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Effect Of Exercise Vs. Attention-Control On Depression Symptomatology In Ovarian Cancer Survivors: The Women's Activity And Lifestyle Study In Connecticut (walc)

Meghan B. Hughes
Yale University, meghan.hughes@yale.edu

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Meghan Hughes

Masters of Public Health Candidate

Division of Social and Behavioral Sciences

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ABSTRACT

Background: With no effective screening tool, ovarian cancer survivors often suffer from unpleasant treatment-related side effects that influence quality of life. Increased physical activity has been associated with lower depression scores in ovarian cancer survivors. However, to date, no randomized controlled trial assessing the effect of exercise on depression has been conducted in this population. The Women's Activity and Lifestyle Study in Connecticut (WALC) was a randomized trial examining the impact of exercise vs. attention-control on quality of life, body composition, and cancer biomarkers in ovarian cancer survivors. This analysis examined the effect of exercise on depression scores.

Methods: We enrolled 144 physically inactive (< 90 minutes per week of exercise) ovarian cancer survivors who had been diagnosed within the past 4 years and completed initial chemotherapy into a six-month randomized controlled trial. Women randomized to the exercise intervention arm (n = 74) received 25 weekly phone calls from a certified cancer exercise trainer and were counseled on increasing their physical activity to 150 minutes per week of home-based aerobic exercise. Women randomized to the attention-control arm (n = 70) also received 25 weekly phone calls to discuss relevant health topics. Depression symptomatology was measured via the Center for Epidemiologic Studies Depression Scale (CES-D) at baseline and six-months. Student's t-test and generalized linear models were used to compare changes in depression from baseline to six-months between the two arms.

Results: All baseline characteristics were similar between the two arms. Adherence to both the exercise intervention and attendance to the weekly calls was outstanding with women on the exercise intervention arm exercising an average of 166 minutes per week and >70% of women on both arms attending $\geq$ 20 calls. At baseline 39 women (27%) had a CES-D score greater than 16, indicating depressive symptomatology. CES-D scores decreased in women on the exercise intervention arm by an average of 2.2 ± 7.0 points (17% decrease) compared to an increase of 0.4 ± 5.6 points (4% increase) in women randomized to the attention-control arm ($p = 0.02$). A dose-response inverse relation of exercise with CES-D score was also observed ($p < 0.01$).

Conclusions: Ovarian cancer survivors are interested in and able to exercise at recommended levels, with exercise decreasing CES-D scores. Exercise above and beyond the attention participants received helped improve depression symptomatology. Exercise programs for ovarian cancer survivors should be implemented in an effort to improve depressive symptoms.

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Meghan Hughes, BSc[1], Brenda Cartmel, PhD[1,3], Yang Zhou, PhD[3], Linda Gottlieb, MA, CPT, CET[1], Elizabeth Ercolano, PhD[2], Harvey A. Risch, MD, PhD[1,3], Maura Harrigan, MS, RD, CSO[1],
Ruth McCorkle, PhD[2,3], Melinda L. Irwin, PhD, MPH[1,3]

Author affiliations:

[1] Yale School of Public Health, New Haven, CT

[2] Yale School of Nursing, New Haven, CT

[3] Yale Cancer Center, New Haven, CT

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INTRODUCTION

In the United States ovarian cancer is the leading cause of death for cancers of the female reproductive system and the fifth leading cause of cancer-related death in women with over 21,000 incident cases and 14,000 deaths due to ovarian cancer every year [1, 2]. There have been some biomedical advances with respect to developing effective therapies that increase length of survival, however, no effective screening test exists for early detection resulting in 61% of cases being detected at a distant stage (stage III/IV) [2]. This causes the standard treatment to be extremely invasive surgery (removal of ovaries, fallopian tubes, uterus, and omentum) and chemotherapy [2]. Such physically demanding treatment can have a dramatic impact on an individual's overall well-being and mental health both during and following treatment with frequent reports of cancer-related fatigue, peripheral neuropathy, and psychological distress [3]. Moreover, the high likelihood of recurrence (five-year survival ranges from 27% for distant cancer to 92% for localized cancer) associated with the aggressiveness of the cancer causes survivors to constantly address physical and psychological morbidities, resulting in negative health related effects such as increased depression and anxiety [2-6].

Depression is one of the most prevalent mental disorders throughout the world, projected to be the second-leading cause of disease burden by 2030 [7-9]. Prior research indicates that depression rates tend to be higher among cancer survivors than compared to the general population, with up to 50% of cancer patients having symptomatology that meets the criteria for a clinical diagnosis [10-12]. Furthermore, depressive symptoms can have detrimental effects on quality of life, motivation, and physical functioning in cancer patients and survivors [10, 13]. Additionally, anxiety and depression rates tend to be higher in ovarian cancer patients as compared to cohorts of other cancers [4, 14].

Due to the physical and mental benefits of exercise, a growing number of studies have examined the associations between physical activity and improved cancer outcomes, particularly cancer-related fatigue and health-related quality of life [15]. Small intervention and cross-sectional studies have shown that exercise and education can improve quality of life in cancer patients and can help increase overall survival [16-19]. In observational and cross-sectional studies, exercise has been associated with better symptoms, well-being, and lower depression scores among individuals on treatment for ovarian and other cancers [20-22]. Cross-sectional research supports that meeting physical activity recommendations is associated with better sleep, psychosocial function, health-related quality of life, and lower self-reported depression, anxiety, and cancer-related fatigue among ovarian cancer survivors [3, 18, 23].

While exercise has been shown to result in positive health outcomes, no large-scale randomized-controlled trial assessing the effect of exercise on depression in ovarian cancer survivors has been conducted. The Women's Activity and Lifestyle Study in Connecticut (WALC) study was a randomized trial examining the impact of exercise vs. attention-control on quality of life, body composition, and cancer biomarkers. The purpose of this analysis was to examine the effect of exercise on depression symptomatology in ovarian cancer survivors participating in WALC. As overall well-being and quality of life are compromised in ovarian cancer patients, we hypothesize that exercise may play an important role for improving depressive symptomatology among ovarian cancer survivors.

METHODS [15]

Study Population

Women with ovarian cancer diagnosed at Connecticut based hospitals were identified and if eligible, invited to participate in the study. Additionally eligible women throughout the US who self-referred for the study were recruited. Participants were randomized between March 9, 2010 and March 20, 2014. Women found to be eligible after screening and baseline assessments were randomized to a six-month home-based aerobic exercise intervention or an attention-control arm. We enrolled 144 women into the WALC study.

Study Sites

There were three study sites where in-person visits and physical exams were performed. All Connecticut based patients were seen at the Smilow Cancer Hospital at Yale New Haven (WALC-CT). Women were also seen at the Dana Farber Cancer Institute (WALC-DF) and Geisinger Health Systems (WALC-G). Additionally, a subset of the study population (self-referred individuals) completed the study remotely and never came to a study site (WALC-N).

Recruitment and Study Visits

The Rapid Case Ascertainment Shared Resource of the Yale Cancer Center (RCA), a field arm of the Connecticut Tumor Registry, was used to identify women with an ovarian cancer diagnosis from all Connecticut-based hospitals. After obtaining physician consent to contact their patient(s), a study recruitment letter was mailed to each woman. Within a week of mailing, each woman was telephoned to assess interest and determine eligibility. Women that were English speaking, physically inactive (< 90 minutes per week of exercise), between the ages of 18-75, diagnosed with ovarian cancer between January 2007 and May 2013, had completed chemotherapy at least one-month prior to randomization, and had physician consent to start an exercise program met eligibility criteria.

Participants considered to be eligible through the initial screening communication were asked to come to their respective study site for a baseline visit. At this visit the women completed questionnaires on demographics, clinical characteristics and medical history, health-related quality of life (including CES-D), physical activity, and they underwent a physical exam (height/weight). Upon completion of this visit, women were randomized to a six-month home-based aerobic exercise intervention program or an attention-control health-education program. Questionnaires and study measurements were also completed at the six-month study visit, with the quality of life assessment also conducted by mail at 3-months.

Additionally, women from throughout the US (WALC-N) who inquired about the study upon learning about it through support groups, interested physicians, or survivor blogs were screened for eligibility and if eligible invited to participate in the study. For these participants, all baseline and follow up assessments were conducted by mail or over the telephone.

The Connecticut Department of Public Health, the Yale Human Investigation Committee, and all associated hospital institutional review boards approved this study.

Measures

At the baseline and six-month study visits, participants completed several questionnaires. The self-reported socio-demographic indicator variables ascertained at baseline included current age, race/ethnicity, education level, employment status, and marital status. Additionally, we collected information on the participant's family history of ovarian cancer, cancer stage, time since diagnosis, history of chemotherapy treatment, recurrence, and depression. Physical activity within the previous six months was assessed using the Modifiable Physical Activity Questionnaire, which ascertained the duration and frequency of participation for 20 recreational activities [24]. Height and weight were measured using standard procedures (weight in light clothing and without shoes was measured using an electronic scale with measurements rounded up to the nearest 0.1 kg and height without shoes was measured using a stadiometer with measurements rounded up to the nearest 0.5 cm). The participant's treating physician verified the reported treatment information through an additional mailed questionnaire.

The main study outcome was depression symptomatology assessed using the 20-item Center for Epidemiological Studies Depression Scale (CES-D), a screening tool recommended by the U.S. Preventive Services Task Force [25, 26]. This measure has been used in populations with diverse socioeconomic and demographic characteristics and has been recognized as a valid and reliable measure of depressive symptomatology with good internal consistency, high alpha coefficients, and adequate test-retest reliability among cancer patients [26-29]. Using a Likert scale from 0 (never or rarely) to 3 (most of the time or all of the time) with reverse coding of the four items that assess positive symptoms, the tool measures symptoms within the past week. Summed scores range from 0-60 whereby higher scores represent increased levels of depressive symptomology. Using the established and validated criteria, participants were classified as being above or below the cutoff for significant depression symptomatology (summed scores $\geq$ 16 or < 16 respectively) [27, 30].

Interventions

The six-month exercise intervention consisted of a home-based moderate-intensity aerobic exercise program facilitated by weekly phone calls from an American College of Sports Medicine certified cancer exercise trainer and health educator. Women were counseled on increasing their physical activity to 150 minutes per week of moderate-intensity aerobic exercise. Adherence was primarily measured using Daily Activity Logs where women self-recorded the type, duration, and intensity (based on heart rate monitors) of exercise. Women also reported their levels of exercise during the weekly telephone calls with the trainer. Using a 26-chapter book developed for the study, the trainer was able to provide weekly counseling and support over the telephone, discuss various educational topics on exercise, and review a weekly ovarian cancer health-education topic to increase participant exercise levels. The attention-control health-education arm also received weekly phone calls from the certified cancer exercise trainer during which the ovarian cancer health-education topics were discussed.

Statistical Analysis

Descriptive statistics were used to describe the study population based on socio-demographic and clinically relevant indicators according to study randomization. Generalized linear models (GLM) comparing the women randomized to the exercise intervention arm and women randomized to the attention-control arm were used to analyze the impact of physical activity on depressive symptomology. Our analysis was performed using the intent-to-treat principle in order to assess significant differences in CES-D score between the baseline and six-month study visits. For those women who did not complete the six-month assessment of depressive symptomatology, the change in CES-D was imputed as 0. Potential covariates included baseline CES-D score, cancer stage, age, time since diagnosis, history of recurrence prior to enrollment, and recurrence of cancer during the study period.

To explore the effect of the amount of exercise on depressive symptomatology, a sub-group analysis among women randomized to the exercise intervention arm was performed. We examined the impact of exercise dose on depressive symptomatology by comparing the women who self-reported participating in an average of at least the recommended 150 minutes of exercise per week and those that did not. Among all participants, we examined the impact of attendance to the weekly telephone calls on depressive symptomatology. Lastly, we performed a stratified analysis to evaluate effect modification by depressive symptomatology at baseline, cancer stage, age, cancer recurrence prior to enrollment and during the study period, attendance to weekly telephone calls, and exercise adherence. All statistical analysis was conducted using SAS, Version 9.3 (SAS, Cary, NC) with a two-sided 0.05 significance level.

RESULTS

Study Population

A total of 767 ovarian cancer survivors were identified within Connecticut between February 2010 and September 2013 (Figure 1). However, 83 women were found to be ineligible. Each survivor's physician was contacted for consent to contact and consent to exercise. Of the remaining 684 patients, recruitment invitation letters were mailed to 545 women (80%) for whom we had received consent. Out of these women, 461 were screened by telephone. An additional 49 women self-referred or were recruited by physicians, resulting in a total of 510 women who completed screening. Of these women, 235 were ineligible and 131 were not interested, which resulted in 144 women being randomized to the study (exercise intervention arm n = 74; attention-control arm n = 70). The majority (66%) of the study population was seen at the Yale site (n = 95). Approximately 5% and 6% of the study came from Dana Farber Cancer Institute (n = 7) and Geisinger Health Systems (n = 8), respectively. The remaining 24% of the study population were self-referred (n = 34) (Table 1).

Baseline Characteristics

On average, participants at enrollment were 57.3 ± 8.6 years old, 1.7 ± 1.0 years post-diagnosis, had a BMI of 29.0 ± 7.0 kg/m^2, and exercised for 28.3 ± 41.6 minutes per week. The majority of the study population were non-Hispanic white (98%), married or living with a partner (73%), had graduated college or had an advanced degree (56%), were diagnosed with stage III/IV disease (55%), and had received chemotherapy prior to enrollment (93%) (Table 1). At enrollment, 39 women (27%) had experienced clinically significant depressive symptomology within the past week based on a CES-D score $\geq$ 16. Of these women, only 21 (54%) also had a self-reported history of depression. The average baseline CES-D score was 12.7 ± 10.5 on the exercise intervention arm, 10.8 ± 9.8 on the attention-control arm, and ranged from 0-47 ($p = 0.27$) (Table 3). All characteristics were similar for both arms ($p > 0.05$).

Adherence to the Intervention

Adherence to both the exercise intervention and attendance to the weekly calls was outstanding (Table 2). For women on the exercise intervention arm, Daily Activity and Call Logs were used to monitor weekly progress towards the weekly exercise goal (150 minutes). During the six-month intervention, women participated in an average of 166.0 ± 66.1 minutes per week (111% of the goal) and 65% were able to exercise at least 150 minutes per week. Furthermore, over 70% of women on both arms attended $\geq$ 20 calls (exercise intervention arm = 80%; attention-control arm = 74%).

Change in Depression Symptomatology

Table 3 shows the baseline CES-D score, the change in CES-D score over the six-month intervention period, and the number of individuals with depressive symptomology based on CES-D. There was no significant difference between the two arms with respect to baseline CES-D scores ($p = 0.27$). Over the 6-month intervention period, a 17% decrease and a 4% increase in scores were observed among women randomized to the exercise intervention arm and attention-control arm, respectively. This represents a statistically significant difference between the arms with respect to the change in CES-D score ($p = 0.02$). There were no significant differences observed between the two arms with respect to the number of women who experienced depressive symptomatology within the past week at baseline (exercise intervention arm = 31%; attention-control arm = 23%; $p = 0.27$) or at six-months (exercise intervention arm = 17%; attention-control arm = 15%; $p = 0.85$). Of the 18 women with a clinically significant CES-D (score $\geq$ 16) at the six-month follow-up, 11 also had a clinically significant CES-D at baseline (exercise intervention arm n = 7; attention-control arm n = 4). Of these 11 individuals, six had a decrease in score (exercise intervention arm n = 5; attention-control arm n = 1). Thirty-two women (22%) did not complete the six-month CES-D questionnaire. The majority (63%) of these individuals did not have a clinically significant CES-D score at baseline (10 women from each study arm). Of the remaining 12 non-compliers who had a clinically significant CES-D score at baseline, only four were randomized to the exercise intervention arm. No statistically significant difference between the arms with respect to non-compliance was observed ($p = 0.36$).

Stratified Analysis

Table 4 highlights the results of the stratified analysis examining the change in CES-D. After adjusting for site, baseline CES-D score, and randomization arm, women who adhered to the exercise intervention goal of 150 minutes per week experienced a highly statistically significant 3.4 point decrease in CES-D score ($p < 0.01$). In comparison, women who reported exercising < 150 minutes per week experienced a 0.7 point decrease in CES-D score and this change was not statistically significant ($p = 0.93$). Looking at the women with early-stage (I/II) diagnoses, women on the exercise intervention arm experienced a borderline significant greater decrease in CES-D as compared to women on the attention-control arm ($p = 0.06$). Additionally, for the women who did not have a recurrence prior to enrollment, women on the exercise intervention arm experienced a significantly greater decrease in CES-D as compared to women on the attention-control arm ($p = 0.03$). Similarly, although statistically insignificant, women on the exercise intervention arm who had a recurrence during the six-month study period also experienced a greater decrease in CES-D score as compared to women on the attention-control arm ($p = 0.21$). Finally, after adjusting for study site and randomization arm, individuals on the exercise intervention arm with baseline CES-D scores $\geq$ 16 experienced a greater decrease in CES-D score as compared to those individuals on the attention-control arm, however, this was not statistically significant ($p = 0.12$). Although we conducted stratified analyses to evaluate effect modification by baseline CES-D score, disease stage, age, recurrence status (both prior to enrollment and during the study period), exercise adherence, and attendance at weekly telephone calls, no significant interactions were observed.

DISCUSSION

We found that a moderate-intensity home-based aerobic exercise program improved depressive symptomatology indicated by a reduction in mean CES-D scores in ovarian cancer survivors. A dose-response inverse relation of exercise with CES-D score was observed, with increased exercise ($\geq$ 150 minutes per week) being associated with more robust decreases in CES-D. Similar positive associations between physical activity and health-related quality of life or depression have been shown through cross-sectional and prospective studies conducted in the general population and among people with depression [9, 31, 32]. Additionally, a systematic review of randomized and controlled clinical trials found that physical exercise during and after cancer treatment has positive effects on psychological well-being and overall quality of life [33]. Furthermore, as seen in this study, greater amounts of physical activity are generally associated with an increased reduction of depression symptoms [34].

While exercise is considered to be an effective antidepressant, the exact mechanism of action is unknown [35, 36]. However, it could relate to various physiologic or psychosocial mechanisms. For example, the monoamine hypothesis states that exercise increases the availability of neurotransmitters that are usually diminished among depressed individuals (e.g. serotonin, dopamine, and norepinephrine) [37]. While these neurotransmitters have been shown to increase peripherally, it is unclear whether neurotransmitter levels increase in the brain [37]. Alternatively, exercise could decrease depressive symptomatology by providing a means for social support. However, as both study arms received support and counseling over the phone, the decreased rates of depressive symptomatology among women on the exercise intervention arm could be due to exercise reducing levels of fatigue making the completion of daily activities easier. Regardless of the mechanism, meta-analytic studies have shown that the effect size of exercise on depression is large (ranging from -0.72 to -1.4) and is equally effective for men and women of various ages and with varying depression levels [35]. As a final caveat, prior research has found that home-based, unsupervised exercise is associated with increased depressive symptoms [35]. Although we were able to see a reduction in depressive symptomatology using a home-based exercise regime, future studies should assess if larger effects can be seen through supervised exercise programs.

Given the population-based recruitment, randomized design with an attention-control arm, large sample size, and six-month intervention period, to our knowledge this is the strongest methodological study that examines the role of exercise in women who have been diagnosed with ovarian cancer. A potential weakness in our design was the reliance on self-report for physical activity and depressive symptomatology rather than using more objective measures (i.e. accelerometers for physical activity or a clinical evaluation for depression). However, recall and responder bias are likely minimized due to the prospective design, daily recording of exercise for those women randomized to the exercise intervention arm, and weekly follow-up calls with the exercise trainer/health educator.

Despite the fact that all women who enrolled had completed treatment, 16% of the study population had experienced a recurrence prior to enrollment and 24% of the study population experienced a recurrence during the six-month study. This, in conjunction with approximately 55% of the study population being diagnosed with distant (stage III/IV) disease, emphasizes the aggressiveness of the cancer. Looking specifically at CES-D, baseline scores in our study population were comparable to the CES-D scores seen in other cancer-patient populations of similar age but tended to be higher than those scores previously reported among healthy-comparison groups [4, 29]. A convenience sample of outpatient epithelial ovarian cancer patients found the mean CES-D score to be 10.2 [4]. Additionally, women scheduled to undergo radiotherapy, chemotherapy, or bone marrow transplantation (BMT) for breast cancer had an average CES-D score of 10.9 (prior to treatment initiation) and an average CES-D score of 12.8 (while on treatment) [29]. In comparison, the mean CES-D score for the healthy comparison group (women with similar demographic characteristics) that was used in the aforementioned breast cancer study was approximately 8 at both time-points [29]. Furthermore, a greater proportion of women in our study had CES-D scores above the clinical threshold warranting a full clinical evaluation as compared to those typically seen in the general population [26, 38]. In our study, 27% of participants at baseline met the CES-D cutoff criteria for a clinical evaluation for depression (CES-D scores $\geq$ 16). This is consistent with what was observed in the convenience sample of epithelial ovarian cancer patients whereby 21% of participants met the cutoff criteria [4]. However, prior estimates using CES-D within the general population have shown the prevalence of depression to be around 15-16% [38].

Even though we consider our study's sample size to be a strength, our study was not powered for stratified analyses. However, the current trends highlight that exercise rather than the attention-control was more effective in reducing CES-D scores among women who were diagnosed with either localized (stage I/II) or distant cancer (stage III/IV) or had a recurrence during the study. Additionally, given that exercise also appears to reduce CES-D scores among women of any age and among those with a clinically significant CES-D at baseline, the use of exercise has many clinical implications.

To summarize, depressive symptoms in this patient population is a concern that has been defined but rarely addressed. Our results indicate that not only is a six-month home-based exercise intervention in ovarian cancer survivors feasible but it is also able to improve depressive symptomatology as measured by CES-D. While women randomized to the exercise intervention arm had an overall decrease in CES-D score, the effect was much stronger among those women who met the weekly exercise goal (150 minutes per week). The limited exclusion criteria and the population-based cohort allowed us to capture a comprehensive sample of inactive ovarian cancer survivors, making the results generalizable to the larger population of ovarian cancer survivors. Furthermore, the nature of the intervention (home-based, moderate-intensity, aerobic exercise program) enables this type of exercise program to be easily adapted and disseminated. Thus, our findings can be used to inform future studies or programs dedicated to improving the lives of ovarian cancer survivors.

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FIGURE 1: Flow of Participants Through the WALC Study

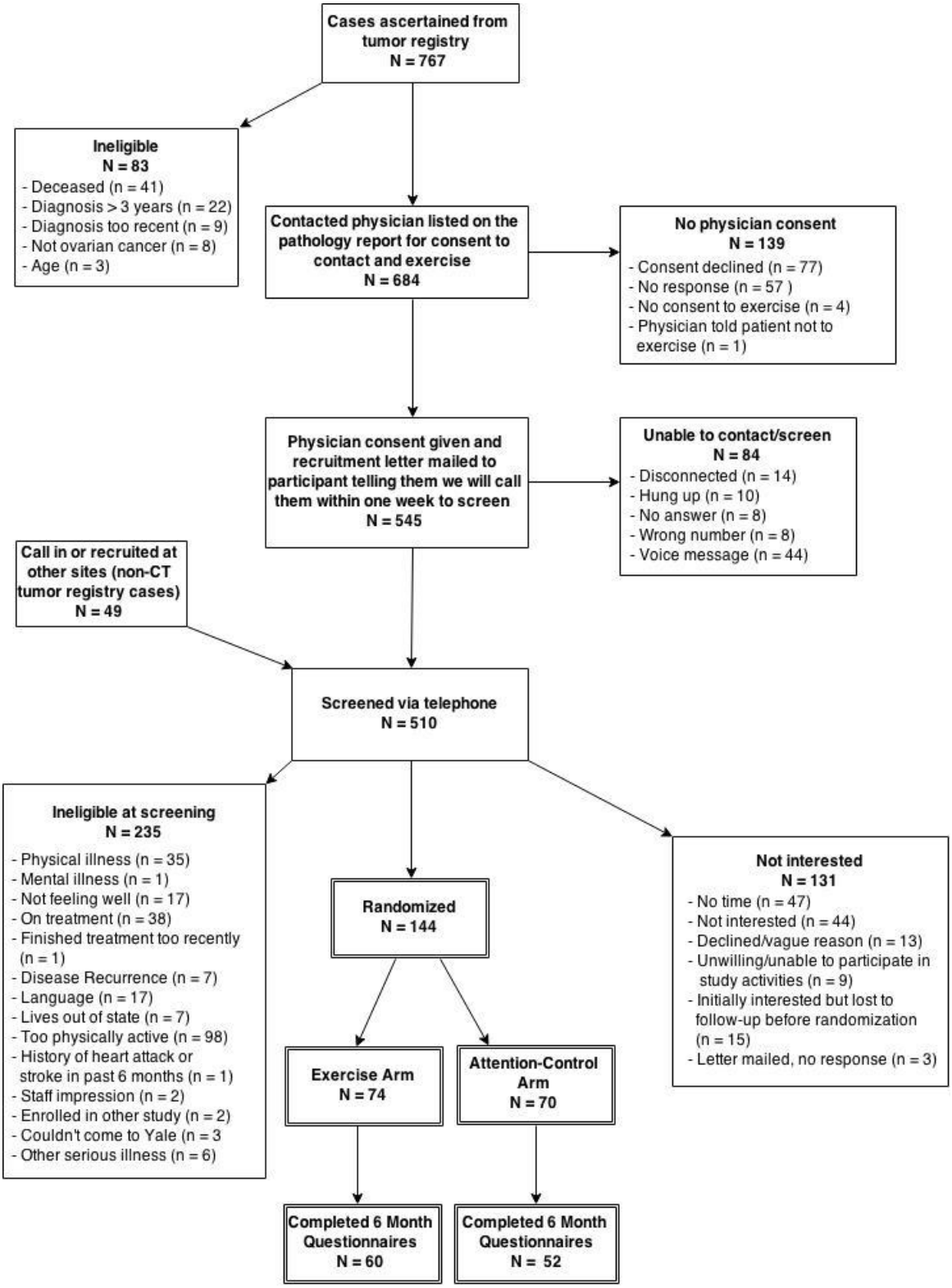

TABLE 1: Description of the Sample at Baseline by Study Arm[a]

Characteristic	Total Study Population (N = 144)[b]	Study Arm		p[c]
		Exercise Intervention (N = 74)[b]	Attention Control (N = 70)[b]	
Study Site				0.94
WALC-CT	95 (66.0)	50 (67.6)	45 (64.3)	
WALC-N	34 (23.6)	16 (21.6)	18 (25.7)	
WALC-G	8 (5.6)	4 (5.4)	4 (5.7)	
WALC-DF	7 (4.9)	4 (5.4)	3 (4.3)	
Age (years)	57.3 ± 8.6	57.3 ± 8.8	57.4 ± 8.5	0.91
Race/ethnicity				0.07
Non-Hispanic white	141 (97.9)	74 (100.0)	67 (95.7)	
Other	3 (2.1)	0 (0.0)	3 (4.3)	
Education Level				0.60
No GED or Equivalent	4 (2.8)	3 (4.1)	1 (1.4)	
GED and Some College/Associates	60 (41.7)	32 (43.2)	28 (40.0)	
College Graduate or Advanced Degree	80 (55.6)	39 (52.7)	41 (58.6)	
Employment Status				0.46
Unemployed/Retired	69 (48.3)	34 (46.0)	35 (50.7)	
Employed Part Time (<35 hrs/wk)	29 (20.3)	18 (24.3)	11 (15.9)	
Employed Full Time (>35 hrs/wk)	45 (31.5)	22 (29.7)	23 (33.3)	
Marital Status				0.24
Single	15 (10.4)	8 (10.8)	7 (10.0)	
Divorced, Separated, or Widowed	24 (16.7)	16 (21.6)	8 (11.4)	
Married or Living with Partner	105 (72.9)	50 (67.6)	55 (78.6)	
Family History of Ovarian Cancer				0.41
Yes	18 (12.7)	11 (14.9)	7 (10.3)	
No	124 (87.3)	63 (85.1)	61 (89.7)	
Cancer Stage at Diagnosis				0.26
Stage I	34 (23.6)	21 (28.4)	13 (18.6)	
Stage II	30 (20.8)	11 (14.9)	19 (27.1)	
Stage III	58 (40.3)	31 (41.9)	27 (38.6)	
Stage IV	21 (14.6)	10 (13.5)	11 (15.7)	
Unknown	1 (0.70)	1 (1.4)	0 (0.0)	
Time Since Diagnosis (years)	1.7 ± 1.0	1.7 ± 0.9	1.7 ± 1.1	0.72
Chemotherapy Prior to Enrollment				0.93
Yes	134 (93.1)	69 (93.2)	65 (92.9)	
No	10 (6.9)	5 (6.8)	5 (7.1)	
Cancer Recurrence Prior to Enrollment				0.59
Yes	23 (16.0)	13 (17.6)	10 (14.3)	
No/Unknown	121 (84.0)	61 (82.4)	60 (85.7)	
Body mass index (kg/m^2)	29.0 ± 7.0	29.0 ± 7.2	29.1 ± 6.8	0.91
Physical Activity (min/wk)	28.3 ± 41.6	26.0 ± 44.2	30.8 ± 38.9	0.50
Self-Reported History of Depression				0.86
Yes	38 (26.4)	20 (27.0)	18 (25.7)	
No	106 (73.6)	54 (73.0)	52 (74.3)	

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables.
[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.
[c] P-value is for t-test (continuous variables), χ^2 test (categorical variables), or Fisher's exact test (cell counts <5).

TABLE 2: Adherence to Intervention[a]

Adherence to Exercise	Exercise Intervention Arm (N = 74)	Attention Control Arm (N = 70)	
Average Minutes/Week of Exercise	166.0 ± 66.1	N/A	
% of Goal (150 Min/Wk)	110.7%	N/A	
% Participants Adhering to			
≥ 150 Min/week (100%)	64.9%	N/A	
≥ 120 Min/week (80%)	83.8%	N/A	
≥ 90 Min/ week (60%)	91.9%	N/A	
≥ 60 Min/ week (40%)	91.9%	N/A	
≥ 30 Min/ week (20%)	98.6%	N/A	
< 30 Min/ week (0%)	100.0%	N/A	
Attendance to Calls	**Exercise Intervention Arm (N = 74)**	**Attention Control Arm (N = 70)**	**P[b]**
Average Attendance to Calls	21.7 ± 5.5	20.4 ± 5.6	0.18
% of Goal (25 Calls)	86.7%	81.7%	
% Participants Adhering to			
25 Calls (100%)	47.3%	19.1%	
≥ 20 calls (80%)	79.7%	73.5%	
≥ 15 calls (60%)	89.2%	86.8%	
≥ 10 calls (40%)	94.6%	94.1%	
≥ 5 calls (20%)	98.6%	97.1%	
≥ 0 calls (0%)	100.0%	100.0%	

[a] Table values are mean ± SD for average values and proportions for adherence between Baseline and 6 Months.
[b] P-value is for t-test (continuous variables)

TABLE 3: Depression Symptomatology by Arm[a]

Characteristic	Study Arm: Exercise Intervention (N = 74)[b]	Study Arm: Attention Control (N = 70)[b]	p[c]
Baseline CES-D Score (Range: 0-60)	12.7 ± 10.5	10.8 ± 9.8	0.27
Range	(0 – 47)	(0 – 45)	
Unadjusted Change in CES-D Score	-2.2 ± 7.0	0.4 ± 5.8	0.02
% Change	-17.3	3.7	
Baseline Depression Symptomatology			0.27
CES-D $\geq$ 16	23 (31.1)	16 (22.9)	
CES-D < 16	51 (68.9)	54 (77.1)	
Six-Month Depression Symptomatology			0.85
CES-D $\geq$ 16	10 (16.7)	8 (15.4)	
CES-D < 16	50 (83.3)	44 (84.6)	

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables.
[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.
[c] P-value is for t-test (continuous variables) or χ^2 test (categorical variables).

TABLE 4: Change in CES-D Stratified by Study Variables[a]

	Change in CES-D Exercise Intervention LSMEAN (SE)	Change in CES-D Attention Control LSMEAN (SE)	p	$p_{interaction}$
BL Depression Symptomatology[b]				
CES-D < 16 (n = 105)	0.2 (0.7)	1.5 (0.6)	0.18	0.57
CES-D ≥ 16 (n = 39)	-7.6 (1.7)	-3.4 (2.0)	0.12	
Cancer Stage[c]				
Stage I/II (n = 64)	-3.0 (1.2)	0.2 (1.2)	0.06	0.22
Stage III/IV (n = 79)	-1.3 (0.9)	0.2 (0.9)	0.26	
Age				
< 57 years (n = 69)	-2.2 (1.0)	-0.1 (1.1)	0.19	0.92
≥ 57 years (n = 75)	-1.4 (0.9)	-0.0 (0.9)	0.29	
Recurrence Prior to Enrollment[c]				
Yes (n = 23)	-0.9 (1.5)	-1.5 (1.7)	0.79	0.35
No (n = 121)	-2.1 (0.8)	0.3 (0.8)	0.03	
Recurrence on Study[c]				
Yes (n = 34)	-1.0 (1.5)	1.4 (1.1)	0.21	0.88
No (n = 110)	- 2.2 (0.8)	-0.4 (0.9)	0.11	
Call Attendance[c]				
< 20 Calls (n = 33)	-1.5 (0.9)	0.3 (0.8)	0.17	0.86
≥ 20 Calls (n = 109)	-2.2 (0.8)	-0.1 (0.9)	0.10	
Exercise Adherence[c]				
< 150 min/wk (n = 26)	-0.7 (0.9)	N/A	0.93	N/A
≥ 150 min/wk (n = 48)	-3.4 (0.8)	N/A	< 0.01	

[a] Numbers are Change in CES-D using least-square mean (SE)
[b] Model controls for study arm and study site
[c] Model controls for study arm, baseline depression CES-D score, and study site