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Physical activity and menopausal symptoms in women who have received menopause-inducing cancer treatments: Results from the Women's Wellness after Cancer Program

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Corresponding Author:	Tom G Bailey, Ph.D University of Queensland Brisbane, Queensland AUSTRALIA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Queensland
Corresponding Author's Secondary Institution:	
First Author:	Tom G Bailey, Ph.D
First Author Secondary Information:	
Order of Authors:	Tom G Bailey, Ph.D
	GREGORE I. MIELKE, PhD
	TINA S. SKINNER, PhD
	Debra Anderson, PhD
	Janine Porter-Steele, PhD
	Sarah Balaam, PhD
	Leonie Young
	Alexandra L McCarthy, PhD
Order of Authors Secondary Information:	
Manuscript Region of Origin:	AUSTRALIA
Abstract:	OBJECTIVE This randomised controlled trial tested a digitally-delivered whole-of-lifestyle program for women previously treated for cancer. We investigated 1) any association between self-reported physical activity (PA) and menopausal symptoms and 2) if the intervention was associated with beneficial changes in PA and menopausal symptoms. METHODS Women were randomised to intervention (n=175) or control (n=176). The intervention targeted lifestyle behaviours including physical activity. Self-reported PA (International Physical Activity Questionnaire – Short Form) and menopausal symptom (Green Climacteric Scale, GCS) data were collected at baseline, with measures repeated at 12 weeks (end of intervention) and 24 weeks (to assess sustainability). Generalised estimating equation models assessed associations between physical activity and GCS scores. Mixed-effects generalised equation models analysed changes within and between groups in PA and GCS scores.

	RESULTS Total GCS score was 1.83 (95%CI: -3.55 to -0.11) and 2.72 (95%CI: -4.33 to -1.12) lower in women with medium and high levels of PA, respectively, than in women with low levels of PA. Total average GCS scores were 1.02 (-2.26 to 0.21) and 1.61 (-2.87 to -0.34) lower in those undertaking moderate or vigorous intensity PA, respectively. Time spent walking, and performing moderate and vigorous PA were not different between intervention and control. The average GCS decrease of 0.66 points (95%CI: -1.29 to -0.03; p time =0.039) was not different between groups. CONCLUSION We established a stepwise association between moderate and vigorous PA and lower menopausal symptoms. The intervention did not increase self-reported PA in women treated for early stage breast, reproductive and blood cancers.

Physical activity and menopausal symptoms in women who have received menopause-inducing cancer treatments: Results from the Women's Wellness after Cancer Program

TOM G. BAILEY[1,2]
GREGORE I. MIELKE[2]
TINA S. SKINNER[2]
DEBRA ANDERSON[3]
JANINE POSTER-STEELE[4]
SARAH BALAAM[1]
LEONIE YOUNG[4]
ALEXANDRA L. MCCARTHY[1,5]

[1]*School of Nursing, Midwifery and Social Work,* The University of Queensland, Brisbane, Australia.

[2]*Centre for Research on Exercise, Physical Activity and Health, School of Human Movement and Nutrition Sciences,* The University of Queensland, Brisbane, Australia.

[3]*University of Technology Sydney, New South Wales, Australia*

[4] *Choices Cancer Support Program*, Wesley Hospital, Brisbane, Queensland, Australia

[5]*Mater Research Institute*, Brisbane, Australia

SHORT TITLE: Menopausal symptoms and physical activity after cancer

CONFLICT OF INTEREST: None

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FIGURES: 2 **TABLES:** 4

AUTHOR FOR CORRESPONDENCE (REPRINTS UNAVAILABLE):

*Dr Tom Bailey, School of Nursing Midwifery and Social Work, The University of Queensland

Email: Tom.Bailey@uq.edu.au

Abstract

OBJECTIVE: This randomised controlled trial tested a digitally-delivered whole-of-lifestyle program for women previously treated for cancer. We investigated 1) any association between self-reported physical activity (PA) and menopausal symptoms and 2) if the intervention was associated with beneficial changes in PA and menopausal symptoms.

METHODS: Women were randomised to intervention (n=175) or control (n=176). The intervention targeted lifestyle behaviours including physical activity. Self-reported PA (International Physical Activity Questionnaire – Short Form) and menopausal symptom (Green Climacteric Scale, GCS) data were collected at baseline, with measures repeated at 12 weeks (end of intervention) and 24 weeks (to assess sustainability). Generalised estimating equation models assessed associations between physical activity and GCS scores. Mixed-effects generalised equation models analysed changes within and between groups in PA and GCS scores.

RESULTS: Total GCS score was 1.83 (95%CI: -3.55 to -0.11) and 2.72 (95%CI: -4.33 to -1.12) lower in women with medium and high levels of PA, respectively, than in women with low levels of PA. Total average GCS scores were 1.02 (-2.26 to 0.21) and 1.61 (-2.87 to -0.34) lower in those undertaking moderate or vigorous intensity PA, respectively. Time spent walking, and performing moderate and vigorous PA were not different between intervention and control. The average GCS decrease of 0.66 points (95%CI: -1.29 to -0.03; p_{time}=0.039) was not different between groups.

CONCLUSION: We established a stepwise association between moderate and vigorous PA and lower menopausal symptoms. The intervention did not increase self-reported PA in women treated for early stage breast, reproductive and blood cancers.

KEY WORDS: Breast cancer, exercise, lifestyle, women's health, post-menopausal

Introduction

Ovarian dysfunction is a common symptom in the large number of women treated for breast, reproductive and blood cancers. Breast cancer is the most common cancer in women worldwide, with over two million new cases in 2018 [1]. In Australia alone, a further 6,454 developed reproductive cancers[2] and 5,286 were diagnosed with blood cancers[3] such as leukaemia, lymphoma and multiple myeloma. Women often report that menopausal symptoms arising from treatment-induced ovarian failure as a distressing side effect that is ongoing long after they resume their usual work and social roles[4].

Menopausal symptoms arise when radiotherapy to the pelvic field, surgical removal or systemic chemotherapy damage the ovaries, initiating ovarian failure. In women who were pre- or peri-menopausal prior to treatment, cancer therapies result in a sudden and sometimes irreversible menopause, the symptoms of which can be far more frequent and severe than in natural menopause[4]. In women who are post-menopausal at the time of treatment, extant vasomotor symptoms can be amplified by the endocrine therapies (e.g. tamoxifen and aromatase inhibitors) commonly prescribed for women with breast cancer[5].

Physical activity is an adjuvant non-hormone therapy that may influence menopausal symptoms and wellbeing in women treated for cancer[6]. Severe menopausal symptoms, including poor mental wellbeing, are associated with a sedentary lifestyle and low physical activity in healthy women who undergo natural menopause[7,8]. Recently we found that women treated for breast cancer who experience worse menopausal symptoms, including vasomotor symptoms, are less likely to engage in health-promoting behaviours[9]. Observational data[10] also suggest that menopausal symptoms are less severe in people with cancer who state they undertake physical activity following treatment. Importantly, whilst higher levels of physical activity have been associated with reduced menopausal symptoms in heathy older women[11], the potential influence of the components of physical activity (e.g. volume and intensity) on the relationship between menopausal symptoms and physical activity has not been investigated.

Targeted interventions that improve health behaviours and increase physical activity could improve menopausal symptoms in women following cancer treatment. For example, in a pilot randomised controlled trial of women with a history of breast cancer treatment (N=53), our group showed that a lifestyle program incorporating a behavioural component aimed at enhancing health-related quality of life elicited clinically significant improvements in menopausal symptoms, including somatic and vasomotor symptoms and sexual function[12].

In this paper we report data from the Women's Wellness after Cancer Program (WWACP) randomised controlled trial[13]. The WWACP trial tested a whole-of-lifestyle program for women previously treated for early stage breast, reproductive and blood cancers. The WWACP promoted evidence-based adoption of a range of lifestyle factors implicated in the development of chronic conditions after treatment in this group. Targeted lifestyle behaviours in the program included physical activity, nutrition, sleep hygiene, stress management, smoking cessation and alcohol minimisation. In women previously treated for early stage breast, blood and reproductive cancers, we aimed to investigate the association between self-reported physical activity levels and menopausal symptoms and if the WWACP intervention was associated with beneficial changes in physical activity and menopausal symptoms. We hypothesised that there would be a strong association between menopausal symptoms and physical activity in women following cancer

treatment, and that greater volume and intensity of physical activity as encouraged in the WWACP would reduce menopausal symptoms experienced by women treated for cancer.

Methods

The dataset presented in this paper was collected as part of the multi-centre, single-blinded, randomised controlled 12-week WWACP[13]. A detailed description of the design, participant eligibility and outcome measures has previously been reported[13].

Participants and study design

Three-hundred and fifty-one women treated for early stage breast, gynaecological or blood cancer within the previous 24 months were enrolled and randomly allocated to intervention (n=175) and control (n=176) groups. Women were recruited by clinicians from five hospitals (public and private); through the Wesley Hospital Choices Cancer Support Centre; and through newsletters, emails and websites of two consumer groups (the National Breast Cancer Foundations' Register4, and the Breast Cancer Network of Australia).

Intervention and control

The WWACP intervention encouraged participants to systematically incorporate a healthy lifestyle (e.g. adherence to international dietary and physical activity guidelines[14], sleep hygiene and stress modification) into daily life for 12 weeks. The intervention was delivered through a combination of a hard copy and digitally-delivered program book, internet interaction and three 'face-to-face' virtual consultations with an experienced cancer care nurse. The virtual consultations, which were undertaken via Skype, FaceTime or phone, were critical to the physical activity component. One consultation was undertaken at baseline to assess participants' physical activity needs and tailor a physical activity program. A mid-intervention consultation was scheduled with participants in Week 6 to review physical activity goals, capabilities and techniques, and modified physical activity as necessary. The third consultation took place at Week 12 (end of intervention), in which physical activity frequency was reviewed, along with participants' goals for physical activity beyond the intervention period. Informal exchanges by phone and email with trained cancer care nurses also took place as the need arose.

The physical activity components of the intervention were delivered through a hard copy book and digitally-delivered program based on the WCRF/AICR recommendations[14] and were approached from a whole-of-lifestyle perspective. The physical activity component of the intervention was introduced in Week 1. In this introduction, the benefits of physical activity were explored along with the types of activity needed to enhance wellbeing and reduce sedentary practices that could compromise health after cancer treatment. Four days of Week 2 explored physical activity in more detail, in the context of participants' busy lifestyles. Interactive content explored balance, core and pelvic floor issues; stretching and flexibility; strength training; and exercises without equipment. At the end of Week 2 and all subsequent weeks, participants were encouraged to reflect on what they had achieved with their physical activity to that point, and the new goals they would like to set for themselves in ensuing weeks of the program. From this point, participants were encouraged to engage in daily diarising of physical activity so that they could track whether this was consistent with recommended guidelines and their own personal goals. Week 4 was designated "Healthy Weight Week", in which participants explored and practised physical activity and nutrition with healthy body composition in mind. Week 5 incorporated six days of physical activity content, introducing exercise with dumbbells, resistance bands and equipment available in fitness centres. Weeks 6 to 8 incorporated content about the role of physical activity in conjunction with diet in preventing lifestyle disease after treatment such as diabetes, osteoporosis and cardiovascular disease. Week 9

focused on the preventing cancer recurrence with a healthy lifestyle. Week 10 comprised a review of the participants' physical activity practices to determine if any changes had been made and where further change might be needed. Weeks 11 and 12 examined motivation strategies to enhance self-efficacy and sustain beneficial practices. Extra evidence updates relating to physical activity were posted on the study website as new evidence became available.

The usual care group received no specific or individual advice, consistent with usual practice. General health information during their clinic visits about the management of all symptoms with physical activity might be provided if the clinician was aware of this. Control participants were offered a hard copy of the WWACP book upon completion of the trial (Week 24), with all content that was provided multi-modally offered to them in print form.

Measures

Data were collected at baseline, Week 12 (end of intervention) and Week 24 (to assess sustainability).

Physical activity was measured with the short version of the International Physical Activity Questionnaire (IPAQ-SF)[15]. Comprising six items, the IPAQ-SF was used to determine the number of days and time spent in the previous week a) walking, b) at moderate-intensity, and c) at vigorous-intensity physical activity, within four domains (occupational, household, leisure-time and transportation). Activities that lasted for at least 10 consecutive minutes were reported.

Total minutes per week spent in each category was calculated by multiplying physical activity frequency and time. Time per week spent in each category was multiplied by a metabolic equivalent task (MET; with one MET representing the energy cost at rest) value according to standard procedures (3.33 MET for walking; 4.0 MET for moderate activity, and 8.0 MET for vigorous activity). MET.minutes per week were summed, with participants' activity categorized as low (0-599 MET.minutes/week); medium (600–1199 MET.minutes/week); or high (1200^{+} MET.minutes per week). The proportion of participants reporting moderate and vigorous-intensity physical activity bouts of at least 10 minutes in duration was also determined. Women were deemed 'active' if they attained the recommended physical activity guidelines of 150 minutes of moderate-intensity or 75 minutes of vigorous physical activity per week[16].

Menopausal symptoms were measured with the Greene Climacteric Scale (GCS)[17]. This 21-item scale assesses the common self-reported vasomotor, somatic and psychological symptoms (anxiety and depression) associated with menopause, as well as sexual function. The total GCS score is the sum of all 21 scores, with a maximum possible of 63. The higher the total score indicates severity of menopausal symptoms. The GCS has good psychometric properties in different cultural and health contexts when used with women experiencing menopause, and is recommended in this particular research context by Cancer Australia[18].

Statistical analysis

Statistical analyses were undertaken with Stata 16 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX). Means, standard deviations and proportions provide the baseline characteristics of the sample. To compare baseline characteristics between the intervention and the control groups, Fisher's exact test for categorical data and the student's t-test for continuous data were used. To explore the two research questions, analyses were conducted in two steps. First, generalised estimating equation (GEE) models were used to assess associations between self-reported physical activity and GCS scores and to account for the clustering of repeat measures

within individuals. Random effect models were used to calculate the average difference with respective 95% confidence intervals in the GCS scores between participants with low, medium and high levels of physical activity. In addition, random effect models were also used to assess the association between reporting at least 10 minutes per week of moderate and vigorous-intensity physical activities with GCS scores. All analyses were adjusted for age, marital status, income, education, smoking, body mass index and menopausal status[19]. Given the exploratory aim of this study, regression coefficients and respective 95% confidence intervals were used to assess the statistical plausibility of the associations.

Second, we investigated the effects of the intervention on physical activity levels and menopausal symptoms. For this, mixed-effects generalised equation models were used to analyse changes within and between groups in physical activity and GCS scores. The models included fixed terms for group and time, with a random intercept for each participant.

Results

At baseline, 278 (79%) participants reported their physical activities (140 intervention; 138 control). Most participants were treated for breast cancer (Table 1). At baseline, there were no differences between groups in age, education, BMI, smoking and menopausal status ($p>0.1$ for all comparisons). Further, ~80% of participants in the intervention and control groups were post-menopausal on diagnosis.

Association between physical activity and menopausal symptoms

The crude and adjusted associations between levels of physical activity and GCS scores are presented in Table 2. The average total GCS score at baseline was 16.0 (SD: 7.6). Overall, physical activity was inversely associated with total GCS scores in the crude and adjusted analyses. In the adjusted analyses, the total GCS score was -1.83 (95%CI: -3.55 to -0.11) and -2.72 (95%CI: -4.33 to -1.12) lower in women with medium and high levels of physical activity, respectively, than in women with low levels of physical activity. Overall, physical activity was also associated with better specific domains of the GCS. With the exception of vasomotor symptoms, women with high levels of physical activity had lower scores for each menopausal domain than women who completed less than 600 MET.minutes per week.

Table 3 shows the association between menopausal symptoms and women reporting that that they undertook moderate or vigorous physical activity each week. Total average GCS scores were -1.02 (-2.26 to 0.21) and -1.61 (-2.87 to -0.34) lower in those undertaking moderate or vigorous intensity physical activity, respectively. These observations in Table 2 and 3 remained when adjusted for potential cofounders. To confirm the robustness of these findings and account for time-invariant characteristics, fixed effect models were used. The changes in GCS scores that were associated with changes in physical activity categories observed in Table 2 and 3 remained following fixed effect analyses (see supplementary, Table 1).

WWACP intervention outcomes

Physical activity

At baseline, ~75% of the cohort were deemed active based on current physical activity guidelines (≥ 600 MET.minutes/week)[20]. Overall, most of the women reported that they were highly active, regardless of group and time point. Physical activity levels (low, medium and high) at each time point are presented in Figure 1. At baseline, the median MET.minutes per week was 1,336 (25^{th}-75^{th}: 740-2,146) in the intervention group and 1,163 (25^{th}-75^{th}: 520-2,338) in the control group. Indeed, 58% of the women in the intervention and 48% of women in the control group reported more than 1200 MET.minutes per week of physical activity (Figure 1 and Table 4). These proportions

increased to 67% in the intervention and 52% in the control group after 24 weeks (T2). Overall, there were no effects of group (OR 1.51; 95%CI: 0.55-4.12; p=0.426), time (OR: 1.16; 95%CI: 0.86-1.56; p=0.339) or interactions between group and time (OR: 1.18; 95%CI: 0.77-1.80; 0.447) when mixed-effects ordered logistic regression models were used.

Time spent undertaking each physical activity intensity (walking, moderate and vigorous) are presented in Figure 2. Time spent walking, and at moderate and vigorous intensity activity was not different between intervention and control, nor did time spent in each intensity significantly change at 12 and 24 weeks. Specifically, there was a small trend for an increase in time spent undertaking vigorous activity in both groups, however this was not significant (time-effect [β: 6.7 (95%CI: -5.3; 18.8); p=0.274] and highly variable (Figure 2; time x group effect [β: 4.4 (95%CI: -12.5; 21.2); p=0.610]).

Menopausal symptoms

Overall, there was an improvement in menopausal symptom scores over time in the intervention group, with an average decrease of 0.66 points (95%CI: -1.29 to -0.03; p_{time}=0.039) in overall GCS score each 12 weeks over the study period (Table 4). The decrease in total GCS score was maintained in the intervention group at 24 weeks compared to control, however this was not significant (Table 4). There were no significant interactions for the overall GCS score or menopausal sub-domains. Specifically, women in both groups reported an improvement in psychological symptoms at 12 and 24 weeks, with negligible changes in somatic, vasomotor and sexual function scores across the study period.

Discussion

The first aim of this study was to establish whether there is an association between physical activity and menopausal symptoms in women treated with menopause-inducing cancer treatments. Overall, undertaking moderate and vigorous intensity physical activity was associated with fewer menopausal symptoms, albeit not vasomotor symptoms, than women who engaged in low intensity physical activity. Secondly, the WWACP intervention did not increase physical activity in women following cancer treatment.

Similar to observations in healthy postmenopausal women[7,8], we observed a clear association between physical activity and overall menopausal symptom severity in women after cancer treatment. There is a large body of research outlining the benefits of physical activity for mental health. It was recently shown that women who report higher levels of physical activity have fewer depressive symptoms associated with menopause [8]. Our results support this. We previously showed that physical activity was a predictor of depressive symptoms in natural menopause, but not treatment-induced menopause after breast cancer[9]. A possible explanation for the clear association between physical activity and menopausal symptoms in this study is the addition of physical activity intensity, as well as volume, into the analysis. This study shows a dose-response association for vigorous and moderate physical activity and overall menopausal symptoms. Our findings also support the benefits of moderate and vigorous physical activity for reducing depressive symptoms in women following cancer treatment.

We did not observe an association between higher physical activity levels and reduced vasomotor symptoms in women following cancer treatment. Instead, supervised and tailored exercise training that targets cardiovascular fitness could be of most benefit in women for alleviation of menopausal symptoms. In a pilot trial in healthy post-menopausal women, supervised and individually tailored exercise training which improved physiological determinants of vasomotor symptoms, including temperature regulation and cardiovascular fitness, alleviated menopausal symptoms[21,22]. As recently highlighted[6], the *type* of physical activity could also be an important issue for investigating the association between physical activity and menopausal vasomotor symptoms[23]. For example, a systematic review and meta-analysis showed that yoga reduced menopausal and vasomotor symptoms[23,24]; whereas evidence for the benefits of aerobic exercise or resistance training on vasomotor symptoms remains inconclusive[25]. Future longitudinal trials should utilise objective measures of physical activity that enable analysis of the frequency, intensity, type and duration of physical activity undertaken. Only then will the modifiable factors associated with reduced menopausal symptoms in postmenopausal women, including those who have undergone cancer treatment, be understood.

Physical activity also reduces the risk of other treatment-related chronic conditions, mortality and cancer recurrence in breast cancer survivors[26]. Recent data indicate that greater physical activity in women with breast cancer improves prognosis, especially for women who were insufficiently active at diagnosis[27,28]. Hence the second aim of this study was to investigate if the WWACP intervention increased physical activity levels and reduced menopausal symptoms in women following cancer treatment. In this sample, self-reported physical activity levels were mostly unchanged by the intervention. This is possibly because of self-selection bias in the sample, given that at baseline both groups were quite active already. In both the intervention and control groups, there was a small trend for a higher proportion of high physical activity (Figure 1) at Week 12 which was sustained at

Week 24. While these changes were not statistically significant, intervention participants engaged in more intense physical activity than controls at all time-points. Overall, there was a small improvement in menopausal symptom scores in the intervention group at 12 weeks, with the decrease in total GCS score maintained in the intervention group after 24 weeks. Recently a positive relationship between cardiorespiratory fitness ($\dot{V}O_{2max}$) and menopausal symptoms was reported in healthy postmenopausal women[29], however the effects in cancer survivors is unknown. Previous studies have also shown that exercise training that directly improves cardiorespiratory fitness reduces menopausal symptoms[22,30]. It is possible that future trials aimed at improving cardiorespiratory fitness by increasing moderate to vigorous physical activity could alleviate menopausal symptoms in women cancer survivors.

While the perceived and actual benefits of physical activity after cancer treatment are well acknowledged[31-33], enhancing and maintaining physical activity in this cohort is an ongoing challenge. Cancer patients generally express a preference for supervised exercise explicitly tailored to their needs like the WWACP, rather than home-based, more generic physical activity programs[34]. A meta-analyses also indicates that closely supervised exercise programs are superior to unsupervised programs in enabling exercise adherence and sustainability in cancer populations[35]. However, the less supervised format of the WWACP was developed in response to women's explicit concerns about distance to exercise facilities, transport, parking costs and time, which they viewed as substantial obstacles to participation in closely-supervised exercise[36,37]. Although the WWACP was developed as a convenient and cost-effective solution to these concerns, the results indicate that more regular supervision of physical activity both during and beyond future programs is warranted. However, it is also seldom feasible for women to continue under the regular care of an exercise physiologist indefinitely without government-supported initiatives. Exercise self-efficacy is therefore critical to the safe and successful transition of women from supervised to unsupervised exercise, and key to the long-term maintenance of healthy lifestyle change following cancer treatment[38].

Limitations and strengths

Self-reported physical activity as described by the IPAQ-SF has limitations. It has been shown that the instrument results in overestimations of physical activities across all intensities and underestimates physical inactivity in cancer survivors at baseline[39]. In this respect, in this cohort only 20-28% of women reported that they did not engage in moderate or high physical activity. This might indicate self-selection bias to the study in this cohort of women; however a previous lifestyle RCT found no self-election bias in those recruited through a registry compared with self-referal[40]. This could further result in biased estimates of effect sizes, which would underestimate the magnitude of the associations between physical activity and GCS scores. Although we adjusted our analyses for potential confounders of the associations between physical activity and GCS, residual confounding could partially explain the associations. However, we observed that the crude and adjusted analyses produced similar magnitude of associations, which suggests that the associations between physical activity and GCS are unlikely to be explained by confounding factors that were measured in our study. In the WWACP program we were not able to record adherence and engagement with specific components, including physical activity. Future iterations should closely monitor and record engagement and adherence to each aspect of the WWACP.

Conclusions

Climacteric symptoms are common and distressing in women previously treated for cancer, although services do not routinely offer post-treatment support. We established a clear stepwise association between moderate and vigorous physical activity levels and less symptoms of menopause in this group. Our 12-week WWACP intervention did not significantly increase physical

activity levels compared to control. Future iterations of the WWACP will utilise closely supervised and prescribed exercise training to target menopausal symptoms and build exercise self-efficacy for longer-term maintenance in women following cancer treatment.

Ethics and trial registration

The protocol for this study is registered with the Australian and New Zealand Clinical Trials Registry (anzctr.org.au Trial ID: ACTRN12614000800628, July 28, 2014). This study was approved by Queensland University of Technology Human Research Ethics Committee (Approval No: 1300000335) in July 2013. The study is also approved by the local ethics committees of all participating hospitals and health services (Peter MacCallum Cancer Centre, Metro South Hospital and Health Service, Royal Prince Alfred Hospital, St John of God Murdoch Hospital) and by the University of Notre Dame.

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Table and Figure Legend

Table 1. Characteristics of intervention and control participants.

Table 2. Linear regression model of climacteric symptoms in women with cancer reporting low, moderate and high physical activity domains

Table 3. Linear regression model of climacteric symptoms in women with cancer answering yes/no to undertaking moderate and vigorous physical activity domains

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Figure 2. Box plot of time (min per week) spent undertaking each physical activity intensity (walking, moderate and vigorous) over 24 weeks in the intervention and control groups. Walk: time x group effect [β: 1.5 (95%CI: -31.8; 34.8); p=0.930]. Moderate: time x group effect [β: 10.0 (95%CI: -16.0; 36.0); p=0.450]. Vigorous: time x group effect [β: 4.4 (95%CI: -12.5; 21.2); p=0.610].

Table 1. Characteristics of intervention and control participants.

Variable	Intervention N=140 n (%)	Control N=138 n (%)	P-value
Age (years)			0.132
< 40	13 (7.5)	4 (2.3)	
40-50	49 (28.3)	50 (28.6)	
50-60	66 (38.2)	77 (44.0)	
60+	45 (26.0)	44 (25.1)	
Marital status			0.845
Married or de facto	133 (77.3)	133 (76.4)	
Separated/widowed/single	39 (22.7)	41 (23.6)	
Education			0.715
≤ Year 10	13 (7.6)	18 (10.3)	
Year 12	17 (9.9)	20 (11.5)	
Technical / Diploma	42 (24.4)	37 (21.3)	
University / Postgraduate	100 (58.1)	99 (56.9)	
Income			0.693
< $60,000	30 (17.5)	24 (13.8)	
$60,000 - $120,000	72 (42.1)	81 (46.6)	
> $120,000	62 (36.3)	60 (34.5)	
Don’t know/missing	7 (4.1)	9 (5.2)	
Smoking status			0.197
Never	116 (66.7)	119 (68.0)	
Past	54 (31.0)	46 (26.3)	
Current	4 (2.3)	10 (5.7)	
Body Mass Index (kg/m^2)			0.876
Normal	51 (35.6)	51 (38.1)	
Overweight	52 (36.4)	45 (33.6)	
Obese	40 (28.0)	38 (28.4)	
Menopausal Status			0.792
Premenopausal	13 (7.5)	10 (5.9)	
Perimenopausal	24 (13.8)	22 (12.9)	
Postmenopausal	137 (78.7)	139 (81.3)	

Table 2. Linear regression model of climacteric symptoms in women with cancer reporting low, moderate and high physical activity domains

Outcome	Random effect model	
	β_{crude} (95% CI)	$\beta_{adjusted}$ (95% CI) [a]
GCS Total		
Low	*Ref*	*Ref*
Moderate	-1.15 (-2.58; 0.29)	-1.83 (-3.55; -0.11)
High	-2.14 (-3.51; -0.77)	-2.72 (-4.33; -1.12)
Psychological		
Low	*Ref*	*Ref*
Moderate	-0.41 (-1.20; 0.39)	-0.63 (-1.58; 0.32)
High	-1.23 (-2.00; -0.47)	-1.31 (-2.22; -0.41)
Somatic		
Low	*Ref*	*Ref*
Moderate	-0.70 (-1.24; -0.17)	-0.80 (-1.42; -0.18)
High	-0.88 (-1.40; -0.36)	-0.96 (-1.54; -0.37)
Vasomotor		
Low	*Ref*	*Ref*
Moderate	0.16 (-0.14; 0.46)	0.19 (-0.18; 0.55)
High	0.14 (-0.15; 0.43)	0.16 (-0.19; 0.50)
Sexual		
Low	*Ref*	*Ref*
Moderate	-0.06 (-0.24; 0.13)	-0.13 (-0.35; 0.09)
High	-0.14 (-0.31; 0.04)	-0.22 (-0.43; -0.02)

Green Climacteric Scale (GCS). Low (<600 MET.min/week); moderate (600-1199 MET.minutes/week); High (1200+ MET.minutes/week).

[a]Adjusted for age, marital status, education, income, smoking status, body mass index and menopausal status

Table 3. Linear regression model of climacteric symptoms in women with cancer answering yes/no to undertaking moderate and vigorous physical activity domains

Outcome	Random effect model	
	β_{crude} (95% CI)	$\beta_{adjusted}$ (95% CI) [a]
GCS Total		
Moderate	-1.06 (-2.07; -0.06)	-1.02 (-2.26; 0.21)
Vigorous	-1.33 (-2.38; -0.27)	-1.61 (-2.87; -0.34)
Psychological domain		
Moderate	-0.82 (-1.38; -0.25)	-0.83 (-1.52; -0.13)
Vigorous	-0.95 (-1.54; -0.36)	-1.20 (-1.92; -0.48)
Somatic domain		
Moderate	-0.15 (-0.53; 0.24)	-0.09 (-0.54; 0.36)
Vigorous	-0.25 (-0.66; 0.17)	-0.10 (-0.58; 0.37)
Vasomotor domain		
Moderate	-0.12 (-0.34; 0.09)	-0.05 (-0.32; 0.22)
Vigorous	-0.12 (-0.35; 0.11)	-0.15 (-0.42; 0.13)
Sexual function domain		
Moderate	-0.11 (-0.24; 0.02)	-0.14 (-0.30; 0.02)
Vigorous	-0.02 (-0.16; 0.11)	-0.06 (-0.23; 0.10)

Green Climacteric Scale (GCS).

[a] Adjusted for age, marital status, education, income, smoking status, body mass index and menopausal status

Table 4. Descriptive statistics for IPAQ-SF and GCS scores at baseline, 12 and 24 weeks between the intervention and control groups. IPAQ-SF data are displayed as median (IQR) and GCS data are displayed as mean (SD) unless otherwise stated.

Variable	**Intervention**			**Control**			**Beta value**	**P Value**
Time-point	Baseline	Week 12	Week 24	Baseline	Week 12	Week 24		
Physical activity								
n	33	50	53	38	52	63		
MET-min/week	1336 (740-2146)	1520 (839-2638	1563 (960-2797)	1163 (520-2338)	1361 (500-3056)	1399 (620-2509)	-97.6	0.337
Green Climacteric Scale								
Psychological symptoms	8.0 (4.8)	6.9 (4.4)	6.7 (4.5)	8.0 (4.9)	7.2 (4.9)	7.5 (5.1)	0.1	0.725
Somatic symptoms	4.1 (3.0)	3.5 (3.0)	3.6 (3.1)	4.7 (3.3)	4.1 (3.2)	4.5 (3.4)	0.2	0.234
Vasomotor symptoms	2.4 (1.7)	2.1 (1.7)	2.3 (1.7)	2.6 (2.0)	2.3 (1.8)	2.4 (1.9)	0.0	0.922
Sexual function	1.4 (1.0)	1.4 (1.0)	1.4 (1.0)	1.5 (1.0)	1.3 (1.0)	1.5 (1.0)	0.0	0.589
Overall GCS score	15.7 (7.3)	13.9 (7.6)	13.9 (7.5)	16.4 (8.0)	14.7 (8.0)	15.9 (9.1)	0.3	0.517

P value represents group x time interaction. Green Climacteric Scale (GCS). Metabolic equivalent (MET).

Figure 1

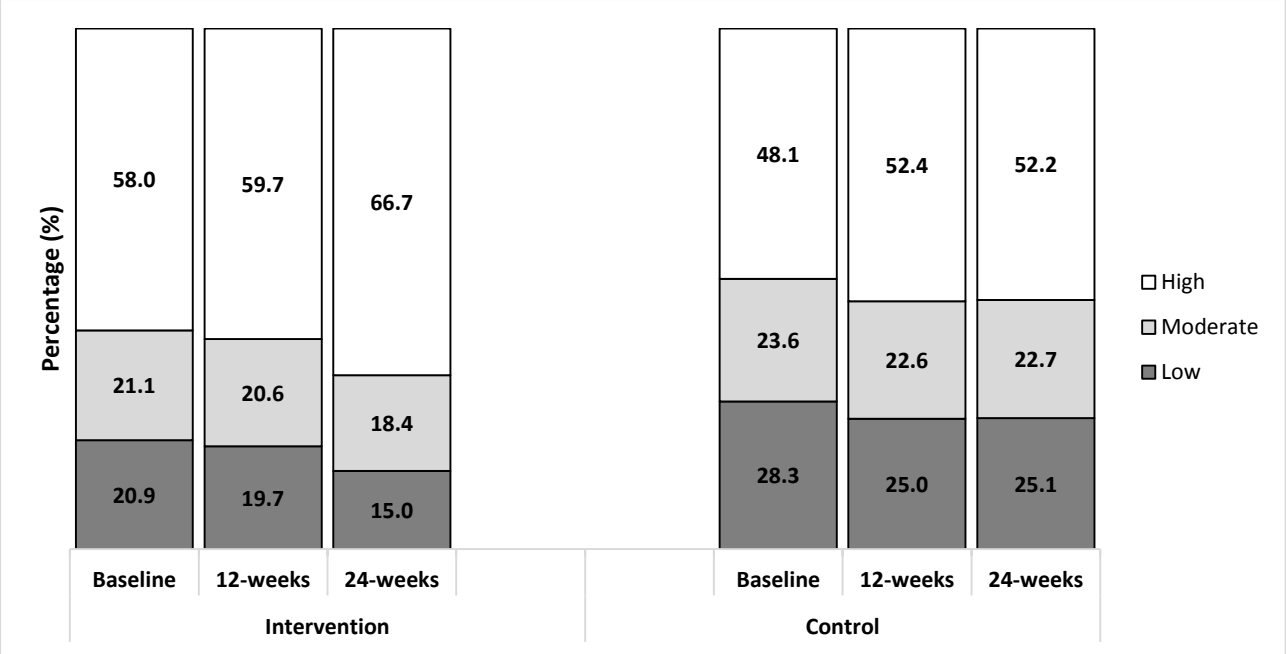

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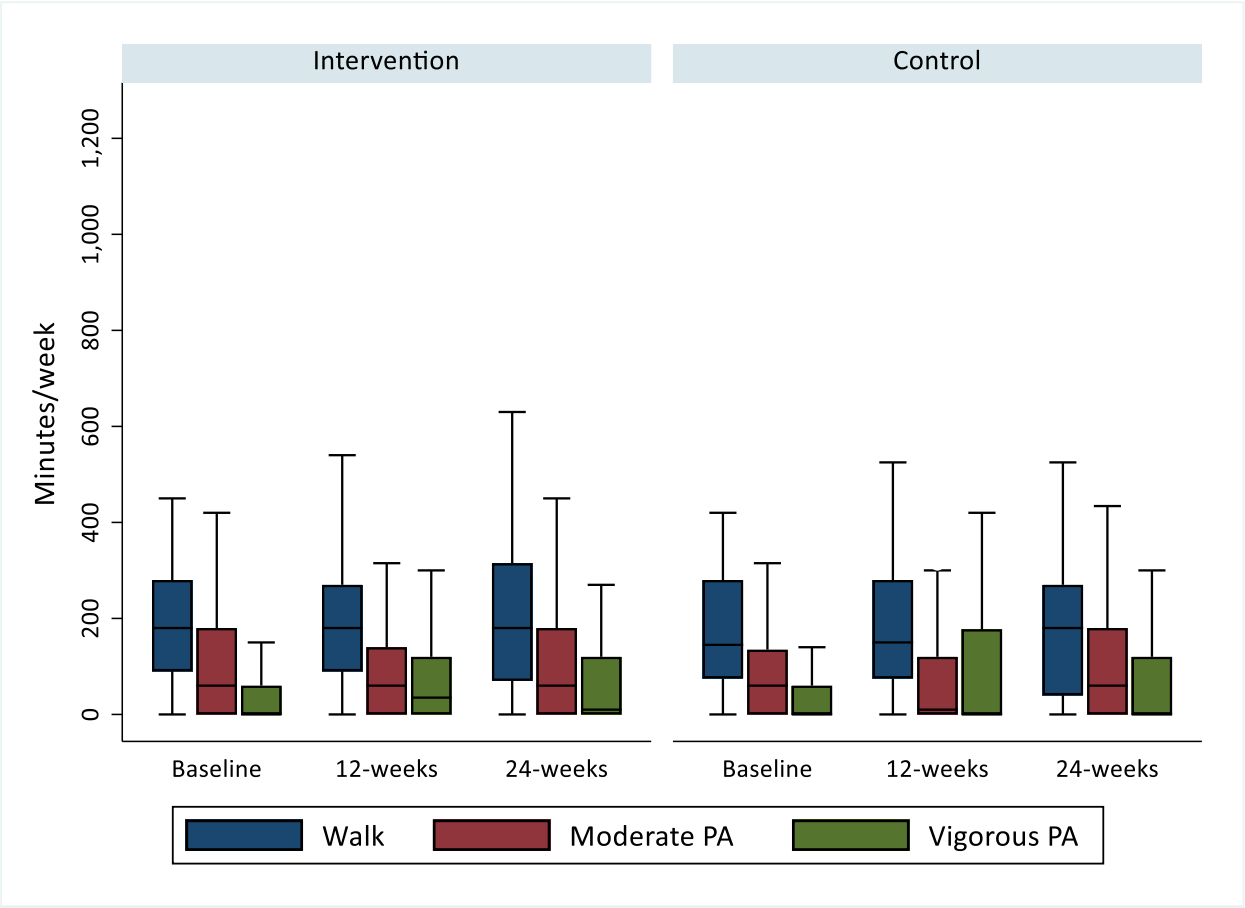
Figure 2



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