An exercise intervention for women undergoing chemotherapy for ovarian cancer: feasibility and preliminary outcomes

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Abstract

Exercise interventions during adjuvant cancer treatment have been shown to increase functional capacity, relieve fatigue and distress and in one recent study, assist chemotherapy completion. These studies have been limited to breast, prostate or mixed cancer groups and it is not yet known if a similar intervention is even feasible among women diagnosed with ovarian cancer. Women undergoing treatment for ovarian cancer commonly have extensive pelvic surgery followed by high intensity chemotherapy. It is hypothesized that women with ovarian cancer may benefit most from a customised exercise intervention during chemotherapy treatment. This could reduce the number and severity of chemotherapy-related side-effects and optimize treatment adherence. Hence, the aim of the research was to assess feasibility and acceptability of a walking intervention in women with ovarian cancer whilst undergoing chemotherapy, as well as pre-post intervention changes in a range of physical and psychological outcomes.

Newly diagnosed women with ovarian cancer were recruited from the Royal Brisbane and Women's Hospital (RBWH), to participate in a walking program throughout chemotherapy. The study used a one group pre- post-intervention test design. Baseline (conducted following surgery but prior to the first or second chemotherapy cycles) and follow-up (conducted three weeks after the last chemotherapy dose was received) assessments were performed. To accommodate changes in side-effects associated with treatment, specific weekly walking targets with respect to frequency, intensity and duration, were individualised for each participant. To assess feasibility, adherence and compliance with prescribed walking sessions, withdrawals and adverse events were recorded. Physical and psychological outcomes assessed included functional capacity, body composition, anxiety and depression, symptoms experienced during treatment and quality of life. Chemotherapy completion data was also documented and self-reported program helpfulness was assessed using a questionnaire post intervention.

Forty-two women were invited to participate. Nine women were recruited, all of whom completed the program. There were no adverse events associated with participating in the intervention and all women reported that the walking program was helpful during their neo-adjuvant or adjuvant chemotherapy treatment. Adherence and compliance to the walking prescription was high. On average, women achieved at least two of their three individual weekly prescription targets 83% of the time (range 42% to 94%). Positive changes were found in functional capacity and quality of life, in addition to reductions in the number and intensity of treatment-associated symptoms over the course of the intervention period. Functional capacity increased for all nine women from baseline to follow-up assessment, with improvements ranging from 10% to 51%. Quality of life improvements were also noted, especially in the physical well-being scale (baseline: median 18; follow-up: median 23). Treatment symptoms reduced in presence and severity, specifically, in constipation, pain and fatigue, post intervention. These positive yet preliminary results suggest that a walking intervention for women receiving chemotherapy for ovarian cancer is safe, feasible and acceptable. Importantly, women perceived the program to be helpful and rewarding, despite being conducted during a time typically associated with elevated distress and treatment symptoms that are often severe enough to alter or cease chemotherapy prescription.

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List of Abbreviations

AAESS	Australian Association of Exercise and Sports Science
BIS	Bioimpedence Spectroscopy
BMI	Body mass index
CA125	Cancer-antigen 125
CBD	Central business district
CDSM	Chronic Disease Self-Management Intervention Model
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EP	Exercise physiologist
ESSA	Exercise and Sports Science Association
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-O	Functional Assessment of Cancer Therapy – Ovary
FIGO	International Federation of Gynecology and Obstetrics
FFM	Fat-free mass
FM	Fat-mass
GOG	Gynecologic Oncology Group
HADS	Hospital Anxiety and Depression Scale
HRmax	Maximum heart rate
IV	Intravenous
IP	Intraperitoneal
MSAS	Memorial Symptoms Assessment Scale
QLD	Queensland
QoL	Quality of life
QUT	Queensland University of Technology
RBWH	Royal Brisbane and Women's Hospital
RDI	Relative dose-intensity
RPE	Rating of Perceived Exertion Scale
USA	United States of America
6MWT	Six-minute walk test

Statement of Original Authorship

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

As a masters student and the only exercise physiologist involved with the study, I was involved in the recruitment, data collection, supervising the walking intervention (both face-to-face and over the telephone) and data entry. I also helped formulate the objectives specific to this thesis, undertook a comprehensive literature review, performed the statistical analyses, presentation of results and subsequent writing of the thesis.

Academic achievements during the course of this masters degree include two conference poster presentations, completion of a health statistical unit and submission of a manuscript to an international journal.

Signature: _____

Date: _____

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Chapter 1: Introduction

1.1 INCIDENCE AND SURVIVAL FOLLOWING OVARIAN CANCER

Cancer of the ovary is the eighth most common female cancer and the sixth most common cause of cancer-related death in Australia, with approximately 1,465 new cases diagnosed each year [1]. In 2010, more than 1,500 women will be diagnosed with ovarian cancer and 850 will die from the disease. While relative survival has improved, incidence of ovarian cancer (approximately 12 cases per 100,000) has remained relatively unchanged in the past 20 years [2]. Incidence increases with increasing age and is most prevalent in the eighth decade of female life [3]. Although it is less common than breast cancer (which affects one in 13 women), proportionally more women die from ovarian cancer because it is usually diagnosed in its advanced stages. Overall, five-year survival is currently 42% but varies with age, stage and cell type of ovarian cancer [1].

Although the causes of ovarian cancer remain relatively uncertain and are less well-established than those for more common cancer types such as breast cancer [4], a number of factors have been recognized as contributing to ovarian cancer risk. Genetic and epidemiologic studies have demonstrated that the most significant risk factor is genetic predisposition. Five to 10% of ovarian cancers are associated with mutations in specific genes, in part, mutations in the tumour suppressor genes BRCA1 and BRCA2 [5]. Other characteristics considered to increase one's risk include older age, family history of ovarian cancer and hormone replacement therapy. Having fertility treatment is also considered a risk factor although the association with ovarian cancer is less well-established than other characteristics noted above.

Several characteristics have been associated with reduced risk of ovarian cancer. The use of the oral contraceptive pill has a strong protective effect, with risk declining with increased duration of use [6]. This risk reduction is maintained even

ten years after discontinuation of use [5]. Multiparity also serves to be protective against ovarian cancer, as well as tubal ligation and hysterectomy, which on average has a 67% risk reduction as observed by cohort and case-control studies [7]. The relationship between ovarian cancer and other characteristics including menopause and lifestyle factors such as the use of talcum powder in genital hygiene, tobacco smoking, psychotropic medication, dietary factors, caffeine consumption, alcohol and obesity, remain less clear [6].

Findings are also unclear with respect to the role of physical activity and risk of ovarian cancer. This could be due to issues such as the use of different definitions of physical activity, differing methods of measurement and different parameters of activity (i.e. frequency, intensity, duration, type). Nonetheless, a meta-analysis of observational studies demonstrated an inverse, albeit weak association, between increasing levels of recreational physical activity and risk of ovarian cancer [8]. Evidence was, however, less consistent for occupational and vigorous activity and for sedentary behaviour.

1.2 DIAGNOSIS, STAGING AND SURGERY OF OVARIAN CANCER

Ovarian cancer is the second most common gynaecologic malignancy, behind cancer of the endometrium [9]. The signs and symptoms of ovarian cancer are often overlooked because they are vague, easily ignored and similar to many other familiar illnesses; in fact, over 50% of the population incorrectly thinks that a pap smear test is designed to detect ovarian cancer [10]. Common symptoms experienced include abdominal swelling, bloating, and fullness, frequent urination and/or burning, abdominal discomfort and/or pain, lower back pain, loss of appetite, diarrhoea and abnormal vaginal bleeding. Physical findings are diverse and include a palpable ovarian mass [11]. Most women are asymptomatic, at least until the disease has metastasised, and hence two-thirds are diagnosed with advanced stage disease [6].

Ovarian cancer is described as a malignant tumour in one or both ovaries [12]. Ovarian cancer can arise from three cell types, specifically epithelial, germ and sex-cord stromal cell. Nine out of ten cases are classified as epithelial ovarian cancer [13], while the remaining are classed as non-epithelial types (germ cell cancer originates from cells that are destined to form eggs within the ovaries; sex-cord stromal cancer begins in the connective cells that hold the ovaries together and produce female hormones) [13]. Fallopian tube and peritoneal cancers are often grouped together with ovarian cancer as they originate from the same area and have the same adjuvant treatment. The research project covered in this thesis includes women diagnosed with any type of ovarian, fallopian tube or peritoneal cancer (discussed in more detail in methods).

If ovarian cancer is suspected on the basis of clinical interview (physical examination and results from imaging tests) surgery is typically needed for a definitive diagnosis. An exploratory laparotomy (incision through abdominal wall) is conducted for histological confirmation, staging and debulking. The benefits of surgery include reduction of tumour load, improvement in disease-related symptoms, optimisation of response to systemic chemotherapy and possibly improvement of patient immunocompetence [13]. Surgery may involve removal of the uterus (hysterectomy), both ovaries and fallopian tubes (bilateral salpingo-oophorectomy) and/or the fatty protective tissue covering the abdominal organs (omentectomy) as well as lymph nodes in the groin. However, it may be even more extensive if other organs are involved (e.g. pleura or diaphragm) [12]. The advantage of surgical debulking and cytoreduction for advanced stage disease has been investigated in a meta-analysis. It was identified that for every 10% increase in cytoreduction there was an associated 5.5% increase in median survival [14].

Staging classification provides an estimate of extent of disease, appropriate treatment, risk of recurrence, disease-free survival and overall survival. The staging of gynaecological cancers has been standardised by The International Federation of Gynaecology and Obstetrics (FIGO) and is described in Table 1.1 below.

Table 1.1: Staging for primary carcinoma of the ovary

Stage	Description
I	tumour is found only in one or both ovaries (limited to)
II	tumour is found in one or both ovaries with pelvic extension
III	tumour is found in one or both ovaries spread to abdominal lining beyond the pelvis, the intestines or lymph nodes
IV	distant tumour has spread outside the abdomen such as liver or lungs

Systemic treatment

Chemotherapy usually begins between four and six weeks after surgery, however some studies have shown a delayed initiation of chemotherapy in elderly women of greater than six weeks [15, 16]. First-line adjuvant chemotherapy (which is used to destroy or slow the growth of the tumour) is usually recommended for all but some stage I tumors and typically involves a combination of two drugs, carboplatin (platinum drugs) and paclitaxel (taxane-based) given intravenously. When patients are not suited for combination chemotherapy, whether that be due to age, being significantly undernourished, medical comorbidities or poor performance status, use of a single agent, Carboplatin is generally indicated [13]. Results of clinical trials undertaken over the last 30 years support the use of six cycles of chemotherapy, every 21 days as standard treatment for women with advanced ovarian cancer [3, 11]. More recently, however, intraperitoneal chemotherapy is being used as a way of delivering the drugs directly into the abdominal cavity. The abdominal cavity is the most common place that ovarian cancer will spread. The rationale for intraperitoneal therapy in ovarian cancer is that the peritoneum receives sustained exposure to high concentrations of antitumor agents while normal tissues, such as the bone marrow, are relatively spared [17]. Clinical trials have shown that this type of chemotherapy is suitable for women with stage III ovarian cancer, with less than one centimetre of tumour remaining at the end of surgery [17]. In particularly advanced cases, women may require neoadjuvant chemotherapy prior to debulking surgery, in an attempt to reduce the size of the tumour. For the 20% to 40% of women who do not respond to first-line chemotherapy and women who have a recurrence, second-line treatment may be prescribed [11].

The ability to adhere and/or complete the prescribed chemotherapy course is difficult for some women. More than one-third of Australian women in an ovarian cancer study were not able to complete their prescribed first-line chemotherapy course. Specifically, 10% required a reduction in agent dose, 13% required removal or replacement of an agent and 5% ceased treatment altogether [18]. Other studies have noted that 56% to 91% of cancer patients had to cancel or delay chemotherapy due to serious complications [19, 20]. Complications include reduction in hemoglobin level and neutrophil counts as well as peripheral neuropathy. First-line chemotherapy completion rates using cisplatin and paclitaxel in advanced stage ovarian cancer have been reported between 83% [21] and 86% [17]. Changes in chemotherapy courses and drug doses can reduce response rates to treatment from 68% to 30% [22].

The goal of treatment is to optimise survival. Unfortunately, each treatment regime has the risk of potential physiological and psychological adverse side-effects that can be the limiting factor for completing chemotherapy. For example, medical chemotherapy will be stopped or reduced if a patient's Eastern Cooperative Oncology Group (ECOG) performance score (a scale used to assess disease progression) is graded two (ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours) or three (capable of only limited self-care, confined to bed or chair more than 50% of waking hours) [23].

1.3 SIDE-EFFECTS OF OVARIAN CANCER TREATMENT

The side-effects of systemic treatment may vary widely and may depend on factors such as the type of drug or drug combination used, dose, method of delivery and patient medications [24]. Treatment side-effects including physical and psychosocial concerns have been well reported in ovarian cancer literature and are discussed in detail below.

Physical

The physical side-effects from surgery and adjuvant chemotherapy for ovarian cancer include changes to bladder and bowel habits, neutropenia, hot flushes, pain, temporary hair loss, menopausal symptoms, body weight fluctuations, alterations in taste, increased risk of infection and poor sleep [9, 25, 26]. Nausea and vomiting are particularly notable symptoms, with ovarian cancer patients rating these as two of the most dreaded side-effects of chemotherapy [26]. Another side-effect as a consequence of paclitaxel and carboplatin chemotherapy combinations is sensory peripheral neuropathy [3]. Neuropathy has been reported in 57% to 92% of all patients treated with cisplatin and 60% of those receiving taxanes [27]. In most cases chemotherapy-induced neuropathy is reversible [24]. Concerns regarding cachexia, which is a progressive weight loss with depletion of adipose tissue and skeletal muscle mass, is also an issue for women with ovarian cancer [28]. In advanced ovarian cancer patients, cachexia is caused by the metabolic effects of the enlarging tumor masses and bowel obstruction and is accountable for up to 20% of cancer deaths [28].

Cancer-related fatigue represents one of the 'most noticed' symptoms by women receiving treatment for gynaecological cancer with its presence severely interfering with lifestyle activities [29]. Fatigue in ovarian cancer patients receiving chemotherapy has been found to peak approximately seven days after each cycle post-treatment and has strong positive correlations with nausea, depression and anger, and negative correlations with haematocrit levels [25]. In the past, people with cancer were encouraged to rest and reduce their amount of physical activity in an attempt to attenuate fatigued [30]. However, such suggestions are now known to compound symptoms and further decrease functional capacity [31].

Psychosocial

The extensive surgery and aggressive chemotherapy regimens such as those faced by women with ovarian cancer have been considered to bring about vulnerability to psychological ill health [32]. Documented psychological side-effects of carboplatin include anxiety, depression, difficulty concentrating, memory loss and mood swings [25]. Both anxiety and depression occur more frequently in patients with cancer

than in the general population, with several studies demonstrating 20% to 30% of ovarian cancer patients experience moderate to severe distress and anxiety [33-36]. Psychological distress among patients with ovarian cancer has been found to be significantly correlated to the number of physical symptoms women experienced [37]. Fear of recurrence or metastases, possibility of death and infertility represent other concerns contributing to psychological ill-health [38].

Quality of life (QoL)

In the past, investigations tended to evaluate the length of survival or the response to treatment with little concern for impact on QoL. Now, QoL is a focal point for most clinical trials [39, 40]. Although there are limited QoL data available following ovarian cancer, existing studies have demonstrated declines in newly diagnosed patients [41] and poorer overall QoL for those receiving chemotherapy for recurrent disease compared with those receiving first-line chemotherapy [42]. However, over the longer term, QoL in ovarian cancer patients has been considered 'good' when compared with QoL of other cancer survivors [43, 44].

1.4 RECOVERY FOLLOWING OVARIAN CANCER

To manage and/or reduce side-effects associated with cancer therapy a diverse range of intervention types has been examined. These can be broadly categorised as psychosocial or behavioural, pharmacological or complementary and alternative therapies [45-48]. Behavioural interventions have used imagery, relaxation training, hypnosis, cognitive/attentional distraction, contingency management and systemic desensitization to reduce nausea and vomiting, anxiety, stress, pain and management of mood disturbances [45]. Behavioural interventions have been accepted widely due to relative ease of application, the immediacy of their positive impact on cancer patients and the sense of control their use provides patients at a time when they feel most vulnerable [45]. Pharmacologic treatments using aspirin, codeine, morphine and non-steroidal anti-inflammatory drugs have been found to assist with neuropathic, postoperative and metastatic bone pain [47]. Therapies such as electrical stimulation, acupuncture, massage therapy, muscle relaxation,

supportive group therapy and aromatherapy have also been successful in reducing pain, relieving dyspnea and reducing incidence of nausea and vomiting [47].

Interest in the area of physical activity following cancer diagnosis has over the past two decades been receiving greater attention. Physical activity has many and varied effects on the human body. Participation in physical activity has the potential to improve digestion, strengthen the skeletal system, improve lung capacity, optimise heart function (e.g., increase stroke volume and decrease resting heart rate), help metabolism become more efficient and reduce stress, anxiety and depression. As a consequence, physical activity offers a holistic approach to positively aid in the cancer recovery process [49]. The effect of physical activity on cancer patients has been examined extensively in over 80 studies (33 during treatment), particularly in the breast cancer population. However, to date, ovarian cancer patients have not been the focus of these trials.

To summarise, we know that ovarian cancer requires significant abdominal surgery and the presence and intensity of symptoms is the limiting factor for chemotherapy completion. The need for intervention strategies to assist in mitigating the adverse effects of cancer and its treatment is evident.

Therefore, the objectives of this work are to:

1. Evaluate feasibility (retention, adherence, compliance) and safety of integrating a walking program during neo-adjuvant or adjuvant chemotherapy for women with ovarian cancer.
2. Measure pre-post intervention changes in functional capacity, body weight and composition, anxiety and depression, treatment-related symptoms and quality of life.
3. Document chemotherapy prescription conformity.

This thesis begins with a literature review (Chapter two), which discusses results from the exercise intervention and prescription research in cancer, as well as the current physical activity trends in ovarian cancer patients. The methods involved

with the research is described in Chapter three, which includes recruitment, data collection and measurement procedures, details regarding the design and implementation of the walking program and the manner by which data collected were evaluated. Results from this work are presented in Chapter four. More specifically, feasibility and safety of the intervention as well as preliminary outcomes and the evaluation of the program are reported in this section. Finally, Chapter five provides a discussion bringing together the major findings of the results chapter and acknowledges the studies limitations and concludes with future recommendations for ovarian cancer research.

Chapter 2: Literature Review

2.1 EXERCISE INTERVENTIONS

Recent investigations have suggested that exercise is a critical complementary/behavioural therapy in the management of many cancers [50]. Review studies have found evidence supportive of the role of exercise in attenuating a range of physical and psychosocial problems associated with cancer or its treatment [51]. During treatment, studies have consistently demonstrated a positive association of physical activity with improved QoL, cardiorespiratory fitness, fatigue, depression, anxiety, muscle strength and anthropometric measures of body weight and body fat [52].

History

A pioneer in the field, Maryl Winningham, started to publish data in 1983 on the role of exercise programs for cancer patients. Her early research was in the breast cancer population using aerobic-based interventions. The mid 1990's saw increased attention to this field [53]. Early work involved conservative, supervised and unsupervised home-based physical activity programs using aerobic-based modes of activity such as walking and bicycle ergometery. Research has continued to evolve overtime with combinations of aerobic and resistance training programs being tested with various cancer groups. Now more than 80 exercise studies have been completed, and include interventions of mixed exercise modes and varying intensities, durations and forms of delivery [54].

Exercise *during* treatment

A recent systematic review and meta-analysis analyzed results of 82 exercise intervention studies conducted with cancer survivors. Of these studies, 40% of studies were carried out during treatment (n=33) [54]. Of those studies performed during treatment, 79% were conducted with breast cancer patients, compared to only 3% with ovarian cancer patients. The mean sample size per intervention group

was reported as 33, with similar average sized control groups (n=32). The majority of studies were randomized controlled trials (90%), 88% required patients to obtain physicians clearance and/or screening prior to participation and 33% of potential participants were excluded based on previous level of physical activity. Thirty percent of during treatment interventions were behavioural change interventions in which the primary aim was to increase physical activity behaviour. Details of the exercise prescription used in these studies are described in chapter two [54].

From the studies that have been explored in these reviews, interventions conducted during chemotherapy have shown that being active during this period is associated with positive results in relation to body composition, bone mineral density, functional capacity, immune variables, muscle strength, neutropenia and aerobic capacity [51, 55, 56]. Reduced impact of disease and treatment-related symptoms and side-effects including nausea, fatigue, difficulty sleeping, pain and diarrhoea, as well as better compliance with treatment regimes have also been reported [57]. Improved mood and reduced distress, depression and anxiety represent psychological changes associated with activity during treatment [51, 57-59]. Independently or collectively the benefits of exercise are likely to positively influence QoL [53]. Conversely, lack of exercise during cancer treatment has the potential to aggravate side-effects and induce loss of function, hence contributing to a diminution of overall QoL [60].

A study of breast cancer patients receiving adjuvant chemotherapy was the first to consider the effect of exercise on chemotherapy completion rates. Women (n=242) were randomly assigned to usual care, a supervised resistance training group or supervised aerobic exercise group. Women who did aerobic exercise three times per week beginning with 15 minutes for one to three weeks and increasing to 45 minutes by week 18 had significant improvements in chemotherapy completion rates (74%) compared with rates in the control group (66%)[61]. Women in the resistance training group were asked to exercise three times per week performing 8-12 repetitions for two sets of nine different exercises (of estimated 1 RM), and also demonstrated improvements in chemotherapy completion rates (78%

completed chemotherapy). Early cessation of chemotherapy has been shown to influence the ability of the drugs to effectively treat the disease, hence impacting on survival.

Exercise *following* treatment

Experimental studies examining the effect of exercise following cancer treatment have been widely presented. Gains in strength, aerobic capacity and flexibility, along with improvements in immune function, blood pressure and body composition have all been linked with exercise programs following cancer treatment [48, 51, 55, 60, 62]. Improvements in psychological well-being, fighting spirit, mood status, self-esteem, and body image and reductions in anxiety, sleeping problems and depression have also been observed [48, 51, 55, 60, 62].

Cancer groups assessed

Undoubtedly, breast cancer has been the most common cancer type studied in cancer-related exercise intervention trials. In a review paper, of the 18 studies undertaken during treatment, nine exclusively involved women with breast cancer and while three others included a mixed cancer group, women with breast cancer comprised 57% of the sample [55]. Other cancer groups investigated include colorectal [63], lung [64], head and neck [65], hematological [56], prostate [66] and gynaecological cancer (including ovarian and cervical)[67], although the body of evidence surrounding exercise and these cancer groups is more limited. A recent systematic review (undertaken as part of this masters and currently under review; Appendix A) evaluated the extent to which women with gynaecological cancer have been involved in exercise intervention trials during and/or following cancer treatment. Of the 12 studies identified (92% of which involved mixed cancer types) only 10% of the total sample of participants (n=212) were women diagnosed with gynaecological cancer (ovarian, endometrial or cervical). Further, there has only been one exercise intervention trial that has involved only a gynaecological cancer (endometrial) cohort [68].

We have much to learn in this setting and in the design of future gynaecological cancer and exercise intervention studies. While it is important to acknowledge what has been learnt from the broader exercise and cancer setting, given the intense nature of ovarian cancer treatment it cannot be assumed that exercise programs designed for breast cancer patients can be applied to ovarian cancer patients without modifications. Future research, in the form of 'proof of concept', is required to better understand how well results found in other cancer cohorts are generalisable to women with ovarian cancer.

2.2 EXERCISE PRESCRIPTION DURING TREATMENT

Despite the abundance of physical activity studies conducted during treatment, the precise exercise prescription, in relation to optimal type, frequency, duration and intensity for cancer patients in general remain unclear.

Mode

The most common exercise interventions assessed are aerobic-based, specifically using a cycle ergometer and/or walking modes, either alone or in combination with resistance training [50, 51, 57-60]. The mode of activity is generally consistent for both intervention during and post treatment. Walking and pedalling exercise have been noted as the safest modalities [31]. Walking is an activity people perform daily and involves the use of major muscle groups. It is also a convenient mode of exercise for most people, irrespective of age and disease status and does not require any exercise equipment and has limited associated cost [60]. In a study examining exercise preferences in 386 endometrial cancer survivors, 69% indicated their preferred mode of activity was walking [69]. Physical activity preferences for ovarian cancer survivors (postal survey of 359 women) were similar, with 63% indicating walking as their ideal mode of exercise [70]. Also, walking was the favoured mode of activity in a home-based exercise program during chemotherapy treatment in patients with solid tumours [67].

Form of delivery, frequency and duration

Exercise prescriptive characteristics vary across studies with interventions during treatment ranging from completely supervised, or completely unsupervised home-based programs [55]. Exercise intervention lengths range anywhere from two weeks to one year [51], with the frequency of sessions ranging from two sessions a day to six sessions per week [51] and the average session length is 30-45 minutes [54]. The latest exercise prescriptions guidelines for cancer patients, from the Australian Exercise and Sports Science Association (ESSA, previously known as the Australian Association for Exercise and Sports Science) position stand (2009) is the same for patients undergoing treatment or following treatment. It recommends at least 20 to 30 minutes of continuous aerobic exercise be undertaken for a frequency of three to five times per week [60]. However, the emphasis for deconditioned patients has been on aerobic activity several times a day for shorter bouts including rest intervals [71]. Consequently, the recommended duration can be accumulated in one session per day or accumulated over the course of a day with benefits achieved irrespective of how duration is accumulated. Progression of exercise is normally prescribed through a combination of increased duration and frequency before increasing intensity level. Progression for some individuals, particularly during periods of treatment, could constitute maintenance of pre-treatment exercise levels [60].

Intensity

Randomised, controlled trials of exercise for cancer patients during treatment have reported various intensities ranging from a minimum of 50%, up to 90% estimated maximum heart rate (HRmax) [51, 55]. General consensus in the literature for cancer patients is exercising at low to moderate intensity either during or after treatment depending on current fitness level and medical treatment. One researcher suggested aerobic exercise intensity in the cancer population should be between 55% and 85% maximum heart rate (calculated by 220 minus person age) [31]. This is confirmed in the ESSA position stand (2009) that outlines exercise intensity during treatment should be moderate, between 60% and 80% heart rate maximum [60]. Intensity may also be measured using the Rating of Perceived

Exertion (RPE) Scale [72]. It is an ordinal scale ranging from six to 19, where six represents “no exertion at all” and 19 reflects “maximal exertion” [72]. To calculate a rating, the person chooses a number that best describes their level of exertion during an activity. Nine corresponds to “very light’, 13 is “somewhat hard’ and 17 is “very hard” equating to exhausting or high-intensity exercise. The rating given should reflect how strenuous the exercise feels combining all sensations and feelings of fatigue, physical stress and effort [72]. However, this is only effective in clinical populations if one particular side-effect does not override another sensation (e.g leg pain over breathing) as this could cause the RPE scale to be potentially limiting. The relationship of all intensity methods can be found in Table 2.1 [73].

Table 2.1: Methods of classification of exercise intensity

% Heart-rate maximum (HR max)	Rating of perceived exertion (RPE)	Class of intensity
<40	<8	Very light/sedentary
40-55	8-10	Light/low
55-70	11-13	Moderate
70-90	14-16	Vigorous/high/hard
≥90	≥17	Very hard

2.2.1 Exercise and safety

Safety considerations for exercise prescription in the cancer population may include risk of bone fractures in those with compromised bone health, the potential to exacerbate treatment side-effects such as pain, lymphoedema, nausea and fatigue and the alleged reduction in the patient’s ability to tolerate exercise after sedentary periods [71]. A list of precautions corresponding to specific considerations when prescribing exercise to cancer patients is shown in Table 2.2 [74].

Table 2.2: Precautions when prescribing exercise to cancer patients

Complication	Procedure
Hemoglobin level <8.0g/dl	Avoid activities that require significant oxygen transport
Absolute neutrophil count <0.5 x 10^9/L	Avoid activities that might increase the risk of bacterial infection (e.g. swimming)
Ataxia/dizziness/peripheral neuropathy	Avoid activities that require significant balance and coordination (e.g. treadmill)
Severe cachexia (excessive loss of premorbid weight)	Loss of muscle usually limits exercise to mild intensity
Shortness of breath (dysnea)	Investigate etiology. Exercise to tolerance
Bone pain	Avoid activities that increase risk of fracture (e.g. high impact exercise)
Severe nausea	Investigate etiology. Exercise to tolerance
Extreme fatigue	Exercise to tolerance
Dehydration	Ensure adequate hydration

Of the more than 1,000 men and women diagnosed with cancer who have participated in exercise interventions, few adverse events have been reported and of those listed, events have been considered minor [75]. Adverse events reported include injuries to the back, shoulder tendonitis and ankle problems and have occurred in resistance exercise interventions or in persons who have exceeded prescription guidelines [48, 75]. Worsening of fatigue was reported by two participants during an aerobic intervention throughout radiation [75]. Most musculoskeletal injuries related to physical activity are believed to be preventable by gradually working up to a desired level of activity and by avoiding excessive amounts of exercise [76]. Of note, however, adverse events or lack thereof, are often not mentioned throughout the literature and therefore caution when dealing with special populations such as ovarian cancer patients is nonetheless needed. At the same time, it is important to ensure that cancer survivors are not unnecessarily restricted from participating in activities that would, at worst, do no harm [60].

In summary, exercise is generally well tolerated among cancer patients and survivors and importantly, there is adequate evidence to support the notion that exercise interventions are safe and effective.

2.2.2 Feasibility

Compliance of cancer subjects involved in exercise intervention studies ranges from 60% to 100%, which in comparison to interventions with the healthy population is high. Adherence to study protocol, although not well reported, is also high, ranging between 64% and 100% [77]. Overall, participation in exercise programs is good, which may be due to motivation to improves one's own health, to 'help others' through research or that a cancer diagnosis is accompanied by a period of self-reflection and thus represents a 'teachable moment' which in turn may contribute to participation rates [78].

2.3 EXERCISE FOR WOMEN UNDERGOING TREATMENT FOR OVARIAN CANCER

It is anticipated that, similar to other cancer groups, women with ovarian cancer participating in regular exercise during treatment may experience reductions in the severity of side-effects, improvements in treatment completion rates and enhancements in psychological well-being. However, the logistics in recruiting and retaining ovarian cancer patients into an exercise intervention during chemotherapy have not yet been explored. Compared with the cancer types more commonly investigated in exercise intervention trials, ovarian cancer patients are predominantly late stage diagnosis, have high risk of recurrence and undergo major abdominal surgery as a primary form of treatment involves, Patients also typically undergo multiple regimens of chemotherapy but may experience reductions in planned chemotherapy due to the presence and intensity of symptoms. While these differences may make including these patients in an exercise intervention study more complex, they also represent reasons as to why exercise may be particularly beneficial to this cohort. However, to date, ovarian cancer patients have not been exclusively investigated in any exercise intervention study.

Physical activity trends

Physical activity levels tend to decrease after cancer diagnosis, with most patients continuing lower levels of activity through treatment and beyond, rarely returning to their pre-diagnostic levels of activity [79]. Courneya and researchers (1997) documented four main patterns of exercise across the cancer experience in a

retrospective trial on breast cancer survivors [80]. Breast cancer survivors were labeled as being *maintainers*, *temporary relapsers*, *permanent relapsers* and *non-exercisers*. *Maintainers* were those who were active prediagnosis, during treatment and post treatment. *Temporary relapsers* were active during prediagnosis, had lower levels during treatment but then returned to pre-treatment levels post-treatment. In contrast, p*ermanent relapsers* were active prediagnosis and became inactive during treatment and remained inactive post treatment. *Non-exercisers* were inactive during all time periods.

General population information reported in the Queensland Cancer Risk Study (n = 4722) showed that almost half of women were classified as having insufficient levels of physical activity to achieve health benefits [81]. In fact, 16.5% of women were sedentary and 27% were insufficiently active (<150 minutes per week of activity) and these results were similar for women aged 40 to 59 years compared with those 60 to 75 years (Figure 2.1).

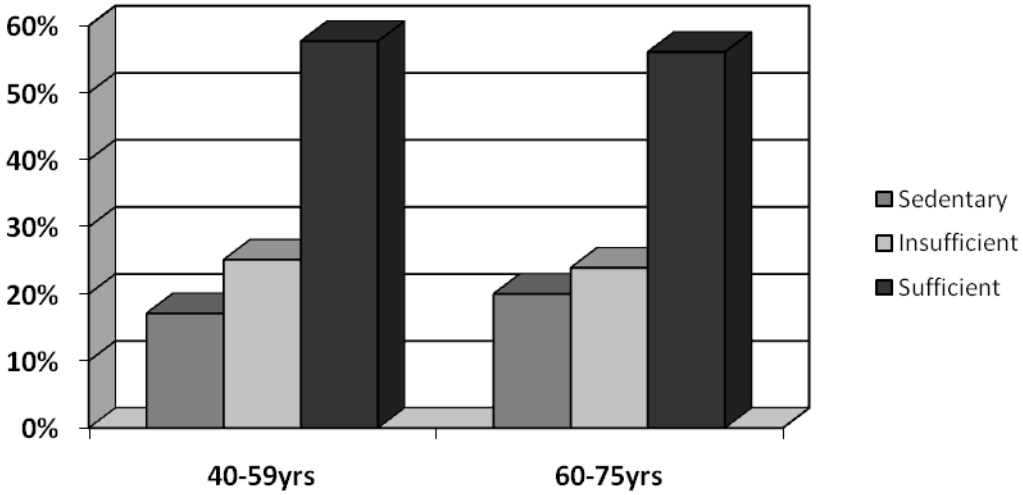

Figure 2.1: Physical activity results by age group from QLD Cancer Risk Study (2006)

Physical activity rates following ovarian cancer

It has been previously reported in a Canadian study that 69% of ovarian cancer survivors are not meeting public health physical activity guidelines [82]. The study involved 359 women with a mean age 60 years and identified that more than two thirds did insufficient levels of activity (included women who were sedentary as well as those who did less than specified guidelines)[82]. Population studies in the USA

have elicited similar physical activity estimates for survivors of gynaecological cancers with only 29% meeting recommended physical activity levels [83]. In comparison, Australian researchers who explored health behaviours in 802 gynaecological cancer survivors (ovarian cancer, n=236) reported that 27% of ovarian cancer survivors were sedentary and 37% insufficiently active (one to 149 minutes per week) using the validated Active Australia survey [84].

To date, only one study has evaluated changes in physical activity levels in women with ovarian cancer. Specifically, a longitudinal study assessed exercise characteristics across several periods (pre-diagnosis, first, second, third and fourth year post-diagnosis) in 518 women. In the year following diagnosis, 41% reported exercising less than once per week, 32% reported exercising strenuously once per week or moderately one to three times per week and 27% reported exercising strenuously two or more times per week or moderately four or more times per week. Few women (14%) with ovarian cancer increased their exercise within the first year after diagnosis and only about one third maintained pre-diagnosis physical activity levels [84].

Recently, Canadian researchers conducted a population-based postal survey on ovarian cancer survivors and found they are more likely to meet physical activity guidelines if they are younger, highly educated, wealthier, employed, had early-stage disease, were disease free and have a healthy body-mass index [70].

2.4 SUMMATION

A diagnosis of ovarian cancer is generally late-stage, and treatment involves significant abdominal surgery and platinum and taxane-based chemotherapy. Risk of recurrence is high with most women having to undergo multiple chemotherapy cycles. Due to common adverse effects of treatment including fatigue, neutropenia, nausea, vomiting and peripheral neuropathy, often prescribed chemotherapy courses are reduced and the specific prescription drug changes, replaced by another drug or ceased altogether. The side-effects which cause changes to chemotherapy regimens also negatively impact on physical and psychological well-

being hence on QoL. We know from research investigating other cancer groups that exercise is beneficial in reducing the impact of symptoms, decreasing fatigue, enhancing mood, reducing depression and distress during treatment for cancer and potentially aiding compliance to treatment regimes. To date, no exercise intervention trial has been conducted solely with women with ovarian cancer.

Chapter 3: Methods

3.1 RESEARCH DESIGN

This research involved a walking intervention of women diagnosed with ovarian cancer whilst undergoing neo-adjuvant and/or adjuvant chemotherapy treatment. The research is a Phase I trial using a one group pre- post-intervention test design. The pre-intervention (baseline) assessment was conducted following surgery but prior to the first or second chemotherapy cycles, while post-intervention (follow-up) assessment was conducted three weeks after the last chemotherapy dose was received.

3.2 RESEARCH OBJECTIVES

The study had three main research objectives:

1. To evaluate feasibility (retention, adherence, compliance) and safety of integrating a walking program during neo-adjuvant or adjuvant chemotherapy for women with ovarian cancer,

2. To measure pre-post intervention changes in functional capacity, body weight and composition, anxiety and depression, treatment-related symptoms and quality of life, and

3. To document chemotherapy prescription conformity.

3.3 RECRUITMENT

Recruitment of patients from RBWH, Queensland (QLD) began in June 2009. Eligible patients include those: aged 18 years or older; living within 60kms of Brisbane CBD; with verified ovarian, peritoneal or fallopian tube cancer; about to start first or second cycle of neoadjuvant or adjuvant chemotherapy; able to complete the questionnaires in English and give informed consent. All histology types were eligible including clear cell, mucinous, endometriod and serous/serous papillary. Women with borderline ovarian tumours or who had a prior malignancy within the

last five years were ineligible. Women who were identified to be too sick, cognitively impaired or non-English speaking were also excluded.

Rationale behind specific eligibility criteria

Cancer type:

Neoplasms are diagnosed in the ovary, fallopian tube and peritoneum. It is widely believed that these are variants of the same malignancy, although little is known about fallopian tube and primary peritoneal cancers [85]. Peritoneal and fallopian tube cancers seem to have the same behavior and prognosis as ovarian cancer, for the purposes of this work, it was considered appropriate to allow women with these diagnosis to participate in this trial.

Residence criterion:

From the exercise, cancer and gyneacological literature, it was determined that optimal exercise prescription and timing of an exercise intervention would differ by gyneacological cancer, sub-type and stage, due to the differences in treatment and prognosis. For women with ovarian cancer, who typically receive extensive, open abdominal surgery followed by repeated regimes of chemotherapy, it was hypothesized that they may benefit most from a tailored exercise intervention during chemotherapy treatment. Conducting the walking intervention only during neo-adjuvant or adjuvant chemotherapy treatment seemed to be the most imperative time where benefits would be greatest. Given no other previous research, the design of the intervention was guided by ESSA guidelines and that the residence criterion was applied so that the intervention could be delivered face-to-face.

Over the first five months of the study (when Brisbane [urban] women were the geographical target group), only three women were deemed eligible (two of whom consented). More patients than expected were ineligible (n=15) because they lived in rural Queensland (outside the 60km Brisbane area). Based on experiences with breast cancer cohorts, and the experiences of dealing with the first two women in the study, to increase recruitment prospects, the geographic location eligibility

criterion was removed. The intervention was then modified for those who lived outside this region, to allow intervention delivery via the telephone.

3.3.1 Recruitment strategy

The gynaecological oncologist or case management nurse briefly introduced the study to eligible women and ascertained women's consent to be contacted by a research nurse who would provide them with more study details and invite them to participate. If women did not wish to be approached by the research nurse, their de-identified details were recorded on a tracking form. Interested women were provided with a detailed information sheet and consent form (Appendix B) by the research nurse who was available to answer any questions they had about the project. Women were encouraged to speak to their family and oncologist about participating in the intervention. Interested women were asked to provide written informed consent. Contact details of the consenting women were given to the exercise physiologist (EP) so that the baseline assessment and commencement of the intervention could be organised.

The EP made phone contact with consenting women within one week of receipt of contact details, during which time the baseline assessment was scheduled. Women were then mailed a letter confirming the scheduled appointment time and day as well as information about parking and suitable attire (comfortable and light fitting clothes and appropriate walking shoes). They were also instructed to avoid vigorous activity within two to four hours of the test, consumption of high fat meals and/or higher than normal caffeine and alcohol intake, and to empty her bladder just before the assessment.

Timing and scheduling

The number of sessions with the EP was determined by the duration of chemotherapy treatment for each participant. For the face-to-face group, the initial session with the EP was scheduled at the baseline assessment and for the women in the telephone group, the first session was scheduled via phone call once the

baseline questionnaires had been returned to QUT. Successive sessions were planned during the previous session, most often attempting to keep the day and time similar. Figure 3.1 illustrates the flow of the intervention for women prescribed three cycles of chemotherapy.

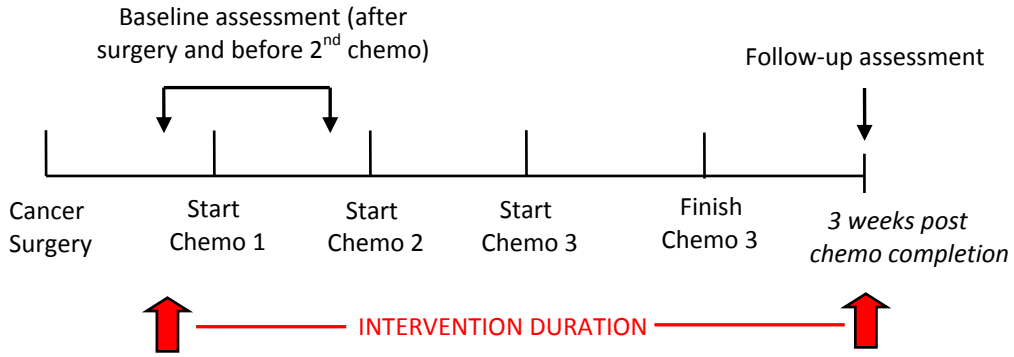

Figure 3.1: Timing of baseline and follow-up assessment and walking intervention

For women in the face-to-face group, if sessions were not able to be conducted in person, then the opportunity to conduct the session over the phone was permitted in order to reduce the number of missed sessions. Furthermore, if the women returned to Brisbane throughout the intervention period, when possible, face-to-face intervention visits were arranged. For women in the telephone group, phone calls were managed using a three step system. If the woman could not be contacted on the pre-arranged day and time, a second phone call attempt was made that same day. If that phone contact was unsuccessful, then a final phone call attempt was made the following day. Three unsuccessful attempts at contact was recorded as a missed session and noted as 'unable to contact'. For the subsequent session (following week), the phone call was made at the same day and time that had been scheduled the previous week.

3.4 DATA COLLECTION AND MEASUREMENT

Data were collected by objective physical measures and via a self-administered questionnaire at baseline and follow-up assessment. The data collection sessions took approximately 45 minutes to complete and were conducted at the Queensland University of Technology (QUT) or at the participant's residence. The baseline (pre-

intervention) assessment was conducted prior to the first or second chemotherapy cycles, while follow-up (post-intervention) assessment was conducted three weeks after the last chemotherapy dose was received.

3.4.1 Physical testing

A series of physical tests were administered by the EP to measure functional capacity and body composition, as well as anthropometric measurements.

Functional capacity

Functional exercise capacity was measured using the 6-minute walk test (6MWT). The test has been widely used for pre- and post-operative evaluations and for measuring the response to therapeutic interventions mainly in chronic conditions including cardiac disease, pulmonary conditions and cancer [86-88]. The 6MWT is a valid and reliable method of assessing functional ability, with strong test-retest reliability (intraclass correlation = 0.97) [89].

In our assessment, the 6MWT was performed outdoors, along a flat, straight pathway on a hard surface. The walking course was ten metres in length and marked every two metres, with the turnaround point being marked with a cone and the starting-line clearly marked on a pathway with tape. Participants were fitted with a Polar^{TM} heart-rate monitor (FS1) before starting the test. Instructions given to each participant were to walk as far as possible in 6-minutes and that they will be informed each time a minute passed. No encouragement was given after starting the walk, as it is known that this can improve performance [90]. The EP used a chronograph digital stopwatch to accurately time 6-minutes, and recorded lap counts to determine distance travelled. At the conclusion of the 6MWT, each participant was instructed to stop walking; the participant's heart-rate was taken; and a chalk mark was placed on the ground to enable distance completed to be measured and recorded.

Body composition

Bioelectrical impedance spectroscopy (BIS) (Impedimed Imp SFB7) was used to measure body composition. The device measures the impedance of the body to an applied electrical current.

Participants were instructed to lie supine with arms slightly abducted, palms down with a towel placed between the thighs. All jewellery was removed from the limbs being measured. Single-tab gel electrodes were placed on selected limbs after they were cleaned with an alcohol wipe and were positioned on the dorsal surface of the wrists (process of radius and ulna bones) and on the left ankle (lateral malleolus of fibula). Impedimed software was utilised to calculate percent and kilogram fat mass (FM) and fat-free mass (FFM) with appropriate equations using the obtained values along with the participant's gender, age, weight and height. The BIS machine was calibrated before each test to optimise accuracy. All measurements were recorded by the EP on assessment sheets (Appendix C) and then uploaded onto the computer.

Anthropometric measures

Anthropometric information including weight, height, waist and hip circumferences were also taken. Height and weight were assessed with the participant barefoot, measured to the nearest 0.5cm and 0.5kg, respectively. Weight was measured using analogue Seca^{TM} scales and height was measured using a stadiometer or KDS^{TM} tape measure. Weight and height were used to calculate body mass index (BMI), using the metric calculation, weight (kg) / height^2 (m^2) to produce a unit of measurement of kg/m^2 [91].

3.4.2 Self-report questionnaires

The self-reported questionnaires (Appendix D) included several items about health and demographic characteristics. Health questions included: pre-existing medical conditions, family history of known medical conditions, current medications, surgical procedures before ovarian cancer diagnosis, general health (smoking,

alcohol), physical activity (concerns, injuries, current exercise, exercise history) and safety issues. Demographic and personal characteristics included: age, relationship status, education level, number and ages of children, household income and level of private health insurance. Validated instruments included the Hospital Anxiety and Depression Scale (HADS), Memorial Symptom Assessment Scale (MSAS), and Functional Assessment of Cancer Therapy - Ovarian (FACT-O). These instruments are described in more detail below.

The Hospital Anxiety and Depression Scale (HADS)

HADS is a self-rated instrument used to detect states of distress in patients [92]. It contains two subscales; anxiety and depression, with seven items per subscale. Patients were asked to circle a response to each item as to how they have been feeling in the past seven days, using a 4-point Likert scale. For each question the response scale is different. By summing the HAD subscale scores for anxiety and depression separately (minimum=0, maximum=21), clinical anxiety and/or depression can be identified. Of the 14 items assessed scores can be converted into three categorical classes including; normal (score zero to seven), cause for concern (score eight to ten) and professional assessment required (11-21). This scale is considered a reliable screening instrument for detecting clinical levels of anxiety and depression and is a valid measure of the severity of these disorders [92]. Both subscales have demonstrated good internal consistency, with values of Cronbach's coefficient (α) 0.80 and 0.76, respectively. HADS has been found to be robust across a wide range of samples and different stratum defined by age, education and gender [93].

The Memorial Symptom Assessment Scale (MSAS)

The MSAS is a multidimensional symptom assessment instrument that captures patient rated frequency, severity and distress associated with prevalent symptoms [94]. The MSAS has been found to be a reliable and valid instrument for the assessment of symptom prevalence, distress and characteristics [94]. It has been validated in the cancer population in patients with prostate [95], colon [95], breast [95] and ovarian cancer [36, 95, 96].

Participants are asked to rate the affect of particular symptoms during the past seven days. Frequency and distress dimensions are rated on a 5-point Likert scale (0 = not at all, 1 = rarely/a little bit, 2 = occasionally/somewhat, 3 = quite a bit/frequently, 4 = very much/almost constantly), while the severity dimension is rated on a 4-point Likert scale, ranging from one to four (1 = slight, 2 = moderate, 3 = severe, 4 = very severe). The 12-item physical symptoms subscale (including lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated and dizziness) and two additional psychological subscale items (including difficulty sleeping and difficulty concentrating) were included. A total score is calculated by dividing the distress score for each dimension by 12. The lower the score the less distress associated with the symptom present.

Functional Assessment of Cancer Therapy - Ovary (FACT-O)

One instrument widely used in clinical trials to measure health-related quality of life, is the General Functional Assessment of Cancer Therapy (FACT-G). It is a self-report measure that assesses four dimensions of well-being: physical (seven items), social / family (seven items), emotional (six items) and functional (seven items). An ovarian cancer-specific subscale of the FACT-G (FACT-O) has been developed and includes an additional 12 items. The 39 items that comprise the FACT-O are measured on a 5-point Likert scale (zero to four) ranging from not at all (0) to very much (4), with the patient asking to respond to each item as it applies to the past seven days. Total scores for the FACT-O ranges from zero to 156, whereby a higher score indicates better QoL. Internal consistency and test-retest reliability of the FACT-O has been reported to be good (Cronbach's $\alpha = 0.92$, $r = 0.81$, respectively) [97].

3.4.3 Medical records data abstraction

Chemotherapy data

At the conclusion of each participant's chemotherapy regimen, the research nurse obtained chemotherapy treatment information from hospital charts. Information from each chemotherapy cycle was recorded onto a clinical form. Data included dates of each chemotherapy cycle; any changes in regimen; dose and/or drug; cancer-antigen 125 (CA125) (U/ml) readings; and any adverse events noted by the oncology team.

Chemotherapy completion data was reported using relative dose intensity (RDI)[98]. Relative dose intensity is a term that refers to the amount of a particular chemotherapy drug given over a specific time (i.e. paclitaxel 250mg/m2 every three weeks) in relation to what was originally prescribed. The patient may be originally ordered 250mg/m2, but due to toxicities have a dose reduction or skip a dose, altering the total amount of chemotherapy they receive [99]. The RDI of each agent was calculated by expressing the total delivered dose of chemotherapy agent per unit time (week) as a percentage of the initial target dose [99]. The RDI's of each agent (commonly two agents prescribed) were then added together to get a total RDI. If the dosage of an agent happened to exceed the initial target dose at some point during the treatment cycles, then the RDI was determined as 100%. Reasons for this could include an increase in body weight of the patient or an excellent response to therapy.

3.4.4 Safety

Adverse events reported by participants

An adverse event was pre-defined as any unfavourable or unintended adverse change from the participant's general/normal condition that limited her from everyday normal living as a consequence of the exercise intervention. Examples of adverse events could include: fall, sprain, fracture, injury, strain, pull, tear of muscle or bone, or any other adverse events the participant believed as being caused as a direct result of walking. These adverse events were self-reported by the participant

to the EP, which was then recorded (with appropriate detail) in the woman's case management folder.

Adverse events reported in patient chart

Adverse events were recorded in the patient chart after each chemotherapy cycle by the oncology staff at the hospital. The research nurse abstracted this data from the patient charts and duplicated the information onto a clinical form at follow-up assessment. Adverse events were graded for severity under the Common Terminology Criteria for Adverse Events (CTCAE) [100]. The CTCAE displays grades one through four with unique clinical descriptions of severity for each adverse event based on this general guideline:

- Grade 1: mild adverse event
- Grade 2: moderate adverse event
- Grade 3: severe adverse event
- Grade 4: life-threatening or disabling adverse event

3.5 WALKING PROGRAM

The intervention consisted of weekly contact with an EP, either over the telephone for rural women or face-to-face for local women. The EP spoke to all women about the same topics but for those who lived locally these conversations were held during a supervised walking session. The maximum length of all sessions (face-to-face or telephone) was 60 minutes including the walk. This allowed time to discuss appropriate exercise goals, education delivery, exercise barriers, side-effects and for the EP to record walking completed from the previous week and schedule the following weeks session.

The specific duration, intensity and frequency for each participant was individualised according to their functional status and previous physical activity. Each week the EP gave each woman weekly individual walking goals to strive towards. The program was designed to be progressive, starting at a low-intensity building to a moderate-intensity. The RPE scale was used to determine the intensity of the walks all women performed.

Progression was achieved through a combination of increased duration and frequency of walking with cool-down (stretching) periods incorporated. There were no restrictions placed on the women with regard to whether the walking was of continuous duration, or divided into several bouts across the day. All details of frequency, intensity and duration were recorded on the physical activity log (both detailed below).

Importantly, participants were not discouraged to perform any other exercise or incidental activity. For instance, if women wanted to participate in line dancing once a month, then they were encouraged to do so at an appropriate level, however this was not recorded on the activity log. In addition, women were informed to do as much incidental activity (household duties, yard work, play with grandchildren) as they could manage during chemotherapy treatment. If planned walking was not an option for a couple of days due to severe side-effects, then incidental activity was particularly encouraged in an attempt to minimize functional capacity declines typically associated with declines in activity. However, this activity was not recorded on the physical activity log.

Case management folder

The participant's health and safety intervention details were recorded in a de-identified case management folder held by the EP. It contained important information from the initial health questionnaire and a summary of details recorded by the EP from each weekly contact. The case management folder followed the Chronic Disease Self-Management Intervention Model (CDSM) [101], which is a patient-centered approach that emphasises working collaboratively with the participant's, offering support and guidance for increasing physical activity, and acknowledging participant's expertise in knowing what works best for them in the context of their lives. This model has been used successfully in populations with diabetes [102, 103] and breast cancer [104]. The CDSM model has four components: 'assess', 'advise', 'assist' and 'arrange'. The 'assess' component relates to the woman's current diagnosis and treatment regime and any current symptoms and medications. It was also used to record any adverse events, as

mentioned by the participant. The protocol was such that, perceived or actual adverse events were to be immediately reported to the treating oncologist and the ethics committees. Information collected within this section ensured the EP was kept up-to-date with treatment and treatment modifications, as well as the presence of treatment-related symptoms, which was necessary to ensure subsequent prescription of the walking program recommended. The 'advise' and 'assist' components were used to record prescribed exercise goals for the subsequent week. Goal setting, problem solving and barrier identification relating to walking were also recorded here as well as defining appropriate motivational and supportive networks. The 'arrange' component was for follow-up and allowed for review and revision of the previous week's exercise goals.

The case management folder and the physical activity log (discussed below) were used to assess the first study objective regarding feasibility. Details about whether the woman reached the exercise goals and adhered to the exercise sessions were extracted from each record.

Educational booklet, physical activity log and pedometer

During the first week, each participant was provided with an educational booklet (Appendix E), physical activity log, pedometer and RPE scale.

The education booklet provided topics of discussion in an easy-to-follow format for the EP and participant to go through during weeks one to four. The purpose of the booklet was to assist in gradually providing women with important information relating to the walking intervention as well as developing rapport between the EP and participant. Topics within the booklet included: being active safely, when not to exercise, incidental activity, talk test, goal setting, problem solving and stretching.

Women were given a physical activity log (plus a whiteboard marker pen) that was laminated with magnets on the back so it could be placed on the fridge and used as a motivational tool and friendly reminder to log details of walking sessions. Details of session duration, frequency and intensity as well as any pedometer readings

were instructed to be included on the log. The EP recorded the details of the previous week's sessions in the case management folder and then the participant's log was wiped clean ready to record details of the following week's walking sessions. It was emphasized by the EP for the women to provide an honest record of their weekly walking sessions and not a record that they thought would please the EP or assist with the results of the study.

The Digiwalker^{TM} (SW-701) pedometer was given to women purely as another impetus to encourage and continue walking. It is small, light-weight and user-friendly with a clip to insert onto a belt or waistband. Women were instructed to wear the pedometer only during their planned walks (not incidental walking) for the study and to record the step count after their walking session onto the physical activity log. Before each planned walk the participant reset the pedometer to zero.

3.5.1 Program feedback

Participant feedback about the walking program was collected using a structured written evaluation form post-intervention, which was sent via mail after the follow-up assessment (Appendix F). Participants were asked how helpful the program was to their recovery and how helpful the education booklet and EP were (seven-point scale: 'very unhelpful'- 'very helpful'). Further questions regarding how often they used other resources such as the exercise tracking sheet and pedometer were asked (three-point scale: 'never', 'occasionally' and 'often'). In addition, three open-ended questions were asked for any suggestions about other ways the program could have been delivered, anything about the program that was found difficult and if the program could be improved. Finally, participants were asked to circle a number that best reflects how they felt about participating in the walking program (seven point numeric scale '1 = not good at all' to '7 = excellent').

3.6 DATA QUALITY AND MANAGEMENT

Participating women's names and personal details were kept confidential and separated from data collection material. Demographic information was kept in a

password-protected electronic file. Questionnaires, case management folders and data collection assessment were identified using a participant code and stored in a key-locked filling cabinet. All information collected via the self-administered questionnaire was entered into an electronic database twice with any anomalies clarified.

3.7 STATISTICAL CONSIDERATIONS

3.7.1 Tests and assumptions for analytical techniques

To determine the correct summary statistics and most appropriate statistical tests, all continuous outcome variables were firstly assessed for normality.

The following criteria were used to determine approximate normality:

- Is mean within ±10% of median value?
- Does the mean ± 3 SD approximate the minimum and maximum values?
- Is skewness coefficient within ± 3?
- Is kurtosis coefficient within ±3?
- Does histogram look bell-shaped?

All variables failed to meet the above criteria and were consequently considered not adequately normal. Non-parametric tests were used with summary statistics involving medians and ranges. All results were analysed in SPSS 16.0. Secondary outcome variables were examined using Wilcoxon Signed Rank Test, due to highly skewed distribution of data. Statistical significance was defined by p value 0.05 for all analyses. Clinically meaningful differences (as outline below) were used to detect associations of potential interest.

3.7.2 Data analysis

Objective One: *To evaluate feasibility (retention, adherence, compliance) and safety of integrating a walking program during neo-adjuvant or adjuvant chemotherapy for women with ovarian cancer.*

Retention

To evaluate feasibility of the walking intervention three factors were assessed: participant retention, compliance and adherence to exercise. Similar to others [105], retention was characterised as the number of participants who completed baseline testing divided by the number who completed follow-up testing (x 100%). A systematic review investigating the acceptability of exercise in cancer patients found a median retention rate of 87% [106]. Based on the literature, we predefined acceptable retention as a conservative 75% or more participants completing follow-up testing.

Adherence

Adherence reflects the proportion of completed sessions relative to scheduled sessions with the EP. Adherence rates to exercise interventions involving cancer cohorts have been reported to be anywhere between 70% and 84% [49, 106, 107]. Acceptable adherence was predefined at the lower end of this range (acceptable adherence as women participating in 75% or more of the scheduled sessions) due to the population being studied and the timing of the intervention.

Compliance

With the progressive nature of the walking program, compliance was determined by comparing the EP prescribed program with the participants completed physical activity log each week. To be considered compliant for each week a participant needed to meet two out of three exercise prescription characteristics (frequency, intensity, duration). For example, if the EP prescribed a frequency of three days per week, at an intensity between 12-14 RPE and a duration of 20 minutes, the participant would have to meet two of these prescription features to be deemed compliant for that week. Pre-defined compliance was for participants to achieve at least two out of three exercise prescription characteristics each week for 75% or more of the total program sessions.

Safety

Any records of adverse events during the intervention were used to determine if the program was deemed to be dangerous or harmful to cancer patients. All case management folders were examined and scrutinized for records of adverse events that occurred during the walking intervention as reported by the participants. To be determined safe, none or limited adverse events were to be stated.

Objective Two: *To measure pre-post intervention changes in functional capacity, body composition, anxiety and depression, treatment-related symptoms and quality of life.*

Functional capacity

Descriptive statistics, including median and ranges (minimum and maximum) as well as proportions were used to report on the functional capacity outcome at baseline and follow-up assessment. In line with previous definitions of clinically relevant gains in functional capacity when assessed by the 6MWT, absolute gains of greater than or equal to 54 meters was considered clinically important [108].

H_o- participants will experience declines in physical function (6MWT distance) between pre- and post-intervention.

H_1- participants will experience no change or gains in physical function (6MWT distance) between pre- and post-intervention.

Body weight

Proportions and ranges (minimum and maximum) were used to explore changes in body weight outcomes between baseline and follow-up assessment. A change in body composition greater than or equal to five percent of baseline body weight was defined as a clinically significant change [109].

H_o- participants will have adverse changes in body weight between pre- and post-intervention.

H_1- participants will have no change or favourable changes in body weight between pre- and post-intervention.

Anxiety and depression

The scores from the HADS were reported as a continuous variable; hence descriptive statistics (proportions) were used to report on baseline and follow-up results. Puhan and colleagues (2009) determined that the minimal important difference of the HADS is approximately 1.5 points in chronic obstructive pulmonary disease patients [110]. In the absence of information to guide clinical important change in ovarian cancer patients, the same criterion was applied.

H_o- anxiety and depression levels will increase between pre- and post-intervention.
H_1- anxiety and depression levels will decrease or remain the same between pre- and post-intervention.

Symptoms during treatment

For the MSAS clinically meaningful change in the physical subscale score was predefined at 0.2. Other researchers using this scale with ovarian cancer patients have classified differences or change in the MSAS of 0.2 or greater as clinically meaningful [111].

H_o- participants will report an increase in the frequency, distress and severity of treatment-related symptoms between pre- and post-intervention.
H_1- participants will report a decrease or maintenance in the frequency, distress and severity of treatment-related symptoms between pre- and post-intervention.

Quality of life

Medians and ranges (minimum and maximum) were used to explore changes in quality of life outcomes between baseline and follow-up assessment. A clinical important change was predefined for the continuous FACT-O subscales (physical, social, emotional, functional), cancer-specific concerns and overall FACT-O scale as a difference of two, three and equal to or above five points, respectively [112, 113].

H_o- participants will experience declines in quality of life between pre- and post-intervention.

H_1- participants will report an increase or maintenance in quality of life between pre- and post-intervention.

Objective Three: *To document chemotherapy conformity.*

Chemotherapy conformity

Chemotherapy conformity was evaluated using RDI. Courneya and colleagues (2007) assess chemotherapy completion rate on breast cancer patients using RDI and reported on the percentage of participants who received equal to or above 85% of their planned dose [61]. Predefined acceptable chemotherapy conformity was women achieving 85% or more of their initial chemotherapy regime. Due to the absence of information to guide clinical important change in ovarian cancer patients, the same criterion was applied as Courneya (2007).

3.8 ETHICAL APPROVAL OF RESEARCH

Ethical approval was sought from and given by all institutions involved, including Queensland University of Technology (0900000333)(Appendix G), Queensland Institute of Medical Research (ACTRN12609000252213)(Appendix H) and Royal Brisbane and Women's Hospital (HREC/08/QRBW/19)(Appendix I).

Chapter 4: Results

4.1 RECRUITMENT

Forty-two women were screened for eligibility in the study, and of these, 29 were excluded as they did not meet the eligibility criteria (Figure 4.1). Thirteen women were eligible to participate but four women refused with reasons being not interested (n=1), too old (84 years) (n=1), and undiagnosed health problems that required hospitalisation (n=2). Nine eligible women provided informed consent to the intervention. The program was delivered to three women via the telephone and to six women via face-to-face. All nine women completed baseline and follow-up assessment with no withdrawals or loss to follow-up.

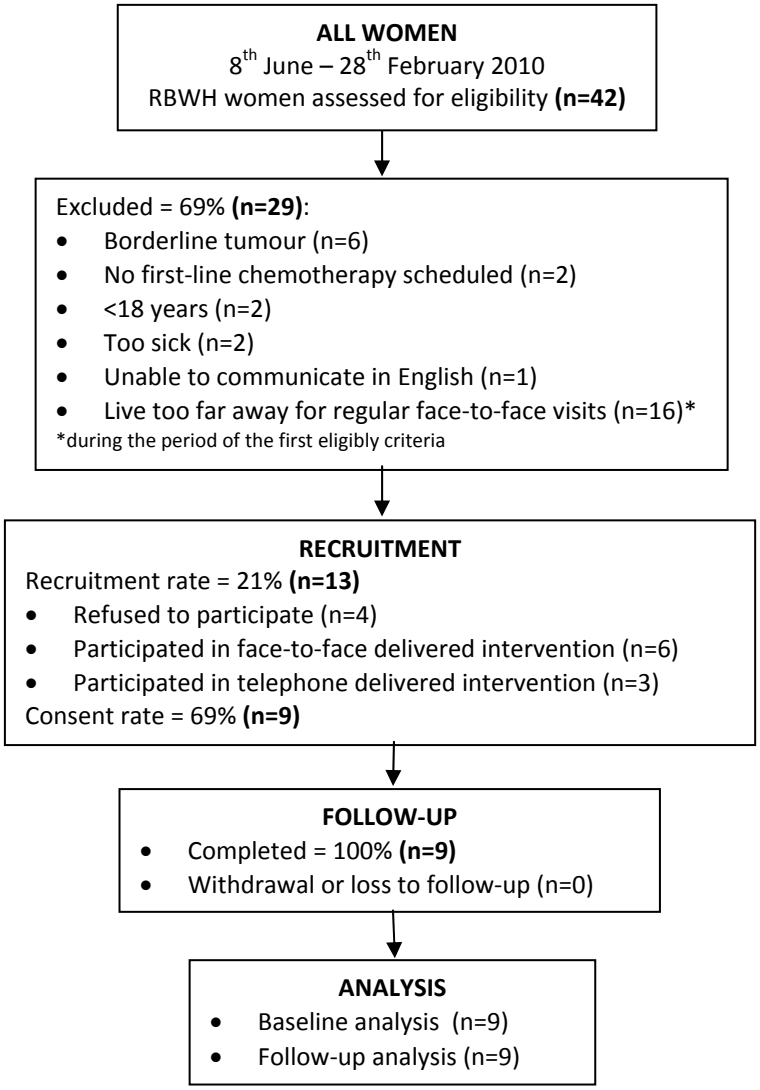

Figure 4.1: Recruitment and assessment process of intervention.

4.2 REPRESENTATIVENESS OF PARTICIPANTS

Presented in Table 4.1 are the characteristics of the walking intervention sample (n=9) compared with ovarian cancer patients from the QLD gynaecological cancer registry (n=1,286) to assess whether they were representative of the target population. While study participants had a higher proportion of older women (60 to 69 years, 66% vs 23%, respectively) than the QLD gyneacological cancer registry women, treatment modality and morphology were similar. The study sample also had higher percentage of late stage disease (more than half) compared with the registry database.

Table 4.1: Demographic and clinical characteristics of study participants compared with ovarian cancer patients from the QLD gynaecological cancer registry data (1993-2003).

	Study participants (n = 9)		**Ovarian cancer patients (n = 1,286)[a]**	
	n	**%**	**n**	**%**
Age (years)				
<30	0	-	62	5
30-39	0	-	89	7
40-49	1	11	182	14
50-59	2	22	342	27
60-69	6	66	289	23
70-79	0	-	246	19
80+	0	-	76	6
Treatment modality				
Surgery + chemotherapy	9	100	958	75
Other	-	-	328	36
Morphology				
Serous/serous papillary	8	88	526	41
Endometriod	1	11	132	10
Clear cell	0	-	152	12
Mucinous	0	-	157	12
Other	0	-	105	9
Disease Stage (FIGO) at diagnosis				
I	1	11	406	32
II	1	11	113	9
III	4	44	648	50
IV	3	33	5	0
Unknown	0	-	0	-

(a) Queensland Centre for Gynaecological Cancer: Outcome data statistical report, 2008.

The characteristics of the nine participants in this study were then compared with the 24 non-participating women (four refuser's plus 20 ineligible) to identify any potential bias (Table 4.2). Disease stage, chemotherapy treatment type and age were similar between study participants and non-participating target group.

Table 4.2: Demographic and clinical characteristics of study participants compared with the non-participating target sample of women diagnosed with ovarian cancer in 2009/2010.

	Study participants (n = 9)		**Non-participating target sample (n = 24)**	
	n	**%**	**n**	**%**
Disease Stage				
I	1	11	3	12
II	1	11	1	4
III	4	44	18	75
IV	3	33	2	9
Chemotherapy type				
Neo-adjuvant	2	22	7	29
Adjuvant	7	77	17	71
Prescribed chemotherapy drug				
Carboplatin & Paclitaxel	9	100	21	78
Carboplatin	0	-	3	12
Prescribed chemotherapy route				
Intravenous (IV)	8	88	20	83
Intravenous/Intraperitoneal (IV/IP)	1	11	4	17
Age (years)	Median	Range	Median	Range
	63	44-69	58	37-84

4.3 PARTICIPANT CHARACTERISTICS

The demographic and clinical characteristics of the nine participants are presented in Table 4.3 and 4.4. Most participants were 51 years or older at diagnosis (range 44 to 69 years); one third were overweight or obese; 44% were married or in a defacto relationship and 55% had completed high school (year 10 to 12) as their highest level of education. A household income of less or equal to $60,000 was common (88%), and many did not have private health insurance (66%). Physical activity levels varied with equal numbers of women being inactive, insufficiently active and sufficiently active. At baseline assessment most women had elevated CA125 levels (88%) and three-quarters of women were diagnosed with late stage disease (III & IV)(77%). Performance status on the ECOG scale was 'normal' for one woman and 'ambulatory with symptoms' for the remaining women (88%). Most of the group who received surgery had no microscopic disease or had equal to or less than 2cm residual disease (77%). Two women participated in the intervention whilst undergoing neo-adjuvant chemotherapy with the remaining women receiving

adjuvant chemotherapy. For seven women, three or six doses of chemotherapy were scheduled to be administered once every three weeks (planned total chemotherapy nine to 18 weeks). Two participants were prescribed either three or six cycles of weekly paclitaxel, followed by a week of a double dose of paclitaxel and carboplatin being administered every third week.

Table 4.3: The demographic characteristics of the nine ovarian cancer participants at baseline assessment (n=9).

Characteristics	**n**	**%**
Demographic		
Age (years)		
44-50	1	11
51-60	4	44
61-69	4	44
Body mass index categories*		
Underweight (<18.5 kg/m^2)	1	11
Healthy weight (18.5-24.9 kg/m^2)	4	44
Overweight (25-29.9 kg/m^2)	1	11
Obese (30+ kg/m^2)	2	22
Marital status		
Never married	3	33
Defacto/married	4	44
Separated/divorced	2	22
Education level		
University	2	22
Technical/trade	2	22
Secondary (grade 10-12)	5	55
Gross household income		
<$20,000	4	44
$20,000 - $60,000	4	44
>$60,000	1	11
Private health insurance		
None - Medicare only	6	66
Hospital only	2	22
Hospital plus extras	1	11
Physical activity at baseline		
Inactive (0 mins/per week)	3	33
Insufficiently active (1-149 mins/per week)	3	33
Sufficiently active (≥150 mins/per week)	3	33

Table 4.4: The clinical characteristics of the nine ovarian cancer participants at baseline assessment (n=9).

Characteristics	n	%
Clinical		
Primary cancer site		
Ovary	6	66
Peritoneum	3	33
Cancer antigen 125 blood level at baseline		
Normal (≤35 U/ml)	1	11
Elevated (>35 U/ml)	8	88
Disease stage (FIGO) at baseline		
I	1	11
II	1	11
III	4	44
IV	3	33
Eastern Cooperative Oncology Group status at baseline		
0 (normal)	1	11
1 (ambulatory with symptoms)	8	88
Debulking surgery		
Yes	7	77
No	2	22
Residual disease following surgery		
No microscopic disease	2	22
≤ 2cm disease	5	55
≥ 2cm disease	1	11
Unknown due to no surgery	1	11
Prescribed chemotherapy drug and regime		
6 x 3 weekly Carboplatin + Paclitaxel	6	66
3 x 3 weekly Carboplatin + Paclitaxel	1	11
6 x weekly Paclitaxel plus 3 weekly Carboplatin + Paclitaxel	1	11
3 x weekly Paclitaxel plus 3 weekly Carboplatin + Paclitaxel	1	11

4.4 FEASIBILITY AND SAFETY OF WALKING INTERVENTION

Objective One: To evaluate feasibility (retention, adherence, compliance) and safety of integrating a walking program during neo-adjuvant or adjuvant chemotherapy for women with ovarian cancer.

Retention

No withdrawals were recorded during the walking intervention. All nine women who completed the baseline assessment also completed the follow-up assessment; hence retention of participants was 100%.

Adherence

Adherence was assessed by comparing the number of sessions completed with the EP with the number of scheduled sessions. The number of possible sessions for each participant was defined by the number of weeks under active chemotherapy and ranged from 11 to 21 sessions (Table 4.5). Note that some of the initially prescribed 18 week chemotherapy courses were extended due to symptoms and delayed administrations. Adherence to scheduled sessions ranged from 55% to 100%, with seven of nine (78%) women in the program participating in at least 75% of scheduled sessions (predefined as clinically important). The number of missed sessions for participants ranged from zero to eight (median 0), with reasons for missed sessions being hospitalisation (n=5), holidays (n=4), too ill from chemotherapy (n=13), did not wish to be contacted (n=4) and inability to get telephone contact (n=3). In addition, eight out of 80 sessions were changed to a telephone session instead of a face-to-face session. Comparing differences in delivery mode (face-to-face, n=6, versus telephone, n=3), adherence was 81.5% and 83%, respectively.

Table 4.5: Adherence data for each study participant of the walking intervention (n=9).

ID	Delivery mode	Stage	Number of possible sessions[a]	Number of completed sessions	Number of missed sessions	Session adherence (%)
1	Face-to-face	I	18	18	0	18/18 (100%)
2	Face-to-face	III	18	14	4	14/18 (77%)
3	Telephone	III	18	18	0	18/18 (100%)
4	Face-to-face	II	18	10	8	10/18 (55%)
5	Face-to-face	IV	13	10	3	10/13 (76%)
6	Telephone	III	20	12	8	12/20 (60%)
7	Face-to-face	IV	21	17	4	17/21 (81%)
8	Face-to-face	III	11	11	0	11/11 (100%)
9	Telephone	IV	19	17	2	17/19 (89%)

(a) Number of possible sessions equates to the number of supervised sessions that were actually conducted (weeks of treatment).

Compliance

With the progressive nature of the walking program, compliance to the exercise prescription was determined by comparing the EP's weekly exercise prescription as recorded in the case management folder with the completed physical activity log each week. To be considered compliant for each week a participant needed to meet at least two out of three exercise prescription goals set (frequency, intensity, duration). For example, if the EP prescribed a frequency of three days per week, at an intensity between 11 to 13 RPE and a duration of 20 minutes, the participant would have to meet at least two of these goals to be deemed compliant for that week. If a participant met two plus goals during six out of ten sessions, then the compliance would equate to 60%. Compliance with at least two of the three individual weekly prescription targets ranged from 42% to 94% (Figure 4.2), although seven out of nine (78%) women demonstrated compliance to the program above 75%. All but one participant who had the program delivered face-to-face were able to comply with above or equal to 75% of the prescription, while two of the three women who had the intervention delivered over the phone were able to do so.

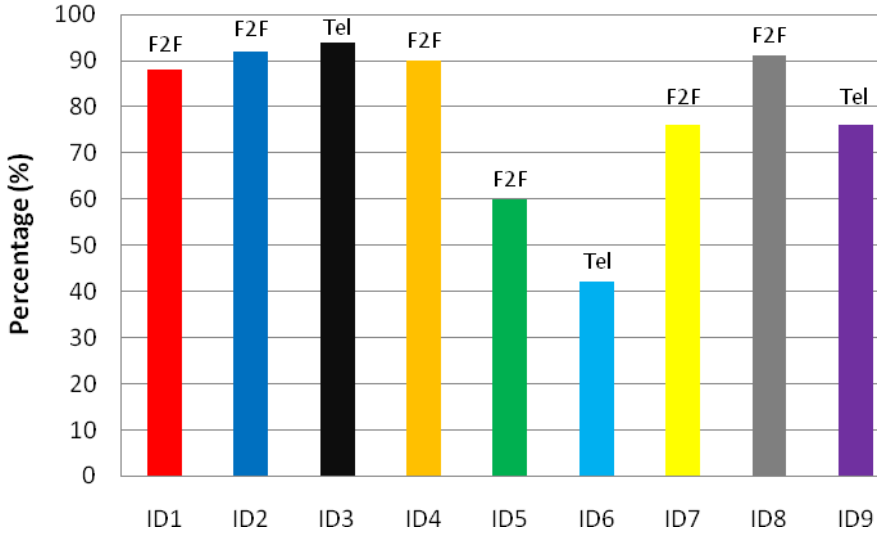

Figure 4.2: Exercise prescription compliance percentages for each study participant (n=9).

The frequency (number of days), intensity (RPE scale) and duration (minutes per week) of weekly sessions for each woman is illustrated in Table 4.6, 4.7 and 4.8. The frequency of walking ranged from zero days to seven days per week. Intensity levels were primarily of a moderate level as described by the RPE scale (11 to 15) and duration of walks were up to 60 minutes for any one session.

Table 4.6: Number of days (frequency) per week of walking for each participant accomplished during the intervention period (n=9).

Frequency	**ID1**	**ID2**	**ID3**	**ID4**	**ID5**	**ID6**	**ID7**	**ID8**	**ID9**
Week 2	2	5	6	1	1	1	0	2	3
Week 3	4	3	7	1	2	2	2	6	0
Week 4	6	7	7	0	0	0	1	4	7
Week 5	3	4	7	0	0	1	0	4	2
Week 6	5	6	7	2	3	0	4	4	6
Week 7	5	5	7	0	0	0	2	5	6
Week 8	5	6	7	4	0	1	1	4	5
Week 9	5	4	7	4	6	1	2	3	7
Week 10	5	7	7	0	0	0	3	4	0
Week 11	4	4	7	4	0	0	0	3	6
Week 12	5	7	6	4	5	0	0	-	3
Week 13	5	7	7	0	4	0	0	-	4
Week 14	5	0	7	0	-	0	0	-	2
Week 15	4	0	7	6	-	0	1	-	4
Week 16	5	0	4	0	-	0	1	-	5
Week 17	5	0	0	7	-	0	6	-	0
Week 18	5	5	6	0	-	0	2	-	5
Week 19	-	-	-	-	-	0	4	-	5
Week 20	-	-	-	-	-	0	3	-	6
Week 21	-	-	-	-	-	-	5	-	-
Median	**5**	**5**	**7**	**4**	**2**	**0**	**2**	**4**	**5**

Table 4.7: The range of intensity levels (measured by Rating of Perceived Exertion scale) per week for each participant during the intervention period (n=9).

Intensity	ID1	ID2	ID3	ID4	ID5	ID6	ID7	ID8	ID9
Week 2	13-14	11	12-13	12	12	11	0	13	12-13
Week 3	12-13	11	11-13	12	13	12	13-14	14	0
Week 4	13-14	11	12-13	0	0	0	14	13-15	13-14
Week 5	13-14	11	12-13	0	0	11	0	13-14	14
Week 6	14-15	11	12-13	12	13	0	12	11-14	14
Week 7	13-14	11	12-13	0	0	0	11-12	13-14	13-14
Week 8	14	11	13	13-14	0	11	11	12-14	13
Week 9	13-14	11	13	13-14	14-15	11	11-12	12-14	13-14
Week 10	13-14	11-12	13	0	0	0	0	12-14	0
Week 11	14	12	13	13-14	0	0	0	13-14	12-13
Week 12	14	11-12	13	13	14-15	0	0	-	12-13
Week 13	14	11	13	0	13-14	0	0	-	12-14
Week 14	14	-	14	0	-	0	0	-	13
Week 15	14	-	13	13-14	-	0	14	-	13
Week 16	13-15	-	12-13	0	-	0	12	-	13
Week 17	13-15	-	0	14	-	0	12-14	-	0
Week 18	13-14	-	12-13	0	-	0	13	-	13
Week 19	-	-	-	-	-	0	13-14	-	13
Week 20	-	-	-	-	-	0	13-14	-	-
Week 21	-	-	-	-	-	-	13-14	-	-

Table 4.8: The range of minutes (duration/time) of walking per week for each participant during the intervention period (n=9).

Duration	ID1	ID2	ID3	ID4	ID5	ID6	ID7	ID8	ID9
Week 2	30-55	15-25	30	20	5	15	0	30-50	10-60
Week 3	30-60	30	30-35	20	15	20-25	20	15-30	0
Week 4	30-50	15-30	30-40	0	0	0	40	25-35	15-35
Week 5	40-60	20-30	30	0	20	25	0	30	35-40
Week 6	35-50	15-30	30-45	20-30	0	0	10-25	25-30	30-40
Week 7	40-55	15-30	30-45	0	0	0	28-30	30	20
Week 8	40-50	15-30	30-45	25-30	30-60	25	17	30-32	25-40
Week 9	40-55	15-30	30-45	25-32	0	25	20-25	30	10-58
Week 10	35-50	30	30-40	0	0	0	8-25	10-30	0
Week 11	40-50	20-30	30	22-32	15-60	0	0	30-35	20-35
Week 12	35-45	20-30	30	28-35	15-30	0	0	-	10-30
Week 13	35-45	0	25-30	0	-	0	0	-	15-30
Week 14	40-45	0	30	0	-	0	0	-	30-35
Week 15	35-45	0	30	30	-	0	25	-	15-60
Week 16	35-60	0	30	0	-	0	20	-	15-30
Week 17	45-55	30-40	-	29-32	-	0	10-35	-	0
Week 18	40-60	-	30	0	-	0	12-30	-	15-35
Week 19	-	-	-	-	-	0	15-35	-	15-30
Week 20	-	-	-	-	-	0	15-35	-	-
Week 21	-	-	-	-	-	-	15-40	-	-

From the above tables, it is evident that the frequency, intensity and duration varied extensively during the walking intervention, not only between participants but within participants. Frequency and duration of walking was the most diverse, regarding upper and lower limits. Figures 4.3 and 4.4 depict the variation experienced by three women in their weekly frequency, intensity and duration. The three women depicted in the figures were purposely chosen as they represent the best, average and worst adherer for frequency and duration, respectively.

The woman that walked the most frequently throughout the walking intervention was ID3. She walked a frequency of six to seven days per week every week of the program except during week 16 and 17 where she walked four and zero days, respectively. The walking frequency for ID1 varied more than ID3. During the intervention, ID1 walked between two and six days a week. This was more of an indication of the 'average' woman in the walking program. ID6 represents the participant least able to comply with the frequency prescription and could only manage to walk a maximum of two days per week over the entire intervention (Figure 4.3).

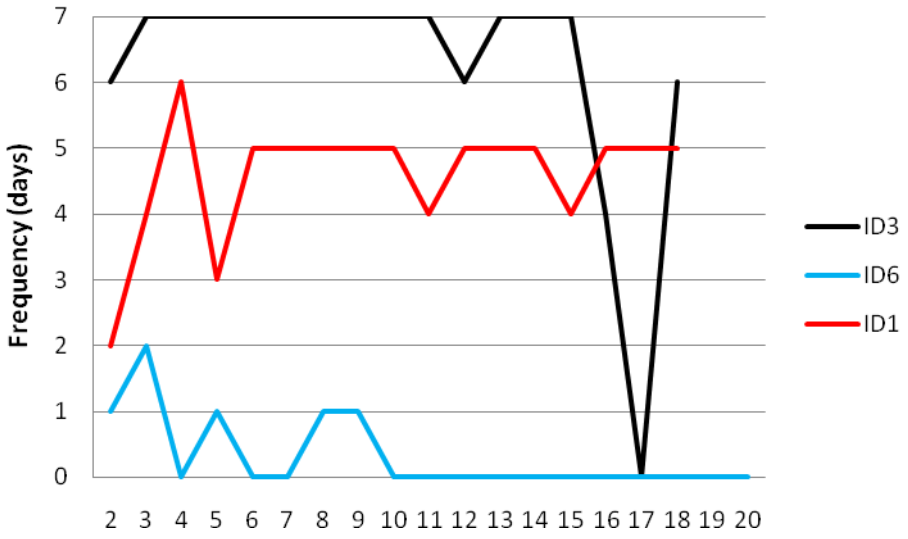

Figure 4.3: Variation reported in three participants demonstrating the upper, middle and lower limits of the frequency (days) prescription parameter.

The duration exercise parameter was even more deviated than the frequency parameter over the intervention period. The highest number of minutes walked was reported by ID1, who walked between 30 and 45 minutes for each session each week. ID9 represents a more 'average' participant with respect to duration. At the beginning of the intervention ID9 undertook for ten minute sessions. By the last week of the intervention she walked 15 minute sessions. However, at certain weeks of the program she managed to walk for a duration of up to 35 minutes. ID1 was an outstanding adherer to duration but the rest of the women were more likely to experience fluctuations. A good example of how duration of walking fluctuated over the course of the intervention is provided by ID9.

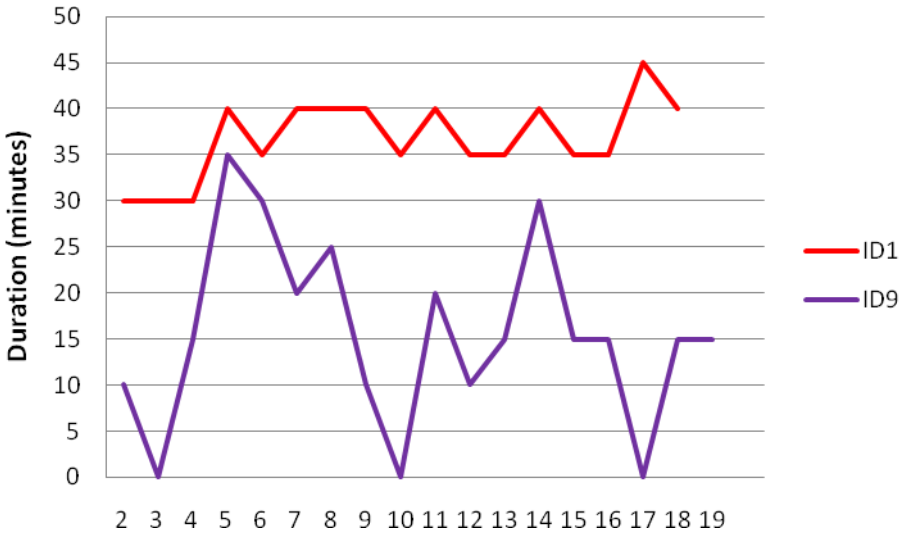

Figure 4.4: Variation reported in two participants demonstrating the upper and middle to lower limits of the duration (minimum number of minutes walked during session per week) prescription parameter.

The median intensity levels (RPE scale) of walking for each woman throughout the program are illustrated in Figure 4.5. The median intensity level was commonly moderate as described by the RPE scale (11-13). Intensity level was fairly stable across all participants.

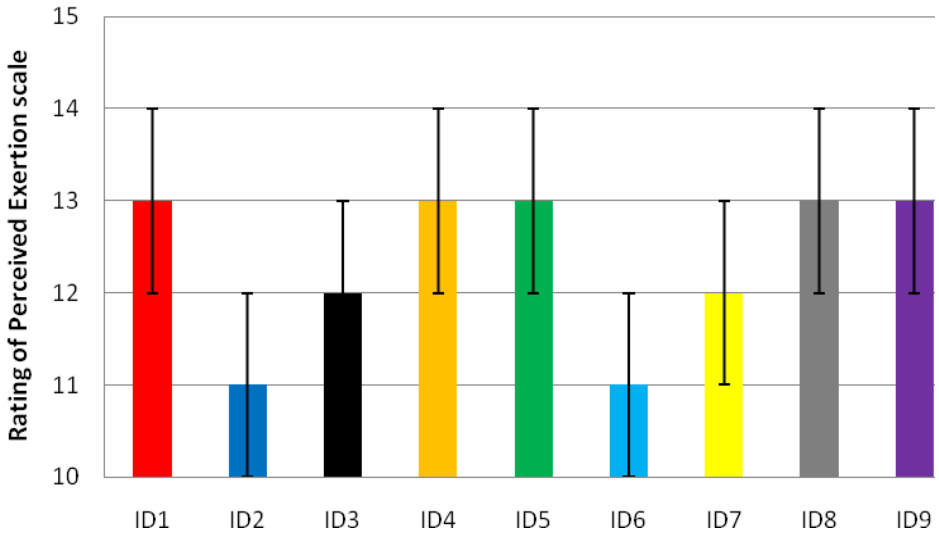

Figure 4.5: The overall median (range) intensity level (measured by the Rating of Perceived Exertion scale) achieved throughout the walking intervention for each study participant.

Adverse events reported by participants

During the intervention period, which was also the chemotherapy period, no adverse events were reported by participants as a direct result of participation in the walking intervention.

Adverse events reported in patient chart

As obtained from the patient chart, a variety of toxicities were experienced by participants at differing severities throughout the chemotherapy period (Table 4.9). The most common adverse events due to chemotherapy included fatigue, nausea, constipation and peripheral neuropathy. Grading of severity under the CTCAE had adverse events ranging from mild to severe. Adverse events seemed to decrease with the increasing number of chemotherapy cycles, that is, cycle six had six adverse events reported compared to cycle one that had 24 adverse events reported. Reasons for all adverse events reported in the patient charts was that they were a side-effect of the chemotherapy or debulking surgery, rather than exercise or a result of partaking in the intervention.

Table 4.9: Adverse events as reported on patient charts throughout neo-adjuvant or adjuvant chemotherapy for all nine study participants.

Adverse event (CTCAE)	Cycle 1 n	Cycle 2 n	Cycle 3 n	Cycle 4 n	Cycle 5 n	Cycle 6 n	Total
Nausea	5	3	2	2	0	1	**13**
Vomiting	2	0	0	0	0	1	**3**
Diarrhoea	2	4	0	0	0	0	**6**
Fatigue	4	4	4	5	2	1	**20**
Drug reaction	1	1	0	0	0	0	**8**
Cytopenias (anaemia, neutropenia)	0	1	1	2	4	0	**2**
Memory or hearing deterioration	0	2	2	0	0	0	**4**
Bowel obstruction	0	0	0	0	1	0	**1**
Peripheral neuropathy	0	0	1	2	3	3	**9**
Reduced appetite	2	1	0	0	0	0	**3**
Constipation	3	3	3	1	1	0	**11**
Genital ulcers	1	0	1	0	0	0	**2**
Skin rash/tenderness	1	1	0	1	0	0	**3**
Restless legs	1	0	0	1	0	0	**2**
Insomnia	1	0	0	0	0	0	**1**
Mood deterioration	0	0	1	2	0	0	**3**
Mucositis	1	0	0	1	0	0	**2**
Dyspnoea	0	0	0	0	1	0	**1**
Pain	0	1	2	2	1	0	**6**
Total	**24**	**21**	**17**	**19**	**13**	**6**	**100**

4.5 PRELIMINARY OUTCOMES OF WALKING INTERVENTION

Objective Two: To measure pre-post intervention changes in functional capacity, body composition, anxiety and depression, treatment-related symptoms and quality of life.

Functional Capacity

Eight participants were included in this analysis, as the objective measurement was unable to be conducted on one woman due to her long-distance location from Brisbane. The median distance walked, during the 6MWT, at the baseline assessment was 337 meters (range 266 to 394 metres), in comparison to 406 meters (range 377 to 490 metres) (p=0.012) walked at follow-up. All participants showed an increase in their absolute 6MWT distance with clinically meaningful improvements (≥54 metres) found in seven out of eight participants over the intervention period. Percent change in the 6MWT ranged from 9.6% (+34 metres) to 51.5% (+137 metres)(Figure 4.6).

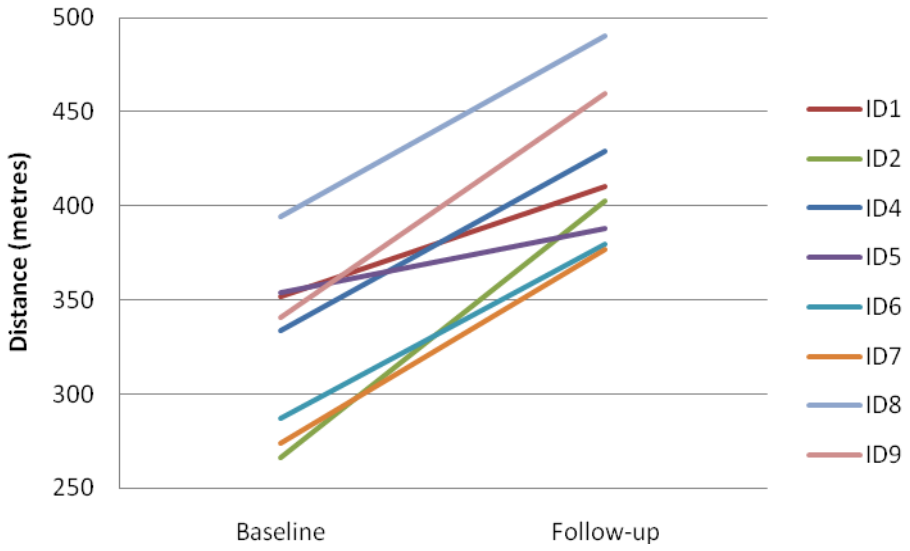

Figure 4.6: Functional capacity (6-minute walk test) measurements at baseline and follow-up assessment for study participants (n=8).

Body weight and composition

Changes in body weight and composition for women participating in the walking intervention are presented in Table 4.10. Again, only eight participants were included in this analysis. Overall weight increased by 3.5kg throughout the intervention period. While seven of eight women showed weight increases (one woman remained stable between pre- and post intervention), only one women showed a clinically important gain in weight (7kg gain for woman weighing <50kg at baseline). Six of eight woman gained absolute FFM (kg) between pre- and post intervention (gain range was 1.2 to 3.9kg) while the other two lost FFM (between 2 and 5kg loss).

Table 4.10: Weight and body composition measurements at baseline and follow-up assessment for study participants (n=8).

ID	Baseline body weight (kg)	Follow-up body weight (kg)	Baseline FFM %	Follow-up FFM %	Baseline absolute FFM (kg)	Follow-up absolute FFM (kg)
1	76.0	77.0	60.1	64.2	45.7	49.5
2	55.0	56.0	61.0	64.8	33.6	36.3
4	54.0	55.5	83.9	75.6*	46.5	41.9
5	54.5	56.5	63.3	63.5	34.7	35.9
6	49.0	56.0*	74.9	70.1	36.7	39.3
7	90.0	91.0	57.1	54.8	51.4	49.8
8	86.0	86.0	51.4	54.8	44.2	47.2
9	62.0	67.5	68.7	68.9	42.6	46.5
Median (min, max)	58.5 (49.0,90.0)	62.0 (55.5,91.0)	62.2 (51.4,83.9)	64.5 (54.7, 75.6)	43.4 (33.6, 51.4)	44.2 (35.9, 49.8)

FFM; fat-free mass

Anxiety and Depression

At baseline, four women (44%) in the study reported elevated levels of anxiety and two women (22%) reported elevated levels of depression. At follow-up anxiety scores returned to 'normal' for two of the women in the 'sub-clinical level' category; however, for one woman anxiety increased to a 'clinical' level (p=0.95). Depression scores remained unchanged (p=0.55) (Table 4.11).

Table 4.11: Hospital Anxiety and Depression Scale scores for study participants at baseline and follow-up assessment.

	Study participants (n=9)	
	Baseline assessment	Follow-up assessment
	n (%)	n (%)
Anxiety		
Normal (0-7)	5 (55)	7 (77)
Sub-clinical levels (8-10)	3 (33)	0 (0)
Clinical levels (11-21)	1 (11)	2 (22)
Depression		
Normal (0-7)	7 (77)	7 (77)
Sub-clinical levels (8-10)	1 (11)	1 (11)
Clinical levels (11-21)	1 (11)	1 (11)

Symptoms during treatment

Physical symptom scores and total score for patients who experienced symptoms are detailed in Table 4.12. Clinically meaningful differences between physical symptoms at baseline and follow-up assessment were found in lack of appetite, lack of energy and dry mouth. Overall physical symptom scores were also clinically important (p=0.374).

Table 4.12: Median and ranges for each physical symptom and total physical subscale score at baseline and follow-up assessment for study participants.

MSAS physical subscale score	**Baseline assessment (n=9)**	**Follow-up assessment (n=9)**
	Median (min, max)	Median (min, max)
Lack of appetite	0.8 (0.0, 1.6)	0.0 (0.0, 2.4)*
Lack of energy	2.4 (0.0, 3.2)	1.6 (0.0, 2.4)*
Pain	1.6 (0.0, 3.2)	1.6 (0.0, 3.2)
Feeling drowsy	1.6 (0.0, 3.2)	1.6 (0.0, 3.2)
Constipation	1.6 (0.0, 2.4)	1.6 (0.0, 2.4)
Dry mouth	0.8 (0.0, 2.4)	0.0 (0.0, 2.4)*
Nausea	0.0 (0.0, 2.4)	0.0 (0.0, 1.6)
Vomiting	0.0 (0.0, 0.8)	0.0 (0.0, 0.0)
Change in taste	0.8 (0.0, 2.4)	0.8 (0.0, 3.2)
Weight loss	0.0 (0.0, 1.6)	0.0 (0.0, 0.0)
Feeling bloated	0.0 (0.0, 2.4)	0.0 (0.0, 4.0)
Dizziness	0.0 (0.0, 1.6)	0.0 (0.0, 3.2)
Total physical subscale[a]	0.93 (0.13, 2.33)	0.60 (0.06, 2.06)*

Clinically meaningful (0.2 score change); *

(a) Higher scores indicate more frequency, severity and distress associated with symptom

Women reported a variety of physical symptoms at the start and end of treatment, with the most frequent symptoms at baseline assessment being constipation (n=8),

pain (n=8) and lack of energy (n=7). By follow-up, constipation (n=5), pain (n=5) and lack of energy (n=5) were still being reported in addition to difficulty concentrating (n=5) and feeling drowsy (n=7). At baseline assessment, there was a median of seven out of 12 possible symptoms being reported per participant. In contrast, a median of three out of 12 possible symptoms were reported at follow-up. The range of symptom frequency, severity and distress scores for each symptom varied (Table 4.13). By follow-up assessment participants reported a reduction in the frequency of lack of appetite (80% vs 0%), reduced severity of nausea (50% vs 0%), and weight loss (75% vs 0%) and more distress associated with pain (13% vs 40%), dizziness (0% vs 33%) and difficulty concentrating (25% vs 40%).

Table 4.13: Moderate to severe physical and psychological symptom characteristics at baseline and follow-up assessment for study participants.

	Baseline assessment (n=9)				Follow-up assessment (n=9)			
	No. with symptoms	Frequency[a] n (%)	Severity[b] n (%)	Distress[c] n (%)	No. with symptoms	Frequency[a] n (%)	Severity[b] n (%)	Distress[c] n (%)
Physical								
Lack of appetite	5	4 (80)	4 (80)	0 (0)	2	0 (0)	2 (100)	0 (0)
Lack of energy	7	6 (86)	6 (86)	1 (14)	5	3 (60)	4 (80)	0 (0)
Pain	8	3 (38)	5 (63)	1 (13)	5	1 (20)	5 (100)	2 (40)
Feeling drowsy	6	4 (67)	5 (83)	1 (17)	7	3 (43)	5 (71)	2 (29)
Constipation	8	3 (38)	6 (75)	0 (0)	5	2 (40)	3 (60)	0 (0)
Dry mouth	5	1(20)	1 (20)	1 (20)	4	3 (75)	3 (75)	0 (0)
Nausea	4	1 (25)	2 (50)	2 (50)	2	0 (0)	0 (0)	0 (0)
Vomiting	1	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)
Change in taste	5	2 (20)	3 (60)	1 (20)	5	1 (20)	4 (80)	1 (20)
Weight loss	4	0 (0)	3 (75)	0 (0)	0	0 (0)	0 (0)	0 (0)
Feeling bloated	4	2 (20)	2 (50)	1 (25)	4	1 (25)	3 (75)	1 (25)
Dizziness	3	0 (0)	0 (0)	0 (0)	3	1 (33)	1 (33)	1 (33)
Psychological								
Difficulty sleeping	4	2 (50)	2 (50)	1 (25)	4	1 (25)	1 (25)	2 (25)
Difficulty concentrating	4	1 (25)	0 (0)	1 (25)	5	4 (80)	0 (0)	2 (40)
Median (range) number of symptoms per patient	7 (2, 13)				3 (1, 11)			

(a)Frequency = scores of frequently and almost constantly
(b)Severity = scores of moderate, severe or very severe
(c)Distress = scores quite a bit or very much

Quality of life

Medians and ranges for QoL scores are presented in Table 4.14. Clinically meaningful improvements between baseline and follow-up assessments were found in FACT-G, physical well-being subscale, emotional well-being subscale, ovarian cancer-specific concerns and total FACT-O. In contrast, there were no changes observed in the social well-being and functional well-being subscales. Six out of nine (66%) women had a positive change in their overall QoL and wellbeing subscales (with the exception of the social subscale). Four women reported clinically important declines in social well-being at the end of the intervention/treatment compared with the start.

Table 4.14: Health-related quality of life (FACT-O subscales) characteristics of study participants at baseline and follow-up assessment.

	Baseline assessment (n=9)	**Follow-up assessment (n=9)**	
	Median (min, max)	Median (min, max)	p-value[a]
Physical (0-28)	18.0 (13.0, 25.0)	23.0 (13.0, 28.0)*	0.04
Social (0-28)	18.0 (12.0, 24.0)	17.0 (11.0, 28.0)	0.67
Emotional (0-24)	18.0 (7.0, 24.0)	21.0 (10.0, 24.0)*	0.15
Functional (0-28)	20.0 (7.0, 28.0)	20.0 (7.0, 28.0)	0.05
Ovarian-specific concerns (0-44)	31.0 (25.0, 41.0)	36.0 (21.0, 44.0)*	0.26
FACT-G (0-108)	72.0 (47.0, 100.0)	78.0 (41.0, 107.0)*	0.19
FACT-O[b] (0-152)	102.0 (72.0, 140.0)	113.0 (67.0, 148.0)*	0.14

Functional Assessment of Cancer Therapy-Ovary; FACT-O, Functional Assessment of Cancer Therapy-General; FACT-G, clinically meaningful (5,3,2 score change); *
(a) Wilcoxon signed ranked test used for analysis
(b) A higher scores indicates a better QoL

Objective Three: To document chemotherapy prescription conformity

Chemotherapy prescription conformity

Seven participants had six cycles of chemotherapy scheduled and two participants had three cycles scheduled. All women were administered the same two chemotherapy agents (Carboplatin and Paclitaxel), however in different doses. Relative dose intensities for chemotherapy treatment ranged from 66% to 100% (median 92%) (Figure 4.7). Eight out of nine (88%) women received equal to or above 85% of their planned RDI. Four women had delays in receiving chemotherapy treatment for reasons not known.

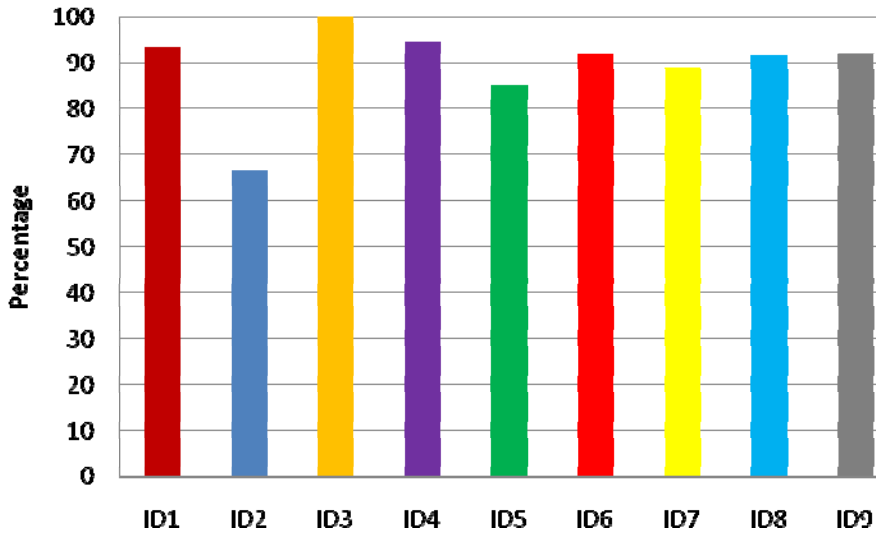

Figure 4.7: Relative dose intensity (RDI) percentages for study participants.

4.6 PROGRAM EVALUATION

Eight women (88%) returned the evaluation form (Appendix D), all of whom found the program either 'helpful or very helpful' to their recovery following ovarian cancer diagnosis. The helpfulness of the educational booklet ranged from 'neither helpful nor unhelpful' (n=1) to 'very helpful' (n=3). One woman wrote that the booklet was initially helpful but didn't refer back to it after starting the program. As for the helpfulness of the sessions with the exercise physiologist, 87% of participants reported that it was 'very helpful'. The majority of women, 87% and 75%, used the physical activity log and pedometer 'often'.

One woman responded to the question "do you have any suggestions about ways the program could be delivered". She wrote "interaction with another participant, doing the same thing could be beneficial. Loneliness is a big killer to enthusiasm". Three participants reported difficulties they found about the program: (1) "motivation to walk when EP wasn't present", (2) "days when feeling sick and weak, the head wanted to keep going but the body could not", and (3) "the pedometer not being accurate enough" ("you sneeze and you've got multiple steps"). There were also three suggestions on how the program could be improved. One woman said "participants need a buddy (another cancer patient) to help keep up the

interest and stop feeling alone". Other women mentioned that the program could run longer and finally, incorporate other activities such as dancing and gardening.

The final question on the evaluation form asked the women to circle a number that best reflected how they felt about participating in the walking program. Six out of eight (75%) women circled seven being 'excellent', with the remaining two women circling a six ('very good').

Chapter 5: Discussion

5.1 OVERVIEW

Research to date on the role of exercise programs during chemotherapy treatment is promising and demonstrates that becoming or staying active during chemotherapy can improve compliance with adjuvant treatment and reduce treatment-related morbidity. However, much of this work involves women with breast cancer and there are currently no data available for women undergoing treatment for ovarian cancer. Women undergoing treatment for ovarian cancer commonly have extensive pelvic surgery followed by moderate intensity chemotherapy and it is unknown whether associations observed in physical activity and breast cancer studies hold true for women receiving treatment for ovarian cancer. The aims of the proposed research were to investigate the feasibility and safety as well as measuring pre-post intervention changes in functional capacity, body composition, anxiety and depression, treatment-related symptoms, quality of life and chemotherapy prescription conformity of a home-based walking intervention in ovarian cancer patients undergoing adjuvant chemotherapy.

This research study yielded two main findings. First, the walking intervention was feasible and safe for the sample of ovarian cancer patients studied. Second, women who participated in the program had improvements in functional capacity and quality of life, as well as reductions in the number and intensity of treatment associated symptoms over the course of the intervention period.

5.2 FEASIBILITY, RECRUITMENT AND SAFETY

Recruitment

A consecutive sample of nine adult women (consent rate 69%), who were generally representative of the wider ovarian cancer patient population, agreed to participate in the trial during the course of their chemotherapy treatment. While they were

more likely to have been diagnosed with later stage (III and IV) compared with the broader population, it was expected that this characteristic was more likely to influence results in the conservative direction. That is, it was anticipated that those with later stage disease would be less likely to participate. Overall, it seemed that the target population was happy to be involved in the program, despite just undergoing extensive surgery and despite the intervention being conducted during their active adjuvant therapy. Participants said that it was motivating to have someone help them walk during a period that was fraught with uncertainly. The program was also viewed as a form of psychological support for some. Specifically, four women involved in the program were living independently without a partner. These women often isolated themselves from public contact (as prescribed by the doctors when immune system was low), hence the EP was utilised as a person of support and companionship.

Retention, adherence, compliance and safety

Overall, study retention, adherence and compliance was high (100%, 78% and 78%, respectively) and compares favourably with feasibility data from previous studies of home-based exercise conducted with patients undergoing chemotherapy for other cancers (between 60% and 90%) [62, 114]. In addition, no adverse events related to participating in the walking intervention were reported by any of the participants, suggesting the program was also safe.

The type of intervention evaluated may have contributed to the high feasibility and safety rates observed. A population-based survey recently reported the most common physical activity preferences for ovarian cancer survivors as being home-based and involving walking [70]. These factors were also substantiated by the participants in this study, who commented positively on their preference for walking and being able to conduct the exercise at home. Also the mode by which the walking program was delivered was flexible (that is, contact with the EP), allowing for intervention sessions to be conducted over the telephone instead of face-to-face, during periods when participants were too unwell (eight out of 80 sessions were changed to telephone sessions as opposed to face-to-face sessions).

Further, intervening during an active treatment period, which often corresponds with reductions in work duties and home-expectations, may have also contributed to the high feasibility rates, as the women who participated highlighted that they had the time and capacity to be involved.

The intervention was individualised according to each participant's circumstances and functional capacity and progression of the walking program was controlled through progressive prescription, minimising potential for delayed onset of muscle soreness (acute tiredness and soreness that can occur from exercise progression)[115]. The participants were also being closely monitored and supervised by an EP, who gave regular personalised feedback, support and advice. These factors likely contributed to the good feasibility rates and no major adverse events.

The participants also acknowledged that while the walking intervention was of interest to them, without it they would not have walked as much or at all during chemotherapy treatment. This is of interest, since it is plausible that there was a response bias to recruitment, whereby the more active women (at least based on pre-diagnosis activity levels) may have been more likely to participate. This could also explain the high consent rate due to a highly motivated group of patients and perhaps as this was a convenience sample. If this was the case, the participants have highlighted how vital a formal intervention is, if activity levels are to be maintained during adjuvant treatment.

During the ethical approval process for the study, many questions were raised over the risks involved with the patients undertaking an exercise program during their adjuvant therapy, whether it was appropriate and whether they could tolerate it and do it safely. To date, ovarian cancer patients have not been the focus of exercise trials, which may have caused concern with the hospital ethical body. Overall, these findings suggest that ovarian cancer patients are interested in and able to participate in a walking intervention during their chemotherapy treatment.

5.3 PRELIMINARY OUTCOMES

Exercise intervention trials have been used as a non-pharmacological approach to manage symptoms arising from cancer and related treatments [45]. This pilot study aimed to measure pre-post intervention changes in several physical and psychosocial outcomes including functional capacity, body weight and composition, anxiety and depression, treatment-associated symptoms and quality of life, and to document chemotherapy conformity. These outcomes are of particular importance as they have been shown to adversely change during chemotherapy treatment [116].

Functional capacity

Until recently, cancer patients were advised to seek periods of rest and to reduce their amount of physical activity during cancer treatment. However, such recommendations can paradoxically compound symptoms, since sedentary habits induce muscle catabolism and thus cause a further decrease in functional capacity [32]. Sedentary habits during and following cancer can become a self perpetuating condition, causing further detraining therefore making everyday lifestyle activities such as cleaning, shopping for groceries and yard work physically taxing. Systematic reviews and meta-analysis illustrate that physical activity during chemotherapy can prevent functional capacity declines and may even lead to functional capacity improvements [49, 51, 58].

The pilot study results indicated that all ovarian cancer participants improved in functional capacity (as measured by 6MWT) from baseline to follow-up assessment. In fact, pre to post intervention there was a significant ($p=0.012$) and clinically meaningful improvement in distance walked (377 to 490 metres). These results are in line with those observed by others investigating aerobic exercise during treatment for breast cancer [87, 117]. Even those participants with the lowest level of adherence showed gains in functional capacity; potentially highlighting that even irregular activity during chemotherapy can prevent functional capacity declines normally associated with an active treatment period. For example, ID6, who had

the poorest adherence and compliance, showed a 93 metre increase over six minutes in distance walked post intervention.

Body weight and composition

No changes in weight and/or body composition were observed in the participants of this pilot study. Since there has been little research to date exploring weight changes following surgery and adjuvant chemotherapy in women with ovarian cancer, it is difficult to determine the relationship between the intervention and weight and body composition. There does not seem to be any association with body composition and whether the women were good or bad adherers to the program. It is plausible that without the intervention, participants may have experienced greater gains in weight and/or may have experienced losses in fat free mass, irrespective of weight changes. However, it is also plausible that the walking intervention had no effect on weight and body composition. Clearly, greater understanding of weight and body composition changes in the absence of an intervention, would aid interpretation of results, as would a randomized-controlled trial.

Anxiety and depression

Generally, the participants in this study did not experience worsening anxiety or depression during their treatment period, and there was evidence of some improvements (one participant had an increased level of anxiety out of nine). It is known, however, that two women did access support from a psychologist after their cancer diagnosis, one woman utilized a telephone based counseling service and one woman contacted the following services: psychologist, psychiatrist and social worker, for support with her cancer (she did have a previous breast cancer diagnosis). The women that received support from three allied health services maintained their clinical levels of anxiety and depression, but the two women who accessed help from a psychologist reduced their levels of anxiety from sub-clinical levels to normal levels. Finally, the woman who used the telephone counseling services increased in her levels of anxiety and depression.

Historical data from the PROSPECT study [18] was used to compare changes in anxiety and depression outcomes in a sample of women who received usual care compared with the ovarian cancer women who completed the walking intervention. In the PROSPECT study, 62 women receiving adjuvant chemotherapy for ovarian cancer were surveyed at the start and end of their treatment course. When comparing the study sample with the PROPSECT study participants, anxiety scores at baseline and follow-up assessment were similar. As for the depression scale, PROSPECT study participants had a higher proportion of women in the 'clinical' level of depression. It seems plausible that the PROSPECT study participants had higher levels of depression following treatment compared to the pilot study women who maintained the same levels of reported depression.

Other exercise intervention studies have reported varied results with regards to the effect of exercise on anxiety and depression outcomes in cancer patients. In two studies of women with breast cancer receiving chemotherapy, levels of anxiety and depression were noted to be significantly lower among exercisers compared to non-exercisers [118, 119]. Porock and colleagues (2000) examined depression and anxiety using the HADS and found no change in depression, but noted a trend towards a decline in anxiety among patients with advanced cancer who exercised [120]. Another study observed a significant inverse correlation between duration of exercise and anxiety and depression among patients receiving high dose chemotherapy and bone marrow transplant [121]. Randomsied, controlled trials suggest exercise may be beneficial or at worst, do no harm to distress in cancer patients.

Symptoms during treatment

Side-effects as a result of surgery and chemotherapy treatment are common and varied for ovarian cancer patients [26]. In comparison to surgery, chemotherapy-induced symptoms can be more debilitating and have the greater impact on quality of life for women with ovarian cancer [38]. The type of chemotherapy agent, dose of agent and pharmaceuticals prescribed to assist in combating symptoms all play a part. The chemotherapy agents used in the treatment of participants in this study

have a wide range of adverse effects, with the main side-effects being fatigue, nausea and vomiting, peripheral neuropathy, and myelosuppression [38]. Because chemotherapy commonly causes these toxicities, a reduction in occurrence and severity of these may assist in completing the originally prescribed treatment regimen, thus increasing survival [122].

Frequency, severity and distress of reported symptoms seemed to decline only slightly from baseline to follow-up in our sample of nine women. Lack of energy was a symptom that was favorably associated with the walking intervention. Fatigue has been observed to be a long-lasting side effect of cancer treatment that affects some patients years after the completion of treatment [62]. A study of 72 newly diagnosed women with breast cancer (a home-based moderate-intensity exercise program) whilst undergoing chemotherapy, revealed that exercise significantly reduced fatigue ($p=0.01$) and as the duration of exercise increased the intensity of fatigue declined ($p=0.01$)[123]. This may indicate that inactive women who are beginning chemotherapy may benefit from an exercise program with respect to fatigue during treatment.

While lack of appetite has not been researched as extensively as lack of energy, one study found that as little as a six-week multidimensional exercise intervention undertaken by cancer patients while undergoing chemotherapy can lead to reductions in lack of appetite [124].

The number of toxicities reported on the patient charts decreased as the number of chemotherapy cycles progressed. At worst, it could be speculated that the walking intervention did not worsen side-effects experienced during treatment. The presence and intensity of side-effects related to treatment may negatively impact on a person's ability and desire to exercise. Collectively the nine participants in the study had 100 adverse events recorded by the oncology team as a consequence of the disease, surgery or treatment. It could be assumed that with the accumulation of regular chemotherapy cycles and such a large number and intensity of toxicities experienced, regularly exercising may be an unreasonable suggestion for the

patients. However, despite the side-effects of chemotherapy, the participants were able to participate and commented positively about the exercise intervention. For instance, one woman commented, “the regular meetings helped me to continue and to motivate me with the program”. Another remarked, “I wouldn’t have been able to go through the chemo course without it”. Lastly, a different participant stated, “a walk quite often helped me cope on the ‘down’ days”.

Quality of life

This pilot study was the first exercise intervention to report quality of life improvements in ovarian cancer patients during chemotherapy treatment. Previous work has suggested that QoL improvements occur after the completion of chemotherapy [42]. Further, those women with recurrent disease have significantly worse overall, emotional and ovarian cancer specific QoL during treatment [42] when compared with those dealing with their first diagnosis. The immediate effects of chemotherapy on QoL in advanced ovarian cancer patients have been reported to be low [42]. The pilot study reported positive changes in physical and emotional well-being and ovarian specific concerns, but negative changes in social well-being (functional well-being did not change). Generally, women who had good session adherence and exercise compliance tended to have better overall QoL improvements. The lack of social well-being improvement may have been a consequence of limited social and group support during a traumatic and uncertain time in the women’s lives, in which the walking intervention did not assist with as the program was delivered on a one-on-one basis (i.e no group exercise). Future interventions could look at including strategies that could protect and/or aid social well-being.

Distinctions between the study participants and the historical PROSPECT study (n=62) which involved women with ovarian cancer can be made for the QoL data [18]. Generally, the PROSPECT study group had higher baseline QoL compared with the study sample, especially in the social well-being subscale. However, study participants had a higher functional well-being subscale and higher ovarian cancer-specific concerns. At follow-up, overall QoL improved by eleven units (clinically

significant) in the study sample, whereas in the PROSPECT study it only improved by four units. Physical well-being subscale scores and ovarian cancer-specific concerns in the study sample exceeded the PROSPECT participants at follow-up assessment. Overall, the positive changes observed in participants of this pilot study were at least as good as that expected and did not harm but more likely did benefit.

Our findings are consistent with previous research examining exercise and quality of life in other cancer survivors, with the largest impact being observed on physical well-being aspects of QoL [59, 114]. Compelling clinical trial data indicate that physical activity can improve QoL during cancer treatment [52]. Porock and colleagues (2000) examined the effect of exercise on advanced cancer patients and observed improvements in overall QoL scores, with scores reported to be significantly higher for women with breast cancer who reported exercising [120]. In this study, improvements in all QoL domains, that is, a reduction in side-effects, enhanced physical and social function and improved mental health contributed to improvements observed in overall QoL.

Chemotherapy prescription conformity

Every woman in the study completed the assigned number of chemotherapy cycles. This was not without delay for a few participants though. A common reason for postponement of administration was hematologic issues, such as cytopenias (leukopenia, neutropenia, thrombocytopenia, anaemia), which can also be dose-limiting factors [125]. Three randomised controlled trials conducted by the Gynecologic Oncology Group (GOG) demonstrated chemotherapy completion rates in intraperitoneal (IP), intravenous (IV) and a combination of IP and IV chemotherapy of advanced ovarian cancer patients [17, 21, 126]. Rates were between 42% (IP arm) to 86% (IV arm)[127]. A recent study by Lesncok and collegues (2010) also found chemotherapy completion rates (83% completing all six cycles) in a group of 103 advanced ovarian cancer patients [128]. Comparing the results of this previous work with results from participants in this pilot study, it seems that at worst, participation in the walking intervention did not hinder the chemotherapy prescription conformity in the current study.

While chemotherapy completion rates are starting to become an outcome assessed during exercise intervention trials, currently there is a paucity of information on the issue. Courneya et al (2007) explored the effect of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy [61]. Chemotherapy completion rate was assessed as the average RDI for the originally planned regimen. The percentage of participants who received >85% of their planned RDI was 78% in the resistance group and 74% in the aerobic group compared to 66% in the control group. Similar to Courneya study, the walking program had 88% (eight out of nine) of women receiving equal to or above 80% of their planned RDI. Comparatively, RDI's from the PROPECT study ranged from 33% to 100% (median 100%), with 79% receiving equal to or above 80% of their planned RDI [18].

In summary, the walking intervention did not prevent the participants from completing their scheduled chemotherapy regimens and has added to documentation of chemotherapy prescription conformity in exercise intervention studies.

5.4 CLINICAL EXPERIENCE FROM CONDUCTING THE WALKING INTERVENTION

From the EP's perspective a few important aspects were noted during the intervention period that helped to understand this cohort and to take their specific concerns into consideration when prescribing exercise. These included: (1) the need to adopt an exercise approach emphasizing a 'here and now' (during chemotherapy) experience rather than focusing on long term rehabilitation goals; and (2) the effect of disease and treatment side-effects are not the same for every woman. It should also not be assumed how any given woman will deal with any given side-effects. That is, all woman cope differently and the EP needs to be guided by their feedback and modify exercise prescription to accommodate their changing circumstances.

For instance, it was often suggested to the ovarian cancer participants during the days when side-effects were severe enough that they didn't feel they could perform a planned walk, to instead do as much incidental activity around the home and

garden as they could. If they required a rest or break then that was also encouraged - shorter but more frequent bouts of incidental activity was prescribed. Interestingly, the effect of the treatment-induced side-effects was often not the same for each woman. For example, one woman may have been able to overcome her feelings of nauseous to persevere with her planned walk whereas another woman just couldn't. Therefore, exercise prescription was dealt with differently not only for their fitness level but for the amount and severity of side-effects they were experiencing. This can be seen in the results chapter when plotting participant's walking frequency. It is noticeable that approximately every three weeks the number of walks per week declines (Figure 4.3). Likewise, this is also evident in the duration of the walking sessions (Figure 4.4). Intensity did not seem to be an issue with the program; however the intervention does need to be flexible in terms of frequency and duration. It's as though the EP had to prescribe certain exercise prescription goals for two weeks of the three week chemotherapy cycle and a different set of exercise prescription goals for one week (week where side-effects are the worst). Most of the time the most severe side-effects lasted up to five days, then woman could get back to their 'usual' walking program. The issue seemed to be that that the woman's symptoms dictated whether they could actually do a walking session. Women often stated that nausea and vomiting and/or diarrhoea, whereby a toilet may have been needed hastily, was the most severe side-effect that impeded walking during chemotherapy treatment. Nonetheless, it was possible for the EP to help the women problem solve how they would try to do some physical activity on the days of heavy symptoms. In one case, a participant felt nauseous and had vomited prior to the face-to-face walking session; she really wanted to go for her regular walk but did not want to possibly vomit in someone's garden, so we walked with a bag just in case she was physically ill. In another scenario, this same participant was having sporadic diarrhoea but remained keen to walk. To accommodate her circumstances, the walking route was modified so that we past her house on several occasions.

Having only one mode of activity (aerobic/walking) may have restricted the women's ability to exercise, that is, there is a need to investigate other forms of

exercise modes such as resistance training and flexibility. For future studies that include a multidimensional exercise program would be ideal for women with ovarian cancer as on days that a woman has diarrhea or minor vomiting bouts she could do a home-based resistance or flexibility exercise program instead of walking. A supervised group exercise program that allows for individualized programming would also be recommended for the possibility of building in a social/support system with other patients.

Finally, even though the walking intervention did not include a resistance training component to it, it must not be underestimated the importance of a multi-modal exercise program. At this point, all of the exercise interventions that have been tested have generated positive effects, and none have caused negative effects [62]. Similar physical and psychosocial benefits have been reported in both aerobic and resistance training exercise interventions during treatment including fatigue, mood, exercise behavior, strength, physical function and quality of life. While walking may be the preferred mode of exercise, increasing the types or modes of activity could help overcome some of the recorded barriers as well as lead to additional and/or accumulative effects. Nevertheless, there is a scope for future studies that need to employ rigorous designs, larger sample sizes, and focus on recruiting minority and underserved patients such as women diagnosed with ovarian cancer.

5.5 STUDY LIMITATIONS AND STRENGTHS

The inability to recruit an adequate sample of ovarian cancer participants is a limitation of this research study and has the potential to influence the findings of the program. Small sample sizes are not uncommon in cancer research especially during 'proof of concept' studies. The convenience sample of women in the study may have been a highly motivated group, with these characteristics influencing the adherence results observed. Nonetheless, these women did have worse disease than the normal population which in turn could have made it more difficult for them to participate.

While only a small number of ovarian cancer women were involved in the walking intervention, improvements in physical and psychological outcomes were reported. It is possible that a learning curve or response shift [129] contributed to the some of these improvements (e.g., in the 6MWT and QoL assessment, respectively). Future work with the inclusion of a control group will clearly assist in identifying the true effect of the intervention on these factors. Nonetheless and importantly, there were few individual deviations from the group change observed, suggesting an association with participation in the walking program and physical and psychosocial outcomes.

Both the intervention (exercise prescription) and the data collection of the pilot study were conducted by the same person (EP). Ideally, these roles should have been undertaken by different people; however, timing and funding restrictions of the study did not allow this to occur. The concern is that the EP may have been more likely to encourage participants more (e.g., during the 6MWT) based on adherence to the walking intervention and thus bias the results. Nonetheless, every effort was made by the EP to ensure data collection procedures were carried out in a standard and objective manner, as defined by the protocol, without bias towards any participant(s) or at any time point. Another limitation of the study was that fatigue was not directly assessed. This is an important outcome to measure in this population of cancer patients as fatigue is one of the most serious and long-lasting side-effects of ovarian cancer disease and treatment.

The strengths of the pilot study were the high acceptance and retention rates achieved. Once the study protocol was extended to include rural women, 69% of women in the target population participated in the study and completed the follow-up assessment. All women reported the program to be helpful towards their recovery and 75% rated the program ‘excellent’ overall. In addition, allowing rural women to participate in the program it had the advantage of reaching women independent of residence.

Another important aspect of the study was that it was home-based in nature. This was a workable approach to reaching women diagnosed with ovarian cancer whilst having treatment locally. Furthermore, using two modes of program delivery, telephone and face-to-face contact, allowed for flexible contact with women, especially during times when women were too unwell to have personal contact. Further, the exercise intervention was supervised and individually prescribed by a qualified EP. Gradual progression of walking and slowly increasing exercise intensity and duration was designed to encourage women to walk during their chemotherapy treatment. The weekly supervision by the EP permitted a controlled and safe exercise program as well as gave the women a non-threatening environment to build rapport.

5.6 FUTURE DIRECTIONS AND CONCLUSIONS

The results of this pilot study highlight an area of exercise and cancer research that requires further research. As a consequence of the nature of the intervention program implemented, it is not possible to determine a clear contribution of walking on ovarian cancer physical and psychological outcomes. The inclusion of a control group, and a greater sample would provide more insight into the potential benefits of a walking intervention during adjuvant treatment for ovarian cancer. In addition, this pilot only investigated the role of walking during treatment and made no attempt to determine the role of physical activity following treatment and to investigate its longitudinal affects. Literature states that participation in physical activity for cancer patients declines at diagnosis and remains low throughout treatment and then following treatment [65]. Future research in the area of ovarian cancer should investigate the best possible time throughout the cancer continuum that initiation of a physical activity intervention will have the greatest affect. It seems likely that those who exercise from point of diagnosis and continue to exercise until complete recovery will be more likely to maintain function and thus QoL throughout the entire cancer journey.

Prior to this pilot study, research has predominantly assessed the physical activity impact of ovarian cancer patients in a mixed tumor setting without separation of results. Exercise prescription guidelines have also been described for general cancer patients rather than for specific cancer groups. This investigation tested the limits of exercise prescription for women diagnosed with ovarian cancer. From the results some exercise prescription recommendations can be made. The results of this work demonstrate that women with ovarian cancer are capable of participating in a walking intervention of up to five times a week, of moderate intensity for up to 30 minutes per session. Key additional findings are that the exercise prescription needs to be flexible to accommodate changes in symptoms that occur throughout various stages of the chemotherapy cycle. Clinical experience also demonstrated the importance of maintaining regular contact with the women (either face-to-face or over the phone) to ensure the woman maintain the confidence to progress throughout their entire chemotherapy treatment period.

These are the first findings derived from an exercise intervention in women diagnosed with ovarian cancer whilst undergoing adjuvant chemotherapy and highlight that this area of research is ripe for further investigation. The results from this study will also contribute to better understanding the ability to recruit women undergoing treatment for ovarian cancer into an exercise intervention study. In doing so, this will provide the necessary preliminary data to support extension of this work into a randomised-controlled trial.

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Title

Exercise interventions involving women with gynecological cancer: A systematic review.

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Abstract

INTRODUCTION: Exercise is recommended during and following cancer treatment, however, the specific role of exercise for women with gynecological cancer is unclear. This systematic review evaluates the involvement of women with gynecological cancer in exercise trials and the effect of these during and/or following gynecological cancer treatment.

METHODS: Relevant key word searches were conducted in PubMed, Medline and CINAHL between 1980 and December 2009. Eligible publications were peer-reviewed and restricted to aerobic- and/or resistance-based exercise interventions that included at least one participant with gynecological cancer. Data on number of gynecological participants, intervention characteristics, outcomes studied, adverse events, withdrawal rates and adherence were extracted.

RESULTS: Twenty-seven publications reporting on twelve individual studies were included. All but one study contained mixed cancer groups. Only 10% (n=212) of the total sample in the eligible trials were women with gynecological cancer. Walking was the most common exercise. Intervention timing, frequency, duration, intensity and mode of delivery varied significantly among studies. Across all participants, adherence and withdrawal rates were acceptable (62-97% and 3-35%, respectively) and adverse events were generally minor. While clinically significant benefits in physical function, body composition and quality of life were reported, studies were not powered for subgroup analysis by cancer type.

CONCLUSIONS: There exists scope and need for optimizing recovery following gynecological cancer. Evidence to support its effectiveness in the gynecological cancer setting is preliminary but positive, with more work required to better

understand the feasibility and effectiveness of exercise programs in this specific cohort.

KEY WORDS: exercise; gynecological cancer; intervention; treatment

Introduction

Gynecological cancer encompasses cervical, ovarian, uterine, vulval and vaginal cancers, with uterine cancer being the most common form in developed countries. Approximately one in six cancer cases among women relates to a gynecological cancer diagnosis.[1] Five-year survival rates differ according to gynecological cancer type (uterine, ~80%[2] vs ovarian, ~50%[2]) and are typically associated with the stage at which the cancer is diagnosed. Nonetheless, overall 5-year survival is 65% and improving.[2]

Depending on site and stage, treatment commonly involves surgery with or without adjuvant therapy but may sometimes involve chemotherapy and/or radiotherapy without surgery. For example, the majority of ovarian cancer patients will have surgery followed by adjuvant chemotherapy. However others may require neoadjuvant chemotherapy administered preoperatively. Patients with early stage cervical cancer traditionally will have a radical hysterectomy but patients with more advanced disease benefit from concurrent chemo-radiotherapy. The majority of patients with uterine cancer will have surgery to remove the female reproductive organs and only a few patients will require postoperative radio- or chemotherapy. Patients with vulval or vaginal cancer are often elderly and require surgery if the tumour

has spread to regional lymph nodes (groins) these women undergo chemo-radiotherapy to the whole pelvis. Unfortunately, the cancer metabolism and cancer treatment can cause a range of side-effects. While fatigue is the most common and troublesome side-effect reported by patients especially after treatment with chemo- or radiotherapy,[3] nausea, difficulty sleeping, sensory neuropathy and taste changes are other frequent and burdensome concerns after chemotherapy.[4] Bowel concerns such as constipation or changes in bowel movements are common after surgery, while urgency of bowels is common after radiotherapy. The combined effects of treatment burden and side effects can lead to high levels of psychological distress as well as earlier than desired treatment cessation.[5]

With increasing incidence, as well as increasing survival rates for gynecological cancers, there is a clear need for improved understanding of ways to minimize and overcome disease and treatment-related side-effects and to optimize recovery.[6] Exercise as an intervention strategy has been shown to be effective in attenuating a range of physical and psychological cancer treatment side-effects. More than 80 intervention trials have been summarized in several reviews, with the results clearly demonstrating a beneficial effect of exercise during and/or following cancer treatment;[7] in particular, cardiovascular, musculoskeletal, immunological and psychosocial benefits, as well as reductions in the number and severity of treatment-related side-effects (Table 1).[8] Patients who reported exercise also seemed to have better adherence to chemotherapy and reported better quality of life compared to patients who did not exercise.

However, the extent to which women with gynecological cancers have been included in exercise intervention trials and the specific role of exercise during and following treatments for gynecological cancer is unknown. The purpose of this systematic review is to evaluate the extent to which women with gynecological cancers have been involved in exercise intervention studies; to describe the intervention and outcome measures assessed; and to report rates of adverse effects, withdrawal and adherence to the intervention.

Materials and Methods

A literature search for studies of exercise interventions involving women with gynecological cancer, published between 1980 (the time during which the pioneering work in the field of cancer and exercise was first published)[9] to December, 2009, was performed using Medline, PubMed and CINAHL. Search terms ('neoplasm' or 'cancer' or 'tumor' or 'tumour') and ('gynecologic*' or 'gynaecologic*' or 'ovarian' or 'uterine' or 'endometrial' or 'cervical' or 'vaginal' or 'vulva*') and ('exercise intervention' or 'exercise therapy' or 'physical fitness') were used. Relevant article titles and abstracts were inspected to determine eligibility, and additional references identified through systematic reviews and meta-analyses were also checked to identify additional potentially relevant papers.

To be eligible, the exercise intervention studies had to include at least one patient who had previously or was currently receiving treatment for gynecological cancer; the intervention needed to be aerobic- and/or resistance-based exercise (excluding primary tai chi or stretching); and be published in English in a peer-reviewed journal. Exercise interventions involving secondary or joint lifestyle interventions, for example

those also offering diet or psychotherapy, were also accepted. Adherence was defined as following the exercise protocol and/or the prescribed exercise sessions and the number of withdrawals was classified as the number of participants voluntarily leaving the study, irrespective of group allocation.

Studies were identified by first author, year of publication and country. Where possible, data such as sample size, number of participants with gynecological cancers included, disease characteristics, prior or current treatment, characteristics of exercise program (frequency, intensity, time, type, mode of delivery), outcomes studied, adverse events, adherence and withdrawal rates were abstracted.

Results

Included studies

The search identified 258 references. Following a review of titles and abstracts, 202 were excluded as they were not exercise intervention studies and/or did not include gynecological cancer patients. The remaining 56 publications were retrieved for more detailed evaluation, of which 29 publications were excluded for not including women with gynecological cancers. Twenty-seven publications reporting on 12 studies were thus included in this review (Table 2).

Study quality

Of the 12 studies that were included in the review, seven were randomized trials, with the remainder quasi-experimental studies (n=5). Eight studies adequately described the sample with regard to cancer diagnosis, treatment course, gender and socio-demographic variables (Study 1, 2, 4, 5, 6, 10-12). Seven studies described

the exercise intervention with inclusion of mode, intensity, frequency, duration of session, and duration of program in a manner that would allow other researchers to repeat their trial. The bulk of studies (66%) did not exclude participants based on previous physical activity levels. One study (a feasibility pilot study) did no statistical testing (Study 5), while the remaining studies evaluated outcomes of interest pre- and post-intervention.

Sample size and participants

All but one of the 12 studies reported on mixed cancer groups, including patients with gynecological cancers, as well as patients with cancer of the head and neck, breast, prostate, lung, colon and/or hematological malignancies. Nine (75%) of these studies comprised a sample of mostly women with breast cancer. Only one study focused solely on women with endometrial cancer (n=45) (Study 4). Across all 12 studies, a total of 212 women diagnosed with gynecological cancers participated, and of these, 62 were diagnosed with ovarian cancer, 47 endometrial cancer, seven cervical cancer and 96 an unspecified type of gynecological cancer (Study 6, 10, 11). Women with gynecological cancer represented a median of 10% (range 2%-100%) of the total sample in the exercise intervention studies.

Although not specified separately for those with gynecological cancers, participants in the studies with mixed cancer cohorts were aged 30 to 82 years and were recruited 29 days to five years post-diagnosis. The mean age of endometrial cancer participants in the lifestyle intervention was 54 years and on average, these women were 21 months post-diagnosis. Three studies were conducted while patients were receiving treatment (Study 1, 3, 10), seven studies commenced after treatment

(Study 4, 6, 8-12), while the remaining two studies involved some patients on active treatment and others who had completed their treatment (Study 2, 7).

Interventions

The intervention periods ranged from six weeks (Study 11) to six months (Study 4). Table 3 describes the exercise prescription details, along with adherence and withdrawal rates. Four studies were unsupervised (usually home-based; Study 3, 4, 6, 7); one of these indicated that telephone support was provided if required (Study 7), while the remaining three incorporated group counselling sessions in conjunction with a home-based exercise program (Study 3, 4, 6). All other studies involved supervised interventions conducted in hospital or clinic settings (Study 1, 2, 5, 8-12). When specified, supervision was typically carried out by physiotherapists or exercise therapists.

All interventions had an aerobic component. The majority of interventions (66%) also included strength training (Study 1, 2, 5, 8-12). Studies prescribing aerobic exercise only (Study 3, 4, 6, 7) typically included walking, swimming and/or cycling modes of activity, with 95% of participants in one study (Study 3) choosing walking as their preferred mode of exercise. Three studies encouraged home-based walking (Study 5, 10, 12) in addition to the prescribed program. Exercise interventions incorporating strength training (Study 1, 2, 5, 8-12) prescribed exercises using machines (in a circuit) and/or exercises such as push-ups, lunges and abdominal crunches. Group sports, games, mobility exercises, relaxation, body awareness and stretching were also included in some of the protocols evaluated (Study 1, 8, 11, 12).

The frequency, duration and intensity of the sessions within the interventions and the speed and manner in which the exercise prescriptions were progressed differed among studies. Exercise session frequency ranged from once per week (Study 5, 12) to five times per week (Study 3, 7) and three studies encouraged additional home-based walking to supplement the intervention (Study 5, 10, 12). Duration of study exercise sessions ranged from 20 (Study 3) to 90 minutes (Study 12). Exercise intensities ranged from low to high, as assessed by heart rate (Study 3, 6) in two studies and level of exercise capacity (Study 7, 9, 10, 12) in four studies; it was undefined in six other studies (Study 1, 2, 4, 5, 8, 11).

Outcome measures

In each study, a range of physical and psychosocial outcomes were assessed using a variety of tools. The most commonly measured outcomes were quality of life (Study 1-3, 6-8,10-12), physical function (Study 1-3, 6, 9, 10, 12), body composition (Study 1-4, 9), physical activity level (Study 1, 2, 4, 10) and mental health (Study 1, 3, 6, 8). The majority of outcomes were self-assessed by validated questionnaires and/or by clinical methods. Self-report questionnaires and interviews were typically used to assess physical activity levels, intervention adherence and appraisal of the intervention (Table 4). Statistically significant improvements were found in outcomes across studies. Only three studies pre-specified what would be considered a clinically important change in quality of life and physical function.

Subgroup analysis, separately addressing outcome change in women with gynecological cancers, was not undertaken in any of the studies. However,

qualitative quotes regarding treatment side-effects and exercise intervention program feasibility for patients with ovarian cancer were presented in two publications.[18,23]

Adverse events

Seven studies did not report whether adverse events occurred in association to the exercise intervention. Adverse events were noted in five studies (Study 1, 2, 5, 7, 10) and ranged in severity. Minor events that were resolved in a short period and saw continued participating in the intervention included injuries (not defined) related to a fall whilst walking, superficial skin wound (scraped knee), two separate muscle strains and elevated heart rate and/or blood pressure in five participants. One serious event was reported where a participant collapsed during an intervention session and subsequently died. Following autopsy, the death was ruled due to cardiac arrest. It is unspecified whether any of these adverse events occurred in women with gynecological cancers.

Adherence to the exercise intervention program

Adherence was assessed in all studies either by self-report diaries (n=4) or attendance records (n=8). However, results were only described in nine studies; in these, adherence ranged from 62-97%. Some reasons noted for patient non-adherence included strict screening and monitoring procedures (Study 1); two studies (Study 1, 10) involved screening whereby participants needed to meet all defined criteria to be able to participate in any given exercise session. Examples of the exclusion criteria applied include: diastolic blood pressure below 45; infection requiring antibiotic treatment; ongoing bleeding; pulse rate above 100 at rest and thrombocyte and leucocyte levels below 50 billion/L and 1billion/L, respectively

(Study 1). Clashes with treatment appointments and scheduled exercise sessions was another reason given for missed sessions (Study 10). In the endometrial cancer patient study, adherence in the intervention group was 73% (Study 4).

Withdrawals from the exercise program

Withdrawals ranged between 3% and 35%, with eight publications not specifying reasons for withdrawal. Reasons specified by others included: felt that they did not belong to the group,[12,18] not fit enough,[10] illness/medical reasons,[11,18,20,21,32,34] work or transport issues,[22] required unplanned surgery,[22] recurrence or metastasis,[29,32,38] personal reasons,[29,33,34,38] not interested anymore,[21,29] injury,[21] distress,[21] out of town,[21] deterioration of condition,[23] nausea[38] and claustrophobia.[38] No data was available to determine the influence of gynaecological cancers or its treatment on withdrawal rates.

Discussion

Physical activity has become a focus for cancer recovery and survival research and has been formalized in Courneya's (2007) Physical Activity and Cancer Control (PACC) framework.[39] The framework is based on observational studies and randomized, controlled trials that have demonstrated that physical activity can alleviate treatment-related morbidities and enhance recovery outcomes. In particular systematic reviews, [6,7] meta-analysis[40,41] and government reports,[42] including mainly studies with breast cancer patients, have concluded that participation in regular physical activity plays an important role in reducing the frequency and intensity of treatment-related side-effects (such as fatigue, pain and psychological distress), and is associated with improvements in physical function, [6,43] and quality of life.[40,44]

Evidence is also developing that supports a role for exercise in facilitating the completion of treatments[5] and optimizing quantity of survival.[45]

While the results in general derived from cancer populations indicate that exercise during and following cancer treatment may be safe, feasible and acceptable to participants, one key recommendation from this review is that further testing of such interventions in women with various types of gynecological cancers is needed. We found that less than 215 women with gynecological cancer have participated in exercise intervention trials worldwide, and that there exists only one study[22] which involved a homogenous gynecological sample (45 participants with endometrial cancer). Furthermore, the majority of the studies that involved women with gynecological cancer were randomized, controlled trials and of those that were pilot studies, small convenience samples were enrolled.

Given the limited involvement of women with gynaecological cancers in exercise intervention studies to date, it is unclear whether the results derived from these trials can be translated into clinical gyne-oncology practice. Studies included in this review revealed positive changes in outcomes observed, as well as good adherence and low withdrawals. Further, few adverse events were reported, and of those that were listed, the majority were considered minor and the most severe, cardiac arrest, was ruled by physicians as not being caused by the exercise intervention. With respect to the implication of these findings in the gynaecological cancer setting, these results should be viewed as positive but preliminary. That is, more work is required to confirm the safety and feasibility of exercise interventions during and following gynaecological cancer treatment. Furthermore, the type, timing of commencement

of the intervention relative to cancer diagnosis, intensity and duration of the interventions investigated within this review varied greatly. Thus, the optimal exercise prescription parameters for this specific cohort is also still uncertain.

It is plausible that optimal exercise prescription and timing of an intervention will differ by gynecological cancer sub-type and stage, due to the differences in treatment and prognosis. For example, uterine cancer is associated with obesity;[46] exercise-based interventions may thus be most useful as a primary and/or secondary prevention strategy with the aim to improve body composition. For women with ovarian cancer, who typically receive extensive, open abdominal surgery followed by repeated regimes of chemotherapy,[47] may benefit most from a tailored exercise intervention during treatment. This could reduce the number and severity of chemotherapy-related side-effects and to optimize treatment adherence, thus possibly improving both quality and quantity of life.

The stage of gynaecological cancer may also influence the mode of exercise intervention delivery. For women with advanced disease, it may be more appropriate to consider clinic-based interventions, in particular during active treatment periods. This would allow for close monitoring of exercise and treatment interactions, as well as observation of factors such as malnutrition and muscle wasting, with minimal additional interruption to their lives as they would be attending the clinic regularly for chemotherapy. However, women with early stage disease considered disease-free after treatment may be assisted more remotely (e.g. using telephone or web-based interventions) to preserve physical function and to reduce the impact of symptoms that commonly persist many years beyond treatment for

gynaecological cancer, such as fatigue, constipation, diarrhea, nausea, mood change, pain, body image and pelvic floor concerns.[46-48] Interventions for these women could be aimed at facilitating a faster recovery and assisting workforce return.

Most women diagnosed with gynecological cancers experience good and improving five-year disease-free survival.[2] Consequently, there is significant scope and need to understand the role that exercise may play in reducing their treatment-related side-effects and optimizing their health outcomes. This review highlights the limited involvement of women with gynaecological cancer in exercise intervention trials. Nonetheless, clinically important and statistically significant changes were observed in those who participated in the interventions evaluated. It is now time to broaden our understanding of the role of exercise specifically following a gynaecological cancer diagnosis and that this should be done by considering the findings of this review and also the advanced evidence-based developed mostly from studying women with breast cancer.

Table 1: Summary of potential benefits of exercise during and/or following cancer treatment

Preservation or improvements	**Reductions**
Muscle mass, strength, power Cardiorespiratory fitness Physical function Physical activity levels Range of motion Immune function Chemotherapy completion rates Body image, self esteem and mood	Number of symptoms and side-effects reported, such as nausea, fatigue and pain Intensity of symptoms reported Duration of hospitalization Psychological and emotional stress Depression and anxiety

*This table has been reproduced, with permission (Hayes et al, 2009)

Table 2: Study details and sample numbers of exercise interventions that involved women with gynecological cancer

Study ref #	Publications	Type	Country	Total sample (N, min-max)	Total sample with gynecological cancer (N, min-max)	Gynecological cancer sample (N, min-max)
S1	Adamsen et al (2003)[10] Adamsen et al (2004)[11] Adamsen et al (2006)[12] Adamsen et al (2009)[13] Anderson et al (2006)[14] Midtgaard et al (2005)[15] Midtgaard et al (2005)[16] Midtgaard et al (2006)[17] Mitdgaard et al (2007)[18] Quist et al (2006)[19]	RCT	Denmark	5-269	1-27	Cervical = 1-6 Ovarian = 1-21
S2	Oldervoll et al (2006)[20]	Quasi	Norway	52	1	Ovarian = 1
S3	Courneya et al (2003)[21]	RCT	Canada	108	6	Ovarian = 6
S4	Von Guenigen et al (2008)[22]	RCT	USA	45	45	Endometrial = 45
S5	Stevinson & Fox (2006)[23]	Quasi	Canada	12	2	Ovarian = 2
S6	Thorsen et al (2005)[24]	RCT	Norway	111	24	Not specified
S7	Wilson et al (2006)[25]	Quasi	USA	39	5	Cervical = 1 Ovarian = 2 Endometrial = 2
S8	Berglund et al (1993)[26] Berglund et al (1994)[27] Berglund et al (1994)[28]	RCT	Sweden	60-199	8-15	Ovarian = 8-15
S9	De Backer et al (2007)[29] De Backer et al (2008)[30]	Quasi	The Netherlands	57-68	8-15	Ovarian = 8-15
S10	May et al (2008)[31] May et al (2008)[32] May et al (2009)[33] Korstjens et al (2008)[34]	RCT	The Netherlands	132-209	13-24	Not specified
S11	Korstjens et al (2006)[35] Korstjens et al (2008)[36]	RCT	The Netherlands	23-658	3-42	Not specified
S12	Van Weert et al (2005)[37] van Weert et al (2006)[38]	Quasi	The Netherlands	72-81	5-6	Not specified

RCT, randomized controlled trial; Quasi, quasi-experimental.

Table 3: Exercise prescription characteristics of the exercise interventions that involved women with gynecological cancer

Study	Location	Supervised Y/N	Exercise mode	Frequency (per week)	Intensity	Duration (weeks)	Session length (mins)	Adherence of all patients to intervention (%)	Sample	Withdrawal n (%)
S1	Centre	Y	Aerobic & resistance	3-5	85-95% 1RM 85-95% HR_{max}	6	90 (PA) 30 (relaxation) 30 (massage)	70-78%	Ex:135 C:134	Ex:11 (8%) C:8 (6%)
S2	Centre	Y	Aerobic & resistance	2	Low	6	50	88%	52	18 (34%)
S3	Home	N	Aerobic♦	3-5	65-75% HR_{max}	10	20-30	84%	Ex:60 C:48	Ex:9 (15%) C:3 (6%)
S4	Home	N	Aerobic	5	Low to moderate	24	45 or more	73%	Ex:23 C:22	Ex:5 (21%) C:2 (9%)
S5	Centre	Y	Aerobic & resistance#	1	Light to moderate	10	60	80%	12	3 (25%)
S6	Home	N	Aerobic♦	2	Borg 13-15 or 60-70% HR_{max}	14	30	97%	Ex:59 C:52	Ex:10 (17%) C:18 (35%)
S7	Home	N (phone support)	Aerobic♦	3-5	50-70% HRR	10-13	20-40	62%	39	10 (26%)
S8	Centre	Y	Aerobic & resistance	1-2	Low to moderate	7	120	NR	Ex:98 C:101	Ex:8 (5%) C:3 (3%)
S9	Centre	Y	Aerobic & resistance	2 (for 12 wks) 1 (for 6 wks)	35-80% 1RM 30-60% MSEC	18	NR	92%	68	11 (16%)
S10	Centre	Y	Aerobic, resistance & sports#	2	30-60% 1RM 50-80% HRR	12	120	83-91%	209	15 (7%)
S11	Centre	Y	Aerobic, resistance & sports	2	Low to moderate	12	120	83.5%	658	86 (13%)
S12	Centre	Y	Aerobic, resistance & sports#	1	50% 1RM ↑ 5-10% 50-80% HRR	15	150	NR	81	18 (22%)

MRmax, maximum heart rate; HHR, heart rate reserve; 1RM, one repetition maximum; NR, not reported; Ex, exercise group; C, control group; ♦, exercise chosen by participant; #, encouraged to supplement exercise intervention with home-based walking.

Table 4: Outcomes assessed and reported results of exercise interventions that involved women with gynecological cancer

Study	Outcome measures	Instrument	Results from all participants including change over time and group level differences (* statistical significance, # clinical significance specified by author)	
			Positive effect	**No change**
S1	Physical function	$V0_{2max}$, 1RM	✓*	
	QoL	EORTC QLQ-C30, SF-36		✓
	Mental health	HADS	✓	
	Body composition	Skinfolds, weight	✓*	
	Physical activity level	NV	✓	
	Side-effects/symptoms	CTC	✓	
S2	Physical function	6MWT	✓*	
	QoL	EORTC QLQ-C30		✓
	Body composition	BMI, weight		✓
S3	Physical function	$V0_{2max}$	✓*	
	QoL	FACT-G	✓	
	Mental health	CES-D, STAI		
	Body composition	Skinfolds	✓*	✓
	Physical activity level	LSI	✓	
S4	Body composition	BMI, weight	✓	
	Physical activity level	LSI	✓	
S6	Physical function	$V0_{2max}$	✓*	
	QoL	EORTC QLQ-C30		✓
	Mental health	HADS		✓
S7	QoL	SF-36		✓
S8	QoL	NV		✓
	Mental health	HADS	✓	
S9	Physical function	$V0_{2max}$, 1RM	✓*	
	QoL	EORTC QLQ-C30	✓*	
	Body composition	BMI, weight, skin-folds	✓*	
S10	Physical function	$V0_2$, dynamometry	✓*#	
	QoL	EORTC QLQ-C30, RAND-36	✓*	
	Physical activity level	PASE	✓*	
S11	QoL	EORTC QLQ-C30	✓*#	
S12	Physical function	Dynamometry, max workload	✓	
	QoL	RAND-36	✓*#	

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire C30; SF-36, Medical Outcomes Study 36-item Short Form; FACT-G, Functional Assessment of Cancer Therapy-General; 6MWT, Six minute walk test; $V0_{2max}$, maximal oxygen consumption; 1RM, one repetition maximum; CTC,Common Toxicity Criteria; PASE, The Physical Activity Scale for the elderly; LSI, Leisure Score Index; HADS, Hospital Anxiety and Depression Scale; CES-D, Center for Epidemiological Studies Depression Scale; STAI, State-Trait Anxiety Inventory; NV, not validated.

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Consent Form (Researcher's copy)

Project Title: Physical activity in ovarian cancer

Investigators: Dr Vanessa Beesley, Dr Sandi Hayes, Dr Monika Janda, Ms Melissa Newton, Dr Penelope Webb, Dr Louisa Gordon, A/Prof Elizabeth Eakin, Prof Peter O'Rourke, Prof Andreas Obermair, Dr Jim Nicklin, Dr Lewis Perrin, Dr Russell Land, Dr Alex Crandon, Dr Marcelo Nascimento, Dr Alessandra Francesconi, Dr David Wyld, A/Prof Paul Mainwaring, Dr Catherine Shannon, Dr Rick Abraham.

- I have read, or had read to me, and understand the Participant Information Sheet and have been given a copy of this to keep;
- I have had any questions or queries answered to my satisfaction;
- I understand that the project is for the purpose of research and not for treatment;
- I understand that the confidentiality of information will be maintained and safeguarded and that the researchers will not reveal my identity or personal details in any information presented about this study in any public forum.
- I freely agree to participate in this project according to the conditions in the Participant Information;
- I give permission for medical practitioners, other health professionals, and/or treating hospital, to release information concerning my disease and treatment which is needed for this trial and understand that such information will remain confidential.

Participant's Name (printed) ……

Signature …… Date ……

Address……

……

Phone (Hm): …….. (Mb): …..…… (Wk): ……

I ……(name of research nurse/study investigator) provided the above named participant with the study information sheet and consent form and believe they understand this information.

Signature …… Date ……

Note: All parties signing the Consent Form must date their own signature.

REVOCATION OF Consent Form (Researcher's copy)

Project Title: Physical activity in ovarian cancer

Investigators: Dr Vanessa Beesley, Dr Sandi Hayes, Dr Monika Janda, Ms Melissa Newton, Dr Penelope Webb, Dr Louisa Gordon, A/Prof Elizabeth Eakin, Prof Peter O'Rourke, Prof Andreas Obermair, Dr Jim Nicklin, Dr Lewis Perrin, Dr Russell Land, Dr Alex Crandon, Dr Marcelo Nascimento, Dr Alessandra Francesconi, Dr David Wyld, A/Prof Paul Mainwaring, Dr Catherine Shannon, Dr Rick Abraham.

I hereby wish to WITHDRAW my consent to participate in the research proposal described above and understand that such withdrawal WILL NOT jeopardize any treatment or my relationship with my treating specialists.

Please tick one:

❑ I am happy for the researchers to keep my confidential data (collected to date)

❑ I would like the researchers to immediately destroy my data

Name (printed).....……

Signature …… Date ……

Address……..

……

Non-obligatory questions for non-participants:

It is useful to know something about the people who do not wish to participate. If you don't mind, it would be most helpful to the researchers if you provide a small amount of information. Please find some questions below. You are under no obligation to complete these questions. However, it would help us compare the characteristics of those who decide not to take part with those who do. This helps us understand how relevant our findings are to all women undergoing ovarian cancer treatment. Even if you are uncomfortable answering certain questions, an incomplete survey will still be of use to us.

Please note that we do not record your name on this sheet and this information will never be used in association with your name.

Today's date: □□/□□/20□□

1. What is your age? _____

2. What is the HIGHEST level of education you have COMPLETED? *(Please tick one)*

   1❑ A university or college degree (*this includes registered nurses)*

   2❑ A trade or technical certificate or diploma (*this includes ENROLLED nurses)*

   3❑ Senior high school (*Grade 12, age 17-18 in QLD)*

   4❑ Junior high school (*Grade 10, age 15-16 in QLD)*

   5❑ Primary school *(Grade 7, age 12-13 in QLD) or no school*

3. What is your relationship status? *(Please tick one)*

   1❑ Single

   2❑ Defacto/Living together/Married

   3❑ Separated/Divorced

   4❑ Widowed

4. How many children aged 0-17 live in your household?

   Enter number | | |

5. How many adults aged 18 years and older live in your household (including yourself)?

   Enter number | | |

Thank you for completing this.

PARTICIPANT INFORMATION and CONSENT FORM

Full Project Title: An exercise intervention for women undergoing primary treatment for ovarian cancer: feasibility and preliminary outcomes

Investigators: Dr Vanessa Beesley, Dr Sandi Hayes, Dr Monika Janda, Ms Melissa Newton, Dr Penelope Webb, Dr Louisa Gordon, A/Prof Elizabeth Eakin, Dr Alessandra Francesconi, Prof Andreas Obermair.

The Participant Information and Consent Form is 4 pages long and has 3 additional forms (2 copies of each) attached: 'consent form', 'revocation of consent form' and 'non-obligatory questions for non-participants'. The orange-coloured forms are copies for you to keep, while the relevant yellow copy is to be signed and returned to research staff (either by handing to the research nurse or by using the reply-paid envelope enclosed).

1. Your Consent

You are invited to take part in a research project. This Participant Information document contains detailed information about this research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

2. Purpose and Background

The purpose of this project is to assess the feasibility of implementing, and potential worth of a home-based walking intervention in ovarian cancer patients undergoing initial treatment. If the program is feasible we will extend this trial to determine the effect on possible ovarian cancer-related symptoms (e.g. fatigue), quality of life, chemotherapy completion and survival. Ultimately, we hope to improve the standard of care for women with ovarian cancer in the future.

3. Procedures

Women being treated for ovarian cancer at one of the participating hospitals are being invited to participate. Agreeing to take part in the study means that you are willing to have exercise formally integrated within your care during chemotherapy. Each participant will be assigned an Exercise Physiologist (EP). The EP will aim to assist participants to achieve 30 minutes of accumulated daily physical activity by the end of the study. The specific exercise prescription including starting and progressing towards this goal will depend on your individual circumstances and response to chemotherapy. The EP will visit your home once a week over the course of your chemotherapy treatment (approximately 18 sessions in total) to help you with this.

All women involved with the study will take part in 2 data collection phases. These will be held just prior to your first or second cycle of chemotherapy and at the end of your

chemotherapy treatment. During these testing sessions (which will take about 20 minutes), we will assess your current physical activity capacity, any limb swelling and ask you to complete a questionnaire about a variety of quality-of-life issues common for women with ovarian cancer, such as fatigue. In the second session we will also ask you what you liked and disliked about the walking program. These testing sessions will be planned during times and at a location convenient to you (e.g. at your home).

4. Possible Benefits

All women will be given the same high level of care that is routinely given to women having ovarian cancer treatment at the participating hospitals. This study will in no way prevent you from taking part in any other activity (in addition to routine standard care) that you choose to participate in, which may, or may not, be related to your treatment for ovarian cancer.

While we know that participating in exercise during treatment for patients with other cancer types is beneficial, the effects of exercise during treatment for ovarian cancer patients are unknown. We can therefore not guarantee that you will receive any direct benefits from participating in this study.

5. Possible Risks

Possible risks, side effects and discomforts include injury to muscles or bones. These are risks of taking part in any exercise program. However, this risk is reduced as the exercise program has been specially designed and is watched over by your exercise physiologist. Participants will be asked to advise the researchers if any concerns arise, so that any problems can be promptly dealt with and managed at that time. In the unlikely event of an injury through participation in the study institution insurance will respond to all claims in accordance with the insurer's policy terms and conditions. Should an injury occur, please call Chief Investigator, Dr Vanessa Beesley on 07 3362 0270.

6. Alternatives to Participation

If you do not wish to participate in this study you may proceed with standard care.

7. Privacy, Confidentiality and Disclosure of Information

We request permission to obtain information about your ovarian cancer diagnosis and treatment from your gynaecological oncologist or hospital records for analysis purposes. This information will not be disclosed to anyone other than the study researchers and will remain confidential and anonymous. Also, your results from the study will only be revealed to the researchers and yourself. We intend to give you feedback on the results of the project when available. Results of the study will be published or presented as aggregated and anonymous data only.

8. New Information Arising During the Project

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be informed right away.

This new information may mean that you can no longer participate in this research. If this occurs, the persons supervising the research will stop you taking part. In all cases, you will be offered all available care to suit your needs and medical condition.

9. Results of Project

When you join this research project, you will be invited to let the researchers know if you are interested in hearing about the final results of the research. The contact details you provide at that time will be used to send a brief report to you if you wish.

10. Further Information or Any Problems

If you need more information or if you have any problems about this project (for example, any side effects), you can contact any of the following people responsible for this project:

- Ms Susan Brown (research nurse): 07 3845 3549; Susan.Brown@qimr.edu.au
- Ms Melissa Newton (exercise physiologist): 07 3138 5831; mj.newton@qut.edu.au
- Dr Vanessa Beesley (chief investigator): 07 3362 0270; Vanessa.Beesley@qimr.edu.au
- Dr Andreas Obermair (gynaecological oncologist): 07 3636 5485; Andreas_Obermair@health.qld.gov.au

11. Participation is Voluntary

Taking part in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. Your decision whether to take part or not take part, or to take part and then withdraw, will not affect your clinical treatment, your relationship with those treating you or your relationship with your health practitioner.

Before you make your decision, a member of the research team will be available to answer any questions you have about the research project. You can ask for any information you want. You may also wish to discuss the project with your gynaecological oncologist or with a relative. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers. If you decide to withdraw from this project, for safety reasons only please notify a member of the research team before you withdraw.

12. Ethical Guidelines and other issues

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

This study has been reviewed and approved by the Royal Brisbane and Women's Hospital Health Service District Human Research Ethics Committee, Mater Health Services Human Research Ethics Committee (Mater and Brisbane Private Hospital), United Health Human Research Ethics Office (Wesley Hospital), Greenslopes Private Hospital Human Research Ethics Committee and the Queensland Institute of Medical Research Human Research Ethics Committee.

Please contact one of the numbers below if you have any concerns or complaints about the ethical conduct of the project. You will need to tell the Coordinator/Chairperson the name of one of the researchers given in section 10 above.

- Queensland Institute of Medical Research: Human Research Ethics Committee, Secretary, Post Office, Royal Brisbane and Women's Hospital Brisbane QLD 4029 or telephone (07) 3362 0117;
- Royal Brisbane & Women's Hospital: Coordinator or Chairperson, Human Research Ethics Committee, Herston, Qld, 4029 or telephone (07) 3636 5490;
- Mater Public and Private Hospital and the Brisbane Private Hospital: Mater Health Services Brisbane, Coordinator, Level 2 Aubigny Place, Raymond Tce, South Brisbane, Qld, 4101 or telephone (07) 3840 1585;

- Queensland University of Technology: Human Research Ethics Committee, Coordinator, Office of Research, GPO Box 2434, Brisbane, Queensland 4101 or telephone (07) 3138 2091;

13. Reimbursement for your costs

You will not be paid for taking part in this project. To cut down costs (financial and time), exercise sessions will be held at a convenient location to you (e.g. your home). However, data collections session (one at the start and one at the end of the study) will be held either at the hospital or at Queensland University of Technology, Kelvin Grove Campus. We will organise these to occur at a time convenient to you and any parking fees incurred will be reimbursed.

14. Final instructions

If you do not wish to take part in this study, please inform the research nurse or your gynaecological oncologist. Unless you do this, study researchers will contact you to discuss the study further. You can, of course, decline at that time. Following contact with the research nurse, if you are interested in participating, you will be asked to sign and return the 'Consent Form (Researcher's copy)' to the research nurse or by using the enclosed reply paid envelope.

"*Physical Activity*

in ovarian cancer"

Data Collection Form

Date: _____/_____/_____		BASELINE / FOLLOW-UP (circle)	
ID:	Age:		
Height: cm	Weight: kg	Waist: cm	Hip: cm

Bioelectrical frequency tests

Confirm in the last 24 hours: Has/Does/Is the participant:	Yes	No
emptied bladder within previous hour		
had a high-fat meal		
had a higher than normal/usual intake of alcohol		
had a higher than normal intake of caffeine		
participated in vigorous exercise or more exercise than usual		
have a pacemaker or defibrillator		
pregnant or lactating		
currently taking any medication		
have any pins/plates or knee/hip replacements		
have any allergies to Elastoplast/bandaids or adhesive material used by a doctor		
Confirm with the participant their menopausal status: Are they:	Yes	No
Postmenopsal		
Premenopausal		
Currently menopausal		

Additional Notes:

File name:	Output #1			Output #2		
Right arm measure	File number:	R_0:	R_i:	File number:	R_0:	R_i:
Left arm measure	File number:	R_0:	R_i:	File number:	R_0:	R_i:
Left arm plus trunk measure	File number:	R_0:	R_i:	File number:	R_0:	R_i:
Body composition	File number:	FFM	FFM%	FM	FM%	
	File number:	FFM	FFM%	FM	FM%	

Right leg measure	File number:	R_0:	R_i:	File number:	R_0:	R_i:
Left leg measure	File number:	R_0:	R_i:	File number:	R_0:	R_i:

Six Minute Walk Test	
Distance walked in 6 minutes	metres
HR @ cessation:	beats/min
RPE @ test cessation:	
Functional capacity:	
Notes:	

Study ID:

"*Physical Activity*
in ovarian cancer"

BASELINE QUESTIONNAIRE

Thank you for agreeing to complete this questionnaire.

Please note that parts of it include standardised questionnaires. Unfortunately, we are unable to modify the questions within these questionnaires. We would greatly appreciate it if you could answer all questions (or as many as you feel comfortable with), even when there may be some questions that you have already answered in an earlier section or when you find some questions are not applicable to you. Just give us the closest response that reflects how you are feeling or what you are doing.

Remember there are no right or wrong answers and everybody's experience is different. If you need any help do not hesitate to call or email using the contact details below.

Dr Vanessa Beesley
Queensland Institute of Medical Research
Post Office, Royal Brisbane Hospital, Q 4029
Phone: 61 7 3362 0270; **Fax**: 61 7 3845 3503;
Email: Vanessa.Beesley@qimr.edu.au

Your general information?

1. Today's date: ☐☐/☐☐/20☐☐
2. Your Date of Birth: ☐☐/☐☐/19☐☐
3. Your Residential Postcode: ☐☐☐☐
4. What is your relationship status? *(Please tick one)*

   1❑ Single
   2❑ Defacto/Living together/Married
   3❑ Separated/Divorced
   4❑ Widowed

5. What is the HIGHEST level of education you have COMPLETED? *(Please tick one)*

   1❑ A university or college degree (*this includes registered nurses)*
   2❑ A trade or technical certificate or diploma (*this includes ENROLLED nurses)*
   3❑ Senior high school (*Grade 12, age 17-18 in QLD)*
   4❑ Junior high school (*Grade 10, age 15-16 in QLD)*
   5❑ Primary school *(Grade 7, age 12-13 in QLD) or no school*

6. How many children aged 0-17 live in your household?

   Enter number | | |

7. How many adults aged 18 years and older live in your household (including yourself)?

   Enter number | | |

8. What is your current gross/annual household income (that is, before tax)? *(Please tick one)*

   1❑ < $20,000
   2❑ $20,000 – less than $40,000
   3❑ $40,000 – less than $60,000
   4❑ $60,000 – less than $80,000
   5❑ $80,000 – less than $100,000
   6❑ $100, 000 +
   7❑ Do not wish to answer
   8❑ Don't know

9. How many people are dependent on this income?

   Enter number | | |

10. Do you have private health insurance? *(Please tick one)*

    1❑ No (Medicare only)
    2❑ Yes – Private hospital insurance only
    3❑ Yes – Private hospital insurance and private health insurance for ancillary services (eg. dental)
    4❑ Yes – Only private health insurance for ancillary services (eg. dental, physiotherapy)
    5❑ Don't know

Have you done any physical activity in the last week?

1. In the last week, how many times have you walked continuously, for at least 10 minutes, for recreation or exercise or to get to or from places?

   ☐☐ **Times**

2. What do you estimate was the total time that you spent walking in this way in the last week?

   ☐☐ **Minutes or** ☐☐ **Hours per week**

3. In the last week, how many times did you do any vigorous gardening or heavy work around the yard, which made you breathe harder or puff and pant?

   ☐☐ **Times**

4. What do you estimate was the total time that you spent doing vigorous gardening or heavy work around the yard in the last week?

   ☐☐ **Minutes or** ☐☐ **Hours per week**

5. In the last week, how many times did you do any vigorous physical activity, which made you breathe harder or puff and pant? (e.g. jogging, cycling, aerobics, competitive tennis, etc.) Do not include household chores or gardening or yardwork.

   ☐☐ **Times**

6. What do you estimate was the total time that you spent doing this vigorous physical activity in the last week?

   ☐☐ **Minutes or** ☐☐ **Hours per week**

7. In the last week, how many times did you do any other more moderate physical activity that you haven't already mentioned? (e.g. gentle swimming, social tennis, golf, etc.)

   ☐☐ **Times**

8. What do you estimate was the total time that you spent doing these moderate activities in the last week?

   ☐☐ **Minutes or** ☐☐ **Hours per week**

Have you experienced any symptoms in the past week?

We have listed a number of symptoms below. Please read each one carefully.

If you have had the symptom during this past week, let us know how OFTEN you had it, how SEVERE it was usually and how much it DISTRESSED or BOTHERED you by ***circling the appropriate number.***

If you did not have the symptom please mark an 'x' in the box marked 'DID NOT HAVE' and go to the next symptom.

DURING THE PAST WEEK Did you experience any of the following symptoms?	**DID NOT HAVE**	**If yes,** How OFTEN did you have it?				**If yes,** How SEVERE was it usually?				**If yes,** How much did it DISTRESS or BOTHER you?				
		Rarely	Occasionally	Frequently	Almost constantly	Slight	Moderate	Severe	Very severe	Not at all	A little bit	Somewhat	Quiet a bit	Very much
Lack of appetite		1	2	3	4	1	2	3	4	0	1	2	3	4
Lack of energy		1	2	3	4	1	2	3	4	0	1	2	3	4
Pain		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling drowsy		1	2	3	4	1	2	3	4	0	1	2	3	4
Constipation		1	2	3	4	1	2	3	4	0	1	2	3	4
Dry mouth		1	2	3	4	1	2	3	4	0	1	2	3	4
Nausea		1	2	3	4	1	2	3	4	0	1	2	3	4
Vomiting		1	2	3	4	1	2	3	4	0	1	2	3	4
Change in taste		1	2	3	4	1	2	3	4	0	1	2	3	4
Weight loss		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling bloated		1	2	3	4	1	2	3	4	0	1	2	3	4
Dizziness		1	2	3	4	1	2	3	4	0	1	2	3	4
Difficulty sleeping		1	2	3	4	1	2	3	4	0	1	2	3	4
Difficulty concentrating		1	2	3	4	1	2	3	4	0	1	2	3	4

How have you been feeling during the past 7 days?

*In this section, please **circle the answer** which best matches your response.*

*How have you been feeling during the **past 7 days**?*

HADS 1	I feel tense or 'wound up'	Most of the time	A lot of the time	From time to time, occasionally	Not at all
HADS 2	I still enjoy the things I used to enjoy	Definitely as much	Not quite so much	Only a little	Hardly at all
HADS 3	I get a sort of frightened feeling as if something awful is about to happen	Very definitely and quite badly	Yes, but not too badly	A little, but it doesn't worry me	Not at all
HADS 4	I can laugh and see the funny side of things	As much as I always could	Not quite so much now	Definitely not so much now	Not at all
HADS 5	Worrying thoughts go through my head	A great deal of the time	A lot of the time	From time to time, but not too often	Not at all
HADS 6	I feel cheerful	Not at all	Not often	Sometimes	Most of the time
HADS 7	I can sit at ease and feel relaxed	Definitely	Usually	Not often	Not at all
HADS 8	I feel as if I am slowed down	Nearly all the time	Very often	Sometimes	Not at all
HADS 9	I get a sort of frightened feeling like 'butterflies' in the stomach	Not at all	Occasionally	Quite often	Very often
HADS 10	I have lost interest in my appearance	Definitely	I don't take so much care	I may not take quite as much care	I take just as much care as ever
HADS 11	I feel restless as if I have to be on the move	Very much indeed	Quite a lot	Not very much	Not at all
HADS 12	I look forward with enjoyment to things	As much as I ever did	Rather less than I used to	Definitely less than I used to	Hardly at all
HADS 13	I get sudden feelings of panic	Very often indeed	Quite often	Not very often	Not at all
HADS 14	I can enjoy a good book or radio or TV program	Often	Sometimes	Not often	Very seldom

How has your wellbeing been during the past 7 days?

Below is a list of statements that other people with your illness have said are important. ***By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.***

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some what**	**Quite a bit**	**Very much**
GP 1	I have a lack of energy	0	1	2	3	4
GP 2	I have nausea	0	1	2	3	4
GP 3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP 4	I have pain	0	1	2	3	4
GP 5	I am bothered by side effects of treatment	0	1	2	3	4
GP 6	I feel ill	0	1	2	3	4
GP 7	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**
GS 1	I feel close to my friends	0	1	2	3	4
GS 2	I get emotional support from my family	0	1	2	3	4
GS 3	I get support from my friends	0	1	2	3	4
GS 4	My family has accepted my illness	0	1	2	3	4
GS 5	I am satisfied with family communication about my illness	0	1	2	3	4
GS 6	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 check this box*** ☐ ***and go to the next section.***					
GS 7	I am satisfied with my sex life	0	1	2	3	4

	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

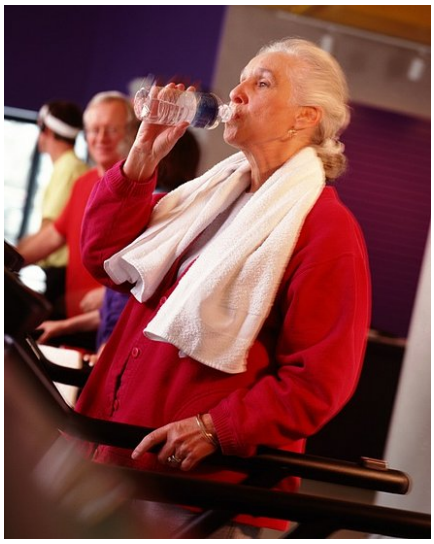
	EMOTIONAL WELL-BEING CONTINUED	Not at all	A little bit	Some what	Quite a bit	Very much
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some what	Quite a bit	Very much
01	I have swelling in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
02	I have been vomiting	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
03	I have cramps in my stomach area	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4

Thank you for completing this questionnaire.

A walking intervention for women going through chemotherapy



Contact Details
Melissa Newton
Accredited Exercise Physiologist
Queensland University of Technology
Ph: 3138 5831 (w) or 0432 496 201
Email: mj.newton@qut.edu.au

Introduction

Exercise during and following treatment for cancer can help to feel better physically and emotionally. Exercise during treatment has also been shown to help people complete their prescribed chemotherapy regime. So far, we do not know if exercise also helps patients with ovarian cancer.

Our aim is to support women undergoing chemotherapy for ovarian cancer to keep walking for exercise. Participants will be encouraged to walk at a low to moderate intensity, daily (or near daily: minimum 5 times per week), accumulating 30 minutes per day. **The specific details of the exercise intervention will be adapted to suit the needs of each woman.** An Exercise Physiologist will visit participants once a week to check on treatment-related side-effects and will adjust the exercise prescription as needed.

What to expect

This booklet is written for women with ovarian cancer who are going through chemotherapy. It aims to help understand the importance of exercise and also provides information about the benefits exercise may have during cancer treatment.

Side effects that may be associated with treatment for ovarian cancer

Some women who receive treatment for ovarian cancer have reported a range of side-effects including:

- fatigue and tiredness
- nausea
- joint and muscle pain
- numbness or tingling in hands and / or feet
- low blood count which may increase risk of infection, cause dizziness or make it easy for you to bruise.
- anxiety
- depression
- temporary thinning or loss of hair
- early menopausal symptoms
- bowel and/or bladder problems
- body weight & composition changes
- lymphoedema (swelling of the legs, feet or trunk)

It is difficult to predict who will experience side effects – some women may experience only mild side effects, while others may find side effects interfere with their daily activities. Importantly though, women who started or continue to exercise, during or following treatments from other cancers, such as breast cancer, have been found to have fewer or less severe side-effects.

Exercise also provides more general health benefits such as helping you sleep better, improves balance and posture, helps controls blood pressure, cholesterol and blood sugar levels, gives you more energy and reduces your risk of other long-term problems such as heart disease and osteoporosis.

These are all good reasons to make exercise a part of your cancer treatment.

Walking

This program is about incorporating planned walking into your life while your having chemotherapy (and hopefully beyond).

Specifically, we will be trying to accumulate 30 minutes of walking on 5 days per week.

Walking uses large muscle groups and causes your heart rate to rise. Over time and with progression, walking improves your heart and lung health and makes strenuous activities of daily living easier.

Walking is a great way to stay active, especially when you are going through ovarian cancer treatment. Walking is the physical activity most preferred by Australians because:

- it's free
- you can walk by yourself or with a friend or family members
- it can be done nearly anywhere, anytime
- just 10 minutes can start improving your health
- you can explore your neighborhood, find different routes
- if you have a treadmill you can walk regardless of the weather conditions
- you can join a walking group (bushwalking, shopping centre fitness walks) and make it social

Incidental activity is a bonus

National physical activity guidelines say **"think of movement as an opportunity, not as an inconvenience and be active everyday in as many ways as you can"**. Any activity you do as part of your normal daily routine can be used to increase your physical activity level. Incidental activities may include:

- doing some gardening
- walking up the stairs instead of using the lift
- household duties such as cleaning, vacuuming, sweeping, washing the car, mowing the lawn
- parking your car further away at the shopping centre or workplace and walking the extra distance
- playing with the children

Even though the planned walking program is our primary focus, any incidental activity is beneficial.

Remember, following surgery you are advised to check with your doctor to determine when you are able to carry out any of the above activities.

Warm-up

A warm-up is important at the start of each exercise session. Warming up helps increase blood flow and oxygen to your muscles and reduces your chance of injury. After a warm-up your muscles are warm and your heart rate is slightly higher than when you are at rest.

A warm-up should move you from being 'at rest' to walking at the desired moderate-intensity pace. It may include some stretches and should take about 5 minutes.

Cool-down

Cooling down is the reverse of a warm-up. It should take you from moderate-intensity walking pace to a low intensity pace over a few minutes. It is then optimal to include some stretches before your exercise session comes to a complete stop. This is a great time to improve your flexibility.

Being active safely

To stay safe during your walking session, we have listed a few tips for you to keep in mind:

- start slow and end slow during each session
- wear comfortable, supportive footwear
- wear loose-fitting, comfortable & light colored clothing
- take a water bottle with you and drink plenty of water during and after your walking session
- be sun sensible, walk during appropriate times of the day and wear a sunscreen & hat
- listen to your body – stop if something's not right
- take a partner or a friend

When starting you may like to go shorter distances (i.e. stay closer to home) until you are comfortable and know how quickly you tire, how you feel and how fast you recover.

You may experience slight muscle soreness following the first few sessions, especially if you have been inactive for some time. This is normal and its called DOMS (delayed onset muscle soreness). This can be prevented or minimized by starting at appropriate levels (i.e. doing less than you think you can do), making sure any increases in your walking are in small increments and doing a warm-up and cool-down. Do not be concerned by DOMS though if you do get it, its temporary and will not last longer than a couple of days.

When not to exercise

Although exercise is generally considered safe during and following cancer treatment certain circumstances exist when you should not exercise.

Do not participate in an exercise session if you have any of the following conditions:

- experiencing chest pain
- unusual fatigue and/or muscle weakness
- recurring leg pain or cramps
- bone, back or neck pain of recent origin
- vomiting within the last 24-36 hours
- feeling disoriented or confused
- feeling dizzy, have blurred vision or faintness
- sudden onset of difficulty in breathing
- foot or ankle sores that won't heal
- a temporary minor illness, such as viral infection

We advise that you seek medical attention or see a doctor if any of the above symptoms are present.

Also, it is important that your treatment-related side-effects are not made worse by exercise. We will work together to ensure your level of walking does no harm but hopefully eases any treatment related side-effects.

The recommended goal

The goal for this program is to get you walking:

- 5 days a week (or more)
- at a moderate intensity
- accumulating 30 minutes (or more) each session

If you can already do this, try walking on more days of the week or gradually increase the time spent walking or the distance you travel in the 30 minutes.

The objective for this walking program is to accumulate 30 minutes each time. Some women may already be able to walk continuously for 30 minutes while others may find walking for 10 minutes difficult. Your Exercise Physiologist will work with you to determine your starting point and how you'll progress towards this goal.

What intensity (how hard) should I be walking?

Walk at a moderate intensity.

It important to find the balance between not working hard enough (will gain fewer benefits) and working too hard (will risk injury or make exercise feel like it's 'too hard').

So, how do I know if I'm working hard enough?

Use the Rating of Perceived Exertion Scale (RPE).

Rating of Perceived Exertion Scale

The RPE scale is one way for you to work out whether you are walking hard/fast enough. On a scale of 6 (nothing at all) to 20 (can't go any harder) you should be around an 11 to 14 for moderate intensity exercise. Don't concern yourself with any one feeling such as leg pain or your breathing, but try to concentrate on your total 'overall' feelings when rating intensity.

Track your exercise

Use your exercise tracker to keep a log of your planned and/or completed walking sessions. Write down how long and how hard you walked. It is a great motivator!

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Walked around park *10 mins* *RPE = 12* *Walked on treadmill* *10 mins* *RPE =12* ***TOTAL = 20 mins***		*Walked on treadmill* *15 mins* *RPE = 12*	*Walked on treadmill* *15 mins* *RPE = 12* *Walked around park* *15 mins* *RPE = 12* ***TOTAL = 30 mins***	*Walked with husband along beach* *25 mins* *RPE = 13*		*Walked with friend around suburb* *30 mins* *RPE = 13*

Identify and problem solve barriers

Despite exercise being linked with a reduction in the number and/or severity of treatment related side-effects, many people decrease there activity during cancer treatment. Identifying why people decrease activity will also help recognise ways these barriers can be overcome.

Some examples of common problems faced by people during cancer treatment include:

Problem **- I'm not confident to go walking on my own?**
= walk with a friend or family member
= hire a treadmill
= only go up and down your street and slowly increase the distance away from home

Problem - **I always feel so tired and lethargic, how do I get enough energy to go walking?**
= take note of the times of the day you feel most fatigued, then attempt to exercise when you feel least tired
= keep a regular sleep schedule
= remind yourself that walking actually gives you more energy
= you can always reduce the intensity of your exercise by reducing the walking pace, decreasing the distance and walking on a flat terrain

If you are finding it difficult to stay or become active during your treatment listed below are some steps that may assist:

- define the problem – write it down
- brainstorm – think of different solutions
- weigh up the solutions – list pros and cons for each solution
- select the best option – the option that has the best chance of succeeding
- take action – plan what to do: who, what, when, how…
- follow-through

Goal setting

When you are involved in an exercise program, like this walking program, it is important to set some goals to work towards. Goals can be broken down into:

- Short term – relate to one week to one month
- Medium term – related to one to three months
- Long term – related to more than three months (once treatment is completed)

A useful way to make goal setting more powerful is to use the SMART method:

Specific – what activity will you do?
Measureable – how many times / minutes?
Attainable – is my body capable of doing it?
Realistic – how will I make the time to do it?
Time framed – for how many weeks or until what date?

Failure to meet goals does not matter, as long as you learn from it. Feed lessons learned back into your goal setting program.

Remember too, that your goals will change as time goes on. Adjust them regularly to reflect what's happening in relation to your treatment for ovarian cancer.

Goal setting

Some examples of short, medium and long term exercise goals are:

Short – Complete a brisk 7 minute walk around the park and then walk slowly for 5 minutes as a cool-down.
Medium – Walk at a moderate intensity for 15 minutes for a minimum of 3 days per week.
Long – Be able to walk 2km continuously without feeling exhausted by the end.

We will work together to set your own short, medium and long term goals. It is often easier to think about long term first, and then break it down by using your medium and short term goals as stepping stones to guide you.

Short term goal:_____
_____
_____
_____
_____

Medium term goal:_____
_____
_____
_____
_____

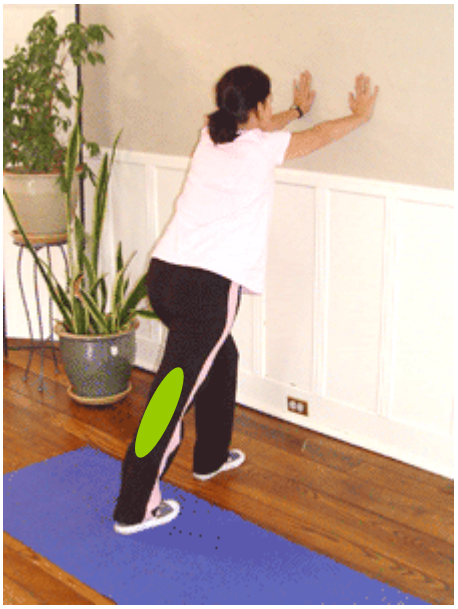
Long term goal:_____
_____
_____
_____
_____

Stretching information

- Hold each stretch position for at least 15 – 30 seconds.
- Extend fully without applying pressure to the joint.
- Breathe normally as you perform the movement.
- Be sure to avoid bouncing, bobbing or excessive pulling.
- Remember to stretch both sides of your body (left and right).
- Stretching exercises can be included in the warm-up and/or cool-down period of your session.

Calf muscle stretch

Keeping you back leg straight, with your heel flat on the ground, lean into the wall until a stretch is felt in the back of the lower leg. Concentrate on keeping the heel of the back leg on the ground and bending your front knee to feel the stretch. Repeat on other leg.



Hamstring muscle stretch

Place the heel of your right foot on a chair or a low step (use a wall or something else to balance if necessary). Keep your back leg straight and abdominals (tummy) tight. Bend over from the waist keeping your torso straight, lowering your upper-body towards your right leg/foot. Repeat on other leg.

Quadriceps muscle stretch

Use a wall or chair for support. Stand on one leg, grasp around the ankle and gently pull up and back towards the buttocks. Keep the pelvis straight and the torso upright. You should feel a stretch through the thigh of your lifted leg. Repeat on other leg.

Example weekly walking program

Week	Warm-up	Activity	Cool-down	Total time
Week #1	Slowly for 5 minutes	Briskly for 5 minutes	Slowly for 5 minutes	15 minutes
Week #2	Slowly for 5 minutes	Briskly for 7 minutes	Slowly for 5 minutes	17 minutes
Week #3	Slowly for 5 minutes	Briskly for 9 minutes	Slowly for 5 minutes	19 minutes
Week #4	Slowly for 5 minutes	Briskly 11 minutes	Slowly for 5 minutes	21 minutes
Week #5	Slowly for 5 minutes	Briskly for 13 minutes	Slowly for 5 minutes	23 minutes
Week #6	Slowly for 5 minutes	Briskly for 15 minutes	Slowly for 5 minutes	25 minutes
Week #7	Slowly for 5 minutes	Briskly for 18 minutes	Slowly for 5 minutes	28 minutes
Week #8	Slowly for 5 minutes	Briskly for 20 minutes	Slowly for 5 minutes	30 minutes
Week #9	Slowly for 5 minutes	Briskly for 23 minutes	Slowly for 5 minutes	33 minutes
Week #10	Slowly for 5 minutes	Briskly for 23 minutes	Slowly for 5 minutes	33 minutes
Week #11	Slowly for 5 minutes	Briskly for 26 minutes	Slowly for 5 minutes	36 minutes
Week #12	Slowly for 5 minutes	Briskly for 26 minutes	Slowly for 5 minutes	36 minutes

Project Title: Physical activity in ovarian cancer

Investigators: Dr Vanessa Beesley, Dr Sandi Hayes, Dr Monika Janda, Ms Melissa Newton, Dr Penelope Webb, Dr Louisa Gordon, A/Prof Elizabeth Eakin, Dr Alessandra Francesconi, Prof Andreas Obermair

The purpose of this questionnaire is to find out what you liked and didn't like about the physical activity and ovarian cancer program. Your feedback will help us improve the program for those who take part in the future.

Please circle the number that best reflects your opinion:

1. How helpful was the physical activity in ovarian cancer program to your recovery following diagnosis?

1	**2**	**3**	**4**	**5**	**6**	**7**
Very unhelpful	Unhelpful	Somewhat unhelpful	Neither helpful or unhelpful	Somewhat helpful	Helpful	Very helpful

Do you have any specific comments on the helpfulness of the program?

_____

_____

_____

_____

2. How helpful was the educational booklet?

1	**2**	**3**	**4**	**5**	**6**	**7**
Very unhelpful	Unhelpful	Somewhat unhelpful	Neither helpful or unhelpful	Somewhat helpful	Helpful	Very helpful

Do you have any specific comments on the helpfulness of the booklet? For example, you may have specific thoughts about the booklet's length, clarity, layout, etc:

_____

_____

_____

_____

3. How helpful were the sessions with your Exercise Physiologist?

1	**2**	**3**	**4**	**5**	**6**	**7**
Very unhelpful	Unhelpful	Somewhat unhelpful	Neither helpful or unhelpful	Somewhat helpful	Helpful	Very helpful

Please use the space below to provide any additional comments. For example, you may have specific thoughts about the frequency, length or number of the sessions with your Exercise Physiologist:

_____

_____

_____

_____

4. How often did you use the exercise tracking sheet? (*Please tick one box*)
   - ☐ Never
   - ☐ Occasionally
   - ☐ Often

   Do you have any specific comments on the helpfulness of the exercise tracking sheet?

5. How often did you use the pedometer? (*Please tick one box*)
   - ☐ Never
   - ☐ Occasionally
   - ☐ Often

6. Do you have any suggestions about other ways the program could be delivered?

7. Was there anything about participating in the program that you found difficult? *(Please tick one box)*
   - ☐ No
   - ☐ Yes – please specify

8. Do you think the program could be improved in anyway? *(Please tick one box)*
   - ☐ No
   - ☐ Yes – please specify

9. One final question. Thinking about all aspects of the exercise program, on a scale of 1-7, with 1 being 'not good at all' and 7 being 'excellent', circle the number that best reflects how you feel about participating in the physical activity and ovarian cancer program:

1	**2**	**3**	**4**	**5**	**6**	**7**
Not good at all						Excellent

THANK YOU VERY MUCH FOR COMPLETING THIS SURVEY!

PLEASE RETURN IT TO US IN THE REPLY–PAID ENVELOPE INCLUDED.

University Human Research Ethics Committee

HUMAN ETHICS APPROVAL CERTIFICATE

NHMRC Registered Committee Number EC00171

Date of Issue: 18/5/09 (supersedes all previously issued certificates)

Dear Ms Vanessa Beesley

A UHREC should clearly communicate its decisions about a research proposal to the researcher and the final decision to approve or reject a proposal should be communicated to the researcher in writing. This Approval Certificate serves as your written notice that the proposal has met the requirements of the *National Statement on Research involving Human Participation* and has been approved on that basis. You are therefore authorised to commence activities as outlined in your proposal application, subject to any specific and standard conditions detailed in this document.

Within this Approval Certificate are:

* Project Details
* Participant Details
* Conditions of Approval (Specific and Standard)

Researchers should report to the UHREC, via the Research Ethics Coordinator, events that might affect continued ethical acceptability of the project, including, but not limited to:

(a) serious or unexpected adverse effects on participants; and
(b) proposed significant changes in the conduct, the participant profile or the risks of the proposed research.

Further information regarding your ongoing obligations regarding human based research can be found via the Research Ethics website http://www.research.qut.edu.au/ethics/ or by contacting the Research Ethics Coordinator on 07 3138 2091 or ethicscontact@qut.edu.au

If any details within this Approval Certificate are incorrect please advise the Research Ethics Unit within 10 days of receipt of this certificate.

Project Details

Category of Approval: Administrative Review

Approved From: 14/05/2009 **Approved Until:** 14/05/2012 (subject to annual reports)

Approval Number: 0900000333

Project Title: An exercise intervention for women undergoing primary treatment for ovarian cancer: feasibility and preliminary outcomes

Chief Investigator: Ms Vanessa Beesley

Other Staff/Students: Dr Sandi Hayes , Dr Monika Janda , Ms Melissa Newton , Dr Andreas Obermair , Adjur Professor Elizabeth Eakin , Dr Penelope M Webb , Dr Louisa G Gordon , Dr Peter O'R Nicklin , Dr Lewis Perrin , Dr Alex Crandon

Experiment Summary:
Assess the feasibility of implementing, and potentially efficacy of a home-based walking intervention in ovarian cancer patients undergoing adjuvant chemotherapy.

Participant Details

Participants:
Group 1 = 50 Ovarian cancer patients (18+)

Location/s of the Work:
Royal Brisbane and Women's Hospital, Herston Mater Misericordiae Adult Hospital and Mater Private Hospital, South Brisbane The Wesley Hospital, Auchenflower Greenslopes Private Hospital, Spring Hill

University Human Research Ethics Committee

HUMAN ETHICS APPROVAL CERTIFICATE

NHMRC Registered Committee Number EC00171

Date of Issue: 18/5/09 (supersedes all previously issued certificates)

Conditions of Approval

Specific Conditions of Approval:
No special conditions placed on approval by the UHREC. Standard conditions apply.

Standard Conditions of Approval:
The University's standard conditions of approval require the research team to:

1. Conduct the project in accordance with University policy, NHMRC / AVCC guidelines and regulations, and the provisions of any relevant State / Territory or Commonwealth regulations or legislation;

2. Respond to the requests and instructions of the University Human Research Ethics Committee (UHREC);

3. Advise the Research Ethics Coordinator immediately if any complaints are made, or expressions of concern are raised, in relation to the project;

4. Suspend or modify the project if the risks to participants are found to be disproportionate to the benefits, and immediately advise the Research Ethics Coordinator of this action;

5. Stop any involvement of any participant if continuation of the research may be harmful to that person, and immediately advise the Research Ethics Coordinator of this action;

6. Advise the Research Ethics Coordinator of any unforeseen development or events that might affect the continued ethical acceptability of the project;

7. Report on the progress of the approved project at least annually, or at intervals determined by the Committee;

8. (Where the research is publicly or privately funded) publish the results of the project is such a way to permit scrutiny and contribute to public knowledge; and

9. Ensure that the results of the research are made available to the participants.

Modifying your Ethical Clearance:
Requests for variations must be made via submission of a Request for Variation to Existing Clearance Form (http://www.research.qut.edu.au/ethics/forms/hum/var/var.jsp) to the Research Ethics Coordinator. Minor changes will be assessed on a case by case basis.

It generally takes 7-14 days to process and notify the Chief Investigator of the outcome of a request for a variation.

Major changes, depending upon the nature of your request, may require submission of a new application.

Audits:
All active ethical clearances are subject to random audit by the UHREC, which will include the review of the signed consent forms for participants, whether any modifications / variations to the project have been approved, and the data storage arrangements.

End of Document

THE QUEENSLAND INSTITUTE OF MEDICAL RESEARCH HUMAN RESEARCH ETHICS COMMITTEE APPROVAL FORM[1] FOR EXPERIMENTS ON HUMANS

Chief Investigator:	Surname	Title	Initials
A	BEESLEY	DR	V
B	GREEN	PROF	A
C	GORDON	DR	L
D	WEBB	A/PROF	P
	O'ROURKE	PROF	P
Scientific Project Title:	An exercise intervention for women undergoing primary treatment for ovarian cancer: feasibility and preliminary outcomes		
Administration Institution:	**The Queensland Institute of Medical Research (QIMR)**		

Human Research Ethics Committee (HREC) Use

Does this Project comply with the provision contained in the NHMRC *National Statement On Ethical Conduct in Research Involving Humans*? (Yes) / No

Does this Project comply with the regulations governing experimentation on humans within your Institution and within your State or Territory? ? (Yes) / No

Comments, provisos or reservations: ***This Approval replaces all previous Approval/s.***

Provisos:

(1) This QIMR-HREC Approval is subject to ethical approval/s from all collaborating HREC/s.

(2) It is a condition of this Approval that written report must be submitted to the QIMR-HREC at least annually (including written advice on commencement and abandonment of project).

HRECMtg07Nov08: The following documents were noted and/or approved, with no concerns:

- 2008-10-22 11:55:27 *Exercise Physiologist assessment form Version 1 (draft)*
- 2008-10-22 11:53:51 *Participant information sheet Version 2 (draft).doc*
- 2008-10-07 09:30:39 *Clinical form (follow-up) Version 1 (draft)*
- 2008-10-06 15:21:48 *Questionnaire (follow-up) Version 1 (draft)*
- 2008-10-06 15:21:10 *Questionnaire (baseline) Version 1 (draft)*
- 2008-10-06 13:02:12 *Physical activity log Version 1 (draft)*
- 2008-10-06 12:57:20 *Consent forms (researcher's copies) – Version 1 (Draft)*
- 2008-10-06 11:17:49 *Clinical form (baseline) Version 1 (draft)*

Name of Responsible Human Research Ethics Committee and Reference No/s:

QIMR-Human Research Ethics Committee (QIMR-HREC) Approval Nos: P1222

Name of Human Research Ethics Committee Representative (Block letters):

Surname	Title	Initials
WILKEY	DR	IS

Signature: [signature]

Date: 7/11/08

[1]Note: This *Form* is based on, and slightly modified from "Form" used for the NHMRC Project Grant.

Please note that the investigators, noted for this project, are not members of the QIMR-HREC.

Royal Brisbane and Women's Hospital
Metro North Health Service District

Queensland Government

Office of the Human Research Ethics Committees

Queensland **Health**

Enquiries to: Odette Petersen Coordinator
Phone: 07 3636 5490
Fax: 07 3636 5849
Our Ref: HREC/08/QRBW/19
E-mail RBWH-Ethics@health.qld.gov.au

Professor Andreas Obermair
Queensland Centre for Gynaecological Cancer
Level 6, Ned Hanlon Building
Royal Brisbane & Women's Hospital
Herston Q 4029

Dear Professor Obermair,

Re: Ref Nº: HREC/08/QRBW/19: An exercise intervention for women undergoing primary treatment for ovarian cancer: feasibility and preliminary outcomes

Thank you for submitting the above project for ethical and scientific review. This project was considered at the Royal Brisbane & Women's Hospital Human Research Ethics Committee (HREC) meeting held on 8 December, 2008.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice.* Attached is the HREC Composition with specialty and affiliation with the Hospital *(Attachment I).*

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the District CEO or Delegate of that site has been obtained.

A copy of this approval will also be sent to the District Research Governance Office (RGO). Please ensure you submit a completed Site Specific Assessment (SSA) Form to the RGO for authorisation from the CEO or Delegate to conduct this research at the Royal Brisbane & Women's Hospital Metro North District.

I am pleased to advise that the Human Research Ethics Committee has granted approval of this research project on 3 April, 2009. HREC approval is valid for three (3) years from the date of this letter. The documents reviewed and approved include:

Document	*Version*	*Date*
Application	2.0	12 November 2008
Covering Letter		06 February 2009
Clinical Form (Baseline) Data sourced from patient chart	3	22 December 2008
Clinical Form (Baseline) Consent to Contact	3	22 December 2008
Physical Activity Log	1	06 October 2008
Budget		
QIMR approval		07 November 2008
NEAF signature pages		
Physical Activity Log "My Weekly Personal Exercise Tracker"	3	19 March 2009
Education Booklet "A Walking Intervention for Women Going Through Chemotherapy"	1	19 March 2009
Health Questionnaire	1	19 March 2009
Clinical Form (Follow-Up) Patient Follow-up	3	22 December 2008
Case Management Folder	1	02 February 2009
Exercise Physiologist Assessment Form Data Collection Form	2	02 February 2009
Protocol		
Questionnaire: Baseline Questionnaire	4	19 March 2009
Questionnaire: Follow-Up Questionnaire	3	22 January 2009
Response to Request for Further Information		
Response to Request for Further Information: Answers to HREC questions		24 March 2009
Response to Request for Further Information: Answers to HREC questions		
Response to Request for Further Information: Email - Partial response to HREC questions		17 February 2009
Patient Information Sheet/Consent Form	6	31 March 2009
Patient Information Sheet/Consent Form: Consent Form (Researcher's Copy)	4	11 March 2009
Patient Information Sheet/Consent Form: Revocation of Consent Form (Researcher's Copy)	4	11 March 2009

Please note the following conditions of approval:

1. The Principal Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including:
    - Unforeseen events that might affect continued ethical acceptability of the project. Serious Adverse Events must be notified to the Committee as soon as possible. In addition, the Investigator must provide a summary of the adverse events, in the

specified format, including a comment as to suspected causality and whether changes are required to the Patient Information and Consent Form. In the case of Serious Adverse Events occurring at the local site, a full report is required from the Principal Investigator, including duration of treatment and outcome of event.

2. Amendments which do not affect either the ethical acceptability or site acceptability of the project (e.g. typographical errors) should be submitted in hard copy to the HREC Coordinator. These should include a covering letter from the Principal Investigator providing a brief description of the changes and the rationale for the changes, and accompanied by all relevant updated documents with tracked changes.

3. Proposed amendments to the research project which may affect both the ethical acceptability and site suitability of the project must be submitted firstly to the HREC for review and, once HREC approval has been granted, then submitted to the Research Governance Office.

4. Amendments to the research project which only affect the ongoing site acceptability of the project are not required to be submitted to the HREC for review. These amendment requests should be submitted directly to the Research Governance Office (by-passing the HREC).

5. Amendments to the research project which may affect the ongoing ethical acceptability of a project must be submitted to the HREC for review. Major amendments should be reflected in a revised online NEAF (accompanied by all relevant updated documentation and a covering letter from the Principal Investigator, providing a brief description of the changes, the rationale for the changes, and their implications for the ongoing conduct of the study). Hard copies of the revised NEAF, the cover letter and all relevant updated documents with tracked changes must also be submitted to the HREC Coordinator as per standard HREC SOP. Further advice on submitting amendments is available from http://www.health.qld.gov.au/cpic/documents/ethics/researcher_userguide.pdf

6. The HREC will be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.

7. The Principal Investigator will provide an Annual Report to the HREC and at completion of the study in the specified format.

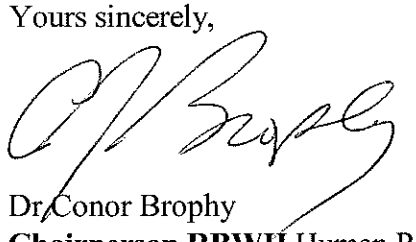
8. The District Administration and the Human Research Ethics Committee may inquire into the conduct of any research or purported research, whether approved or not and regardless of the source of funding, being conducted on Hospital premises or claiming any association with the Hospital, or which the Committee has approved if conducted outside Royal Brisbane & Women's Hospital Metro North Health Service District.

Should you have any queries about the HREC's consideration of your project please contact the HREC Coordinator on 07 3636 5490. The HREC terms of Reference, Standard Operating Procedures, membership and standard forms are available from http://www.health.qld.gov.au/cpic/ethics/reagu_homepage.asp

Once authorisation to conduct the research has been granted, please complete the Commencement Form *(Attachment II)* and return to the office of the Human Research Ethics Committee.

The HREC wishes you every success in your research.

Yours sincerely,



Dr Conor Brophy
Chairperson RBWH Human Research Ethics Committee
Metro North **DISTRICT**
03/04/2009

cc Dr Vanessa Beasley