exercise intervention group. If I am allocated to the control group, I will take fitness tests and activity assessments throughout the study. I will later be offered an individualised exercise prescription and advised of exercise options available to me. If I am allocated to the exercise group, I will attend an individualised 8-week exercise programme which is built up gradually each week. I understand that taking part in this study involves a fitness assessment and follow-up questionnaires before allocation to the programme, within 9-10 weeks and also 3 months afterwards.

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 had, the treatment/procedures I received and other medical conditions that might affect my activity levels. 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.

Investigator's signature:
Date:

WHY IS THIS CALLED THE PEACH TRIAL?

The PEACH trial stands for;

P: Prescribed

E: Exercise

A: After

CH: Chemotherapy

As this is a trial, you will be randomly selected to either enter the exercise programme or to carry on as normal with follow-up in terms of your fitness.

DOES MY DOCTOR ENDORSE THIS PROGRAMME?

Your Oncologist in St. James's Hospital/St. Luke's Hospital is fully aware of this programme. All suitable patients are encouraged to consider taking part in this trial.

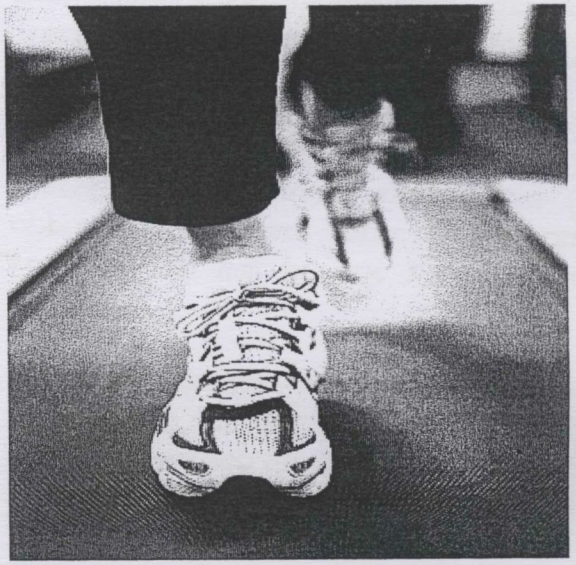
WHERE CAN I FIND OUT MORE INFORMATION?

Programme phone:
(087) 0679445

You can find out more information or register your interest by calling Julie Walsh at (087) 0679445or (01) 8962110

HRB
Health Research Board

Would you like to increase your fitness after chemotherapy?



The PEACH Trial

St. James's Hospital

ABOUT THE PEACH TRIAL

This is an exercise programme run as part of innovative research in St. James's Hospital investigating the role of exercise during and after cancer treatment.

We want to see whether a formal exercise programme helps people to recover their fitness after chemotherapy any quicker than gradually getting back to life as normal.

To see whether you qualify for this exercise trial, answer the following questions;

1. Did you have surgery or radiotherapy with chemotherapy (before or after)?

2. Are you aged between 20-70 years?

3. Has your fitness level decreased?

If you answered 'yes' to all these questions above you may qualify for this programme. However, there are a number of additional criteria which we have to check prior to enrolling you on this programme.

Please note we welcome **both males and females** to participate in this trial.

HOW DOES THE PROGRAMME WORK?

1. Contact us for further information and /or to register for the programme.

2. We will check to see if you are suitable for the trial.

3. If you meet all the inclusion criteria, we will carry out a fitness test - which is a walking test wearing a heart rate monitor.

If that fitness test shows good results, the programme is not suitable for you and you will be advised to continue your current activities.

If you meet all the criteria and your fitness is not good, you are then eligible for the trial. At that point, you will be allocated to the exercise group or the control group.

WHAT IF I AM ALLOCATEDTO BE PART OF THE EXERCISE GROUP?

The exercise group means you will participate in an 8-week exercise programme, run by an experienced physiotherapist with a special interest in oncology research.

The exercise class will be fun and informal. It will consist of walking on a treadmill, using bikes and other gym equipment.

The class is designed to increase your fitness but we will tailor it to your individual needs, and start very gently if you are not fit.

Where: Physiotherapy Department in St. James's Hospital

When: Monday & Wednesday

Time: 4-5pm*

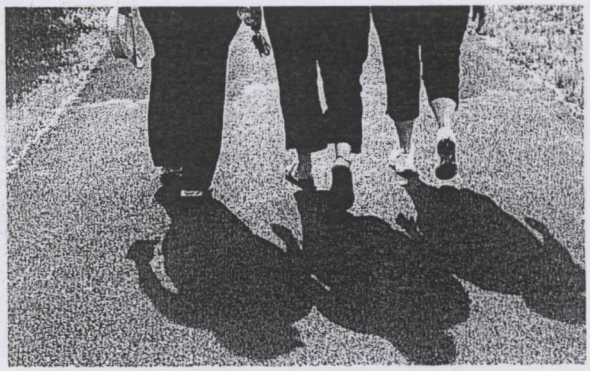
*These times & days can be flexible depending on what suits the group

WHAT IF I AM ALLOCATED TO BE PART OF THE CONTROL GROUP?

The control group means you will carry on as normal. You will not be offered a structured exercise programme at that point.

However we will provide you with an opportunity to learn more about your fitness, by carrying out fitness tests (a walking test on a treadmill) at intervals during your recovery from chemotherapy.

After the trial is over, we will offer you personalised advice about suitable exercise to improve your fitness.



Appendix XV Left Ventricular Ejection Fraction Inclusion/Exclusion criteria background

Patients who receive anthracycline chemotherapy and/or Herceptin therapy are deemed at risk of LVEF deterioration in routine clinical practice. Patients receiving these treatments have LVEF routinely measured by MUGA or ECHO at the start of systemic treatment. In those patients receiving only anthracyclines, LVEF is measured at the end of treatment; that

measurement then constitutes the entry criterion for this study (ie > 50% absolute and not > 20% decline since the start of treatment).

In patients receiving ongoing herceptin treatment after the end of systemic treatment, the LVEF is checked at 3-monthly intervals. In these patients, the most recent LVEF, which must not be any longer than 6 weeks from study entry, is the entry criterion. These patients are eligible to enter the study as per study by Courneya et al. 2007 (Courneya et al., 2007). If, during the course of the study any patient on Herceptin only treatment develops a significant drop in LVEF > 20% or to below 50%, her data will be excluded from retrospective analysis of the primary end-point.

APPENDIX XVI PROGRAMME EVALUATION

PEACH Trial Feedback Form: (Exercise Arm)

What did you like about taking part in the PEACH trial?

What did you not like/what would you change about taking part in the PEACH trial?

Have you any suggestions for improvement?

PARTICIPANT FEEDBACK

Participant Feedback

As this was a feasibility study, participant feedback was sought, the results of which are below

PEACH Trial Feedback

Q1 What did you like about taking part in the PEACH Trial?

'Enjoyed it all'
'Atmosphere, people, individual attention'
'It got me motivated and working out regularly, very quickly I realized the benefits of exercising, better sleep, fitness level improved feel good emotionally and physically'
'Being part of a group team effort'
'Great motivation in the group'
'I thought the PEACH trial was brilliant, motivation to get back to exercising again and I must add that Julie and Jennifer were so caring but gave that little push that we needed also'
'I really enjoyed getting fit and the way the course was run not allowing me to overdo it. I think the monitor is a brilliant idea when you are exercising at home, it gives you a safe feeling when you are starting to exercise after your treatment. I found the instructors excellent and would like to thank them for all their help and encouragement'
'The care and attention that Julie and Katie gave to us as individuals'
'Great motivation'
'I feel great after the exercise and want to continue doing the exercise'
'The staff are very good and helpful'
'It increases my strength'

Q2 What did you not like/would you change about taking part in the PEACH Trial?

'Better stretch-out area (mats), perhaps little relaxation at end of the class'
'There really was nothing that I can say that I didn't like about the PEACH trial'
'Nothing'
'The bicycle'
'Nothing'
'Bigger group'
'A bigger group and more equipment'
'Nothing it was super'
'Nil'

Q3 Have you any suggestions for improvement?

'More equipment-cross trainer'
'Everyone should be able to do it'
'More up-to-date equipment'
'Parking available'
'Classes X 3 times per week'
'Maybe a possible diet plan to incorporate both exercise and cancer'

'Nothing'
'Would like it to be available to a wider section of people so that all could enjoy the experience of getting fit after trauma'
'Nil'

APPENDIX XVII HOME EXERCISE PROGRAMME

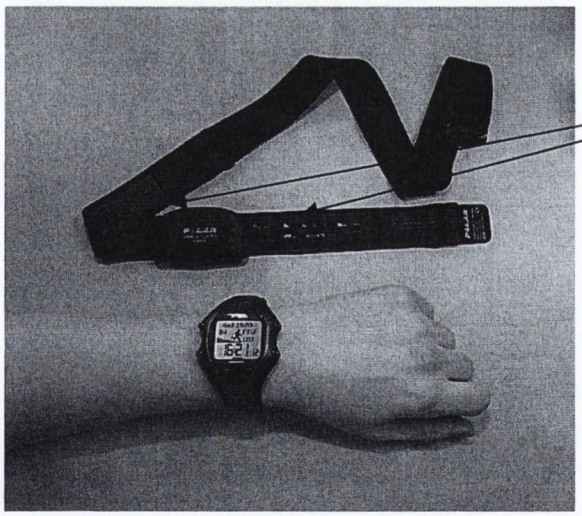
PEACH Trial - WEEK 1 Goal

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:



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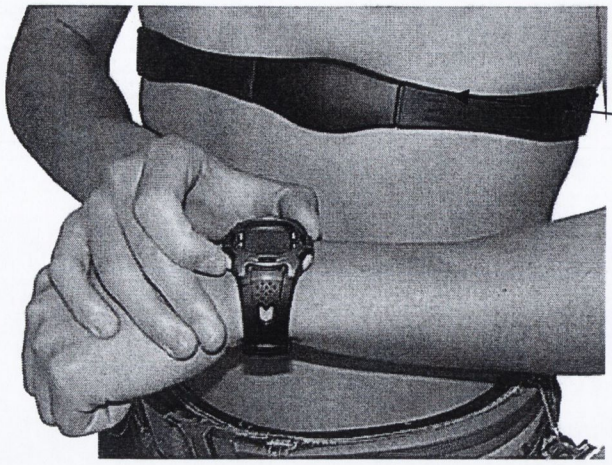


Position of chest strap

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

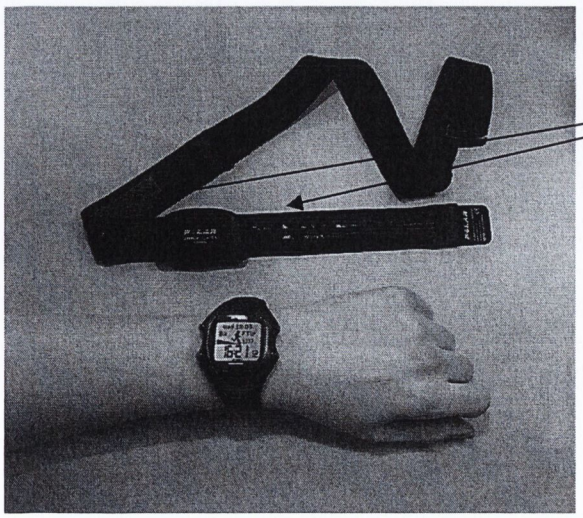
Name	
Date	

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:



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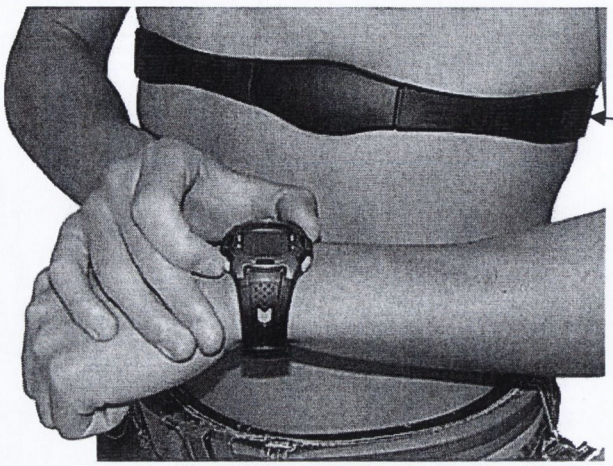


Position of chest strap

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

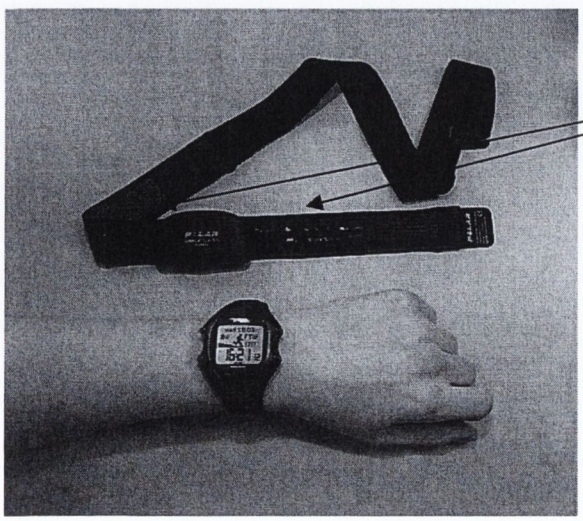
Name	
Date	

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:



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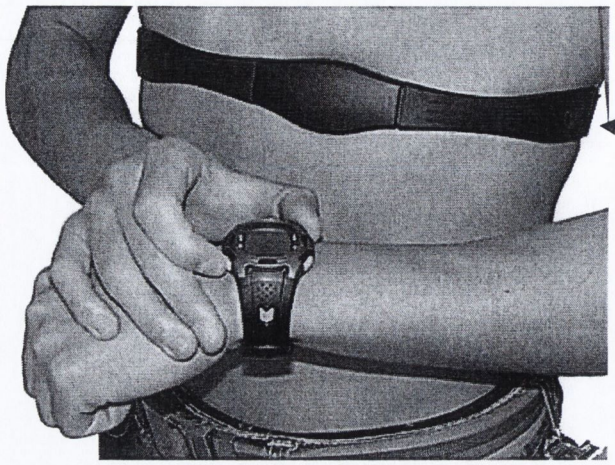
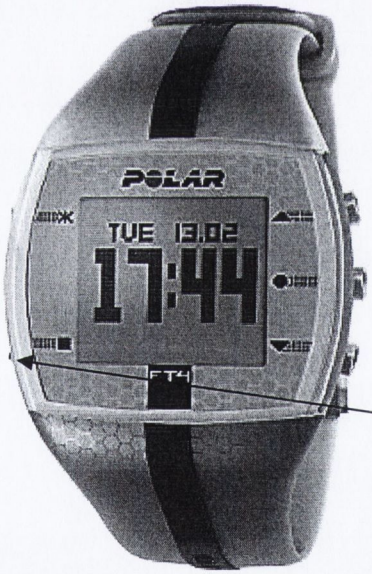


Position of chest strap



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

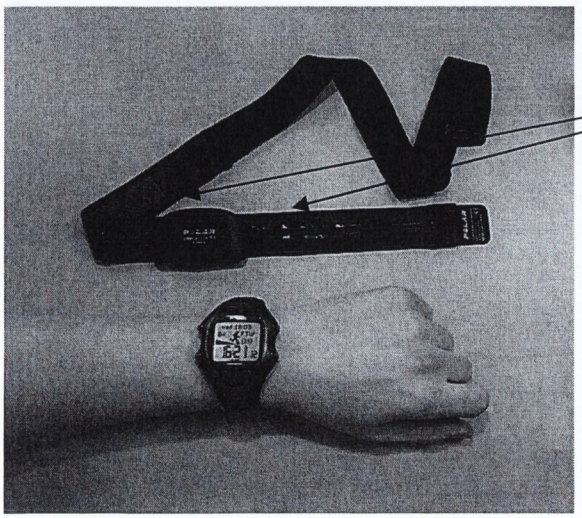
Name	
Date	

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**
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Use your polar monitor to record your exercise sessions:



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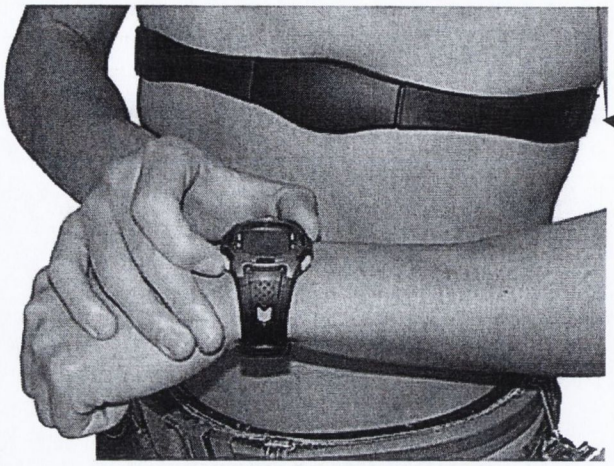
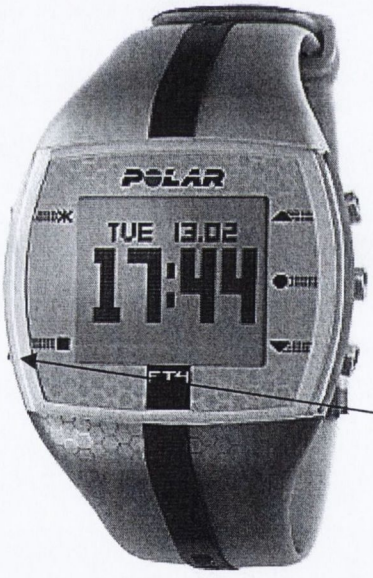


Position of chest strap



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

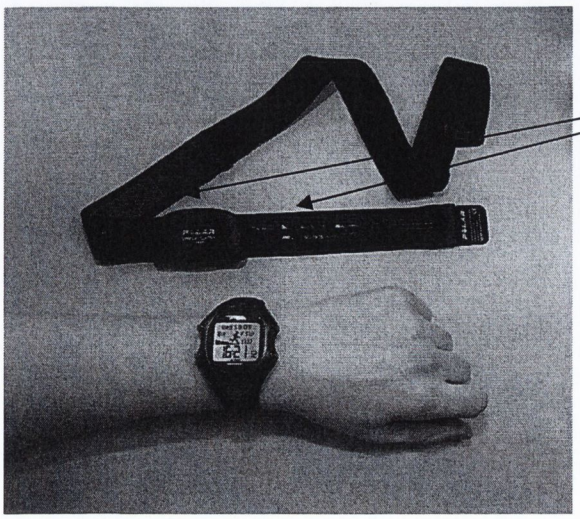
Name	
Date	

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
Monday	Class		
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Use your polar monitor to record your exercise sessions:



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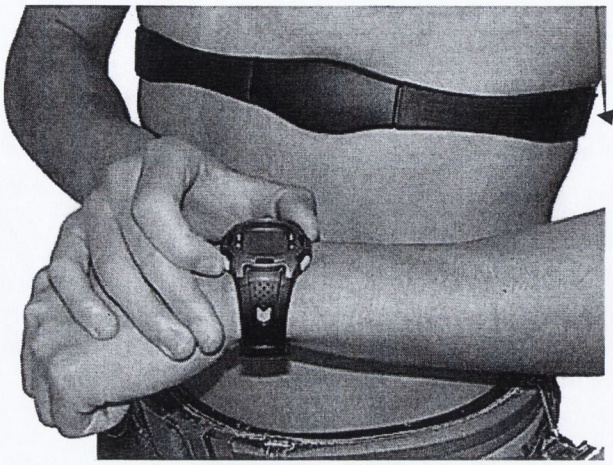
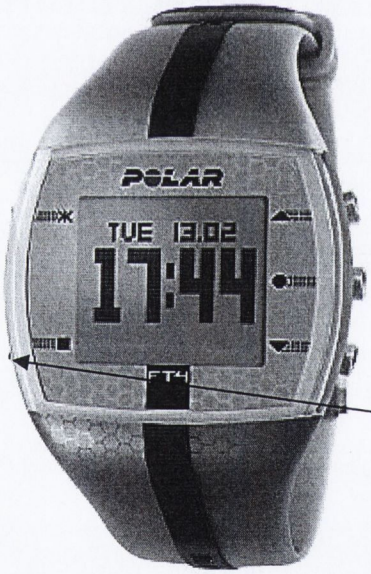


Position of chest strap



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

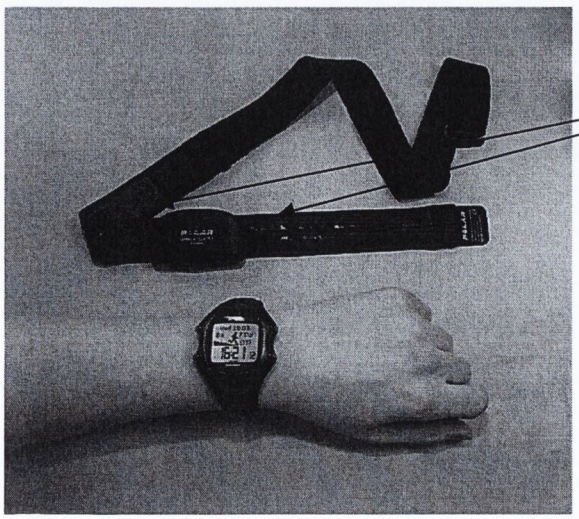
Name	
Date	

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
Monday	Class		
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Use your polar monitor to record your exercise sessions:



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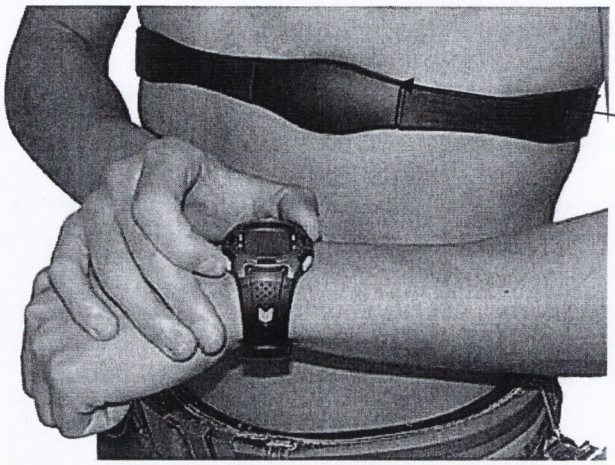
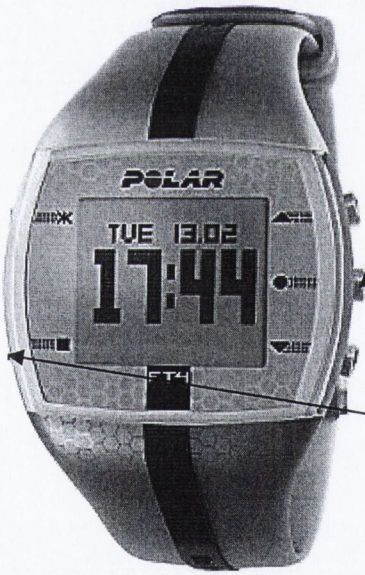


Position of chest strap



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

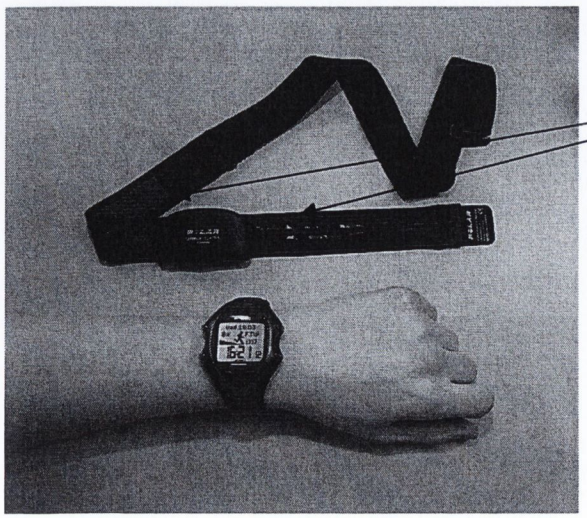
Name	
Date	

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
Monday	Class		
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Use your polar monitor to record your exercise sessions:



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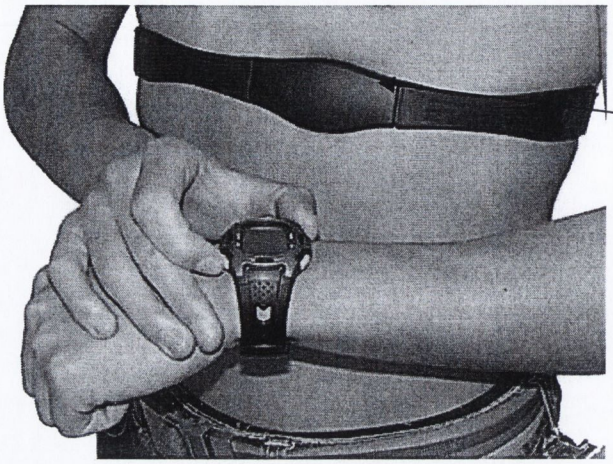
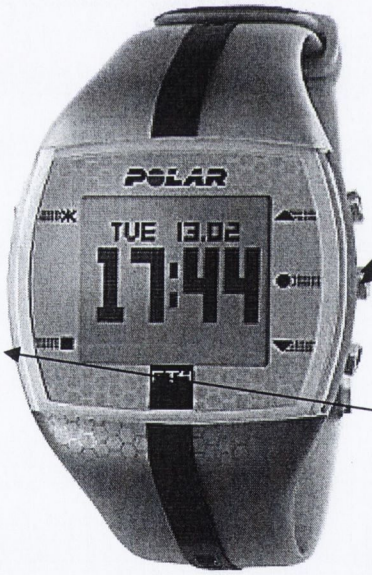


Position of chest strap



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

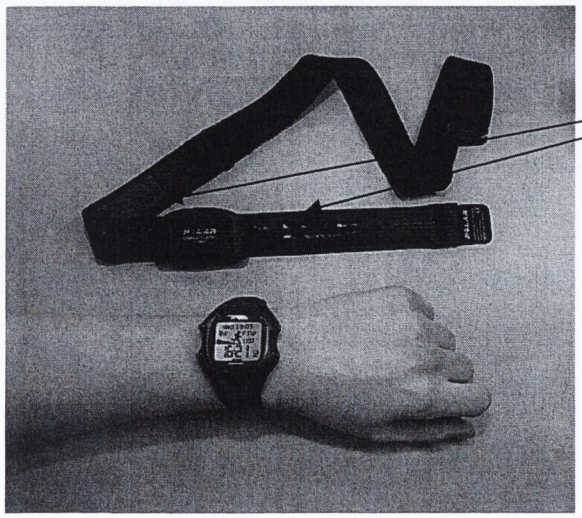
Name	
Date	

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
Monday	Class		
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Use your polar monitor to record your exercise sessions:



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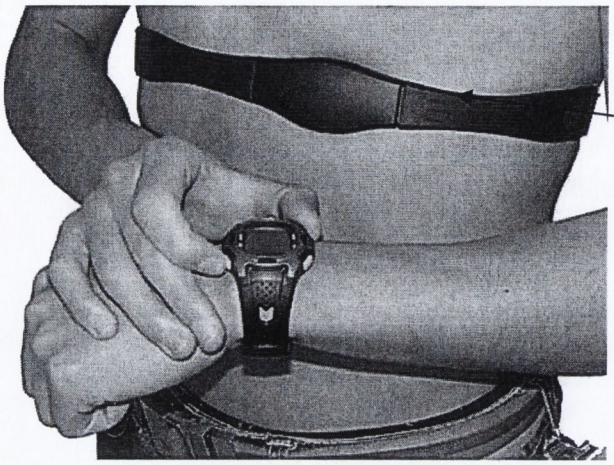

Position of chest strap

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

APPENDIX XVIII - PROTOCOL FOR ASSESSING RESTING HEART RATE

Heart rate will be assessed at either carotid artery or the radial artery.

Procedure for determination of heart rate will be as follows:

1. The anatomical palpation site will be located.
   - Carotid pulse: carotid artery at the side of the neck.
   - Radial pulse: radial artery at the lateral side of the wrist.

2. The index and third finger will be placed over the palpation site.

3. The two fingers will be gently pressed down over the palpation site.

4. The number of pulsations over 30 seconds will be counted.

5. Counting will begin at 0 if the first pulsation and timing is started simultaneously. If a time lag occurs after the start time and the first pulsation, counting will begin at 1 for the pulsations.

6. The number of pulsations over 30 seconds will be multiplied by 2 to measure heart rate.

From: AMERICAN COLLEGE OF SPORTS MEDICINE. (2009) *ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription.* 6th ed. Philadelphia: Lippincott Williams & Wilkins.

Appendix XIX - PROTOCOL FOR ASSESSING RESTING BLOOD PRESSURE

1. Patient will be sitting quietly in a chair for at least 5 minutes with back supported. Feet on the ground, arm supported at heart level.

2. The cuff will be wrapped firmly around upper arm at heart level; aligned with brachial artery.

3. The bladder within the cuff should encircle at least 80% of the upper arm. Many adults require a large adult cuff.

4. The stethoscope bell will be placed below the antecubital space over the brachial artery.

5. The cuff pressure will be inflated quickly to 20 mm Hg above the first Korotkoff sound.

6. The pressure will be released slowly at rate equal to 2 to 5 mm Hg per second.

7. Systolic BP is the point at which the first of two or more Korotkoff sounds is heard (phase 1) and diastolic BP is the point before the disappearance of Korotkoff sounds (phase 5).

8. At least two measurements will be made, at least one minute apart.

Phase 1 (SBP)	First, initial sound of faint, repetitive, and clear tapping sounds. Approximates the SBP
Phase 2	A soft tapping or murmur sound that has a swishing quality. It begins 10-15 mm Hg after the onset of sound or below phase1 sound.
Phase 3	Return of loud tapping sounds which are crisper and louder thatn 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.

Table 1: Korotkoff sounds (SBP = systolic blood pressure, DBP = diastolic blood pressure)

APPENDIX XX CONTRAINDICATIONS TO EXERCSISE TESTING AND TRAINING FOR PATIENTS WITH CANCER

		Yes	No
Factors related to cancer treatment	No exercise on days of intravenous chemotherapy or within 24 hours of treatment		
	No exercise prior to blood draw		
	Severe tissue reaction to radiation therapy		
Hematologic	Platelets <50,000		
	While blood cells <3,000		
	Hemoglobin <10g.dL^{-1}		
Musculoskeletal	Bone, back or neck pain of recent origin		
	Unusual muscular weakness		
	Severe cachexia		
	Unusual/extreme fatigue		
	Poor functional status: avoid exercise testing if Karnofsky Performance Status score ≤60%		
Systemic	Acute infections		
	Febrile illness: fever >100°F (38°C)		
	General malaise		
Gastrointestinal	Severe nausea		
	Vomiting or diarrhoea within 24-36 hours		
	Dehydration		
	Poor nutrition: inadequate fluid and/or food intake		
Cardiovascular	Chest pain		
	Resting HR>100 bears per min^{-1} or <50 beats per min^{-1}		
	Resting SBP >145mm Hg and/or DBP >95mm Hg		
	Resting SBP <85mm Hg		
	Irregular HR		
	Swelling of ankles		
Pulmonary	Severe dyspnea		
	Cough, wheezing		

	Chest pain increased by deep breath		
Neurological	Significant decline in cognitive status		
	Dizziness/ lightheadedness		
	Disorientation		
	Blurred vision		
	Ataxia (i.e., inability to co-ordinate voluntary movement		

PRECAUTIONS REQUIRING MODIFICATION AND/OR PHYSICIAN APPROVAL

		Yes	**No**
Factors related to cancer treatment	Caution if on treatments that affect the lungs and/or heart: recommend medically supervised exercise testing and training		
	Mouth sores/ulcerations: avoid mouthpieces for maximal testing; use face masks		
Hematologic	Platelets >50,000-150,000: avoid tests that increase risk of bleeding		
	White blood cells >3,000-4,000: ensure proper sterilization of equipment		
	Hemoglobin >10g.dL^{-1}: caution with maximal tests		
Musculoskeletal	Any pain or cramping investigate		
	Osteopenia: avoid high-impact exercise if risk of fracture		
	Steroid induced myopathy		
	Cachexia: multidisciplinary approach to exercise		
	Mild to moderate fatigue: closely monitor response to exercise		
Systemic	Recent systemic illness or infection: avoid exercise until asymptomatic for > 48 hours		
Gastrointestinal	Compromised fluid and/or food intake: recommend		

	multidisciplinary approach/consultation with nutritionist		
Cardiovascular	Caution if at risk of cardiac disease: recommend medically supervised exercise testing and training		
	If on antihypertensive medications that affect HR, THR may not be attainable; avoid overexertion		
	Lymphedema: wear compression garment on limb when exercising.		
	Mild-moderate dyspnea: avoid maximal tests		
Pulmonary	Mild cognitive changes: ensure that patient is able to understand and follow instructions		
Neurologic	Poor balance/peripheral sensory neuropathy: use well-supported positions for exercise		

From: AMERICAN COLLEGE OF SPORTS MEDICINE. (2009) *ACSM's Exercise is Medicine. A Clinician's Guide to Exercise Prescription.* 6[2nd] ed. Philadelphia: Lippincott Williams & Wilkins

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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 corre-

sponds 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

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

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 variables 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 popula-

tion 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.

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