Impact Of A 6-Month Exercise Intervention On Cognitive Function Among Ovarian Cancer Survivors: The Women’s Activity And Lifestyle Study In Connecticut (walc)

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Impact of a 6-Month Exercise Intervention on Cognitive Function Among Ovarian Cancer Survivors:
The Women’s Activity and Lifestyle Study in Connecticut (WALC)

BY
Jonica Y. Kao

A thesis submitted in fulfillment of the requirements for the degree of

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CHRONIC DISEASE EPIDEMIOLOGY

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Committee Member: Melinda L. Irwin, Ph.D, MPH
Impact of a 6-Month Exercise Intervention on Cognitive Function Among Ovarian Cancer Survivors: The Women’s Activity and Lifestyle Study in Connecticut (WALC)

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ABSTRACT

Purpose: Cancer survivors often exhibit symptoms of impaired cognitive abilities after chemotherapy treatment. Physical activity has been shown to be promising in improving cognitive function among survivors for various types of cancer. However, very few studies have addressed this concern among the ovarian cancer patient population specifically.

Methods: The study randomized 111 physically-inactive ovarian cancer survivors into a 6-month exercise intervention (n=59) or an attention-control group (n=52). The FACT-Cog scale was self-reported to understand survivor perceptions of cognitive abilities at baseline and at 6 months. Generalized linear models (GLMs) were executed to examine the effect of the intervention versus attention-control on change in cognitive function.

Results: The 6-month change in perceived cognitive impairments (CogPCI) and perceived cognitive abilities (CogPCA) was significantly different between the two treatment groups. For CogPCI, there was a 1.9% improvement in women randomized to exercise and a 2.7% reduction in women randomized to attention-control (p=0.025). For CogPCA, there was a 4.2% improvement in the exercise group and a 8.9% reduction in the attention control group (p<0.001). Among women ≥ 57 years, those randomized to the intervention had increased CogPCI (p=0.008) and CogPCA (p=0.013) compared with those in the control. Among women < 57 years, those in the exercise group had increased CogPCA compared to the control (p=0.038).

Conclusion: A 6-month home-based exercise program led to improved cognitive function among women treated for ovarian cancer. These findings serve to inform more discussions about the role of physician activity in survivorship care and suggest that incorporating exercise regimens following treatment may be beneficial in improving cognitive function in ovarian cancer patients.
ACKNOWLEDGEMENTS

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INTRODUCTION

Ovarian cancer is the fourth leading cause of cancer mortality among women in the United States, after breast, lung, colorectal, and pancreatic cancer.\(^1\) It comprises approximately 5% of all cancer deaths among women, which is the highest out of all gynecologic cancers. In 2019, an estimated 22,530 new cases were diagnosed in the United States, most (90%) of which were epithelial ovarian cancers.\(^1\) The five-year relative survival rate for all-stage ovarian cancer is only 47%.\(^2\) Unfortunately, due to difficulty in treating ovarian cancer as patients are often asymptomatic until late stages, only 15% of ovarian cancer patients are diagnosed with early stage or localized disease.\(^3\) Due to the lack of recommended screening tests for ovarian cancer, most women, about 59%, are diagnosed with stage 4 disease, for which the five-year survival is just 29%, compared with 92% for localized disease, thus citing an urgent need to develop effective survivorship programs.\(^1,3\)

“Chemo brain”, also known as “chemo fog”, is a term commonly coined for cancer-related cognitive impairment. Patients often display signs and symptoms of cognitive dysfunction, such as mental fogginess, confusion, verbal and visual memory issues, and/or difficulty with concentration.\(^4\) Up to 75% of cancer patients experience cognitive difficulties during or after chemotherapy with up to 35% of patients having persistent symptoms months or years following treatment.\(^5,6\) Survivors often report the negative impact of cognitive impairments on their personal, professional, or social lives and, in some instances, express difficulty with returning to work.\(^7,8,9\) The Thinking and Living With Cancer (TLC) study by Mandelblatt et al. was a case-control study reporting on symptom burden in 362 breast cancer survivors and 350 controls. Results indicated a greater loss of well-being, with cognitive function being significantly impaired, over time in older survivors than in comparable non-cancer populations.\(^10\)
Cognitive impairments from cancer-related treatment can have detrimental effects on a cancer patients’ health-related quality of life (HRQOL), thereby increasing need for researchers and clinicians to better understand how to alleviate these symptoms. A growing body of research has confirmed the many health benefits of physical activity, one of those being improved mental ability. However, most cancer survivors do not meet the American Cancer Society physical activity recommendations of 150 minutes per week of moderate-intensity exercise, which have been shown to improve physical and mental wellbeing.\textsuperscript{11,12}

To our knowledge, there has only been one other randomized control trial involving exercise in ovarian cancer patients. Zhang et al. examined the effects of a home-based physical activity and cognitive behavioral therapy intervention on cancer-related fatigue among 72 ovarian cancer patients during and after chemotherapy.\textsuperscript{13} For women in the intervention, total fatigue scores were significantly reduced from baseline (T1) to 3 months (T2), to 3 months after the sixth chemotherapy treatment (T3) (p<0.001 using Piper Fatigue Scale). Women in the control group had no change in total fatigue scores over time.\textsuperscript{13} A larger body of evidence for exercise trials exists for other cancer patients, especially among the breast cancer population. Derry et al. implemented a yoga exercise trial in 200 breast cancer survivors, finding that women randomized to exercise experienced fewer cognitive problems and reported cognitive complaint scores 23\% lower compared to their control counterparts (p=0.003 using BCPT Cognitive Problems Scale).\textsuperscript{14} Furthermore, Oh et al. studied the effects of medical Qigong, a Chinese exercise and healing technique involving meditation, controlled breathing, and movement exercises, in 81 cancer patients and also noticed vast improvements in cognitive function within patients with all types of cancers (p=0.014 using EORTC-CF scale; p=0.029 for CogPCI, p=0.024 for CogQOL, and p=0.031 for CogPCA using FACT-Cog scale).\textsuperscript{15}
Major limitations within current published studies include short intervention duration, small sample size/low power, lack of adherence to the trial, reliance on self-report data, and issues with generalizability. Thus, to better understand the impact of exercise on cognitive function, we conducted the Women’s Activity and Lifestyle Study in Connecticut (WALC), the largest randomized trial of exercise in ovarian cancer participants to date. The purpose of this study was to examine the 6-month change in cognitive function among women randomized to a home-based exercise program versus women randomized to an attention-control group.
METHODS

All study procedures and guidelines, including informed consent, were reviewed and approved by the Connecticut Department of Public Health Human Investigation Committee, Yale University School of Medicine Human Investigation Committee, Dana-Farber/Harvard Cancer Center Institutional Review Board (IRB), Geisinger Health Systems IRB, and IRBs from all 21 Connecticut hospitals.16

Study Population

To be eligible for the study, participants must have been diagnosed with Stage I-IV invasive epithelial ovarian cancer, according to the American Joint Committee on Cancer staging system, within the past four years and be between the ages of 18-75 years during the time of the screening phone call. Participants must have completed chemotherapy and/or radiation therapy at least one month prior to randomization and display a sedentary activity pattern (< 90 minutes per week of moderate-to-vigorous intensity exercise). All participants within the study were randomized to either the exercise group or the attention-control group between the dates of May 1, 2010 and March 20, 2014. Other inclusion criteria included women receiving physician consent to exercise, agreeing to be randomly assigned to either treatment group, providing informed consent, having transportation available to New Haven for baseline and six-month visits, being accessible through telephone, and speaking English as their primary language. Participants who had experienced a stroke or myocardial infarction within the past 6 months were excluded from the study.

Recruitment

Cases of ovarian cancer were identified from the Connecticut Tumor Registry, a population-based resource for examining cancer occurrences and patterns across the state of
Connecticut. Upon identification of women diagnosed with Stage I-IV ovarian cancer within the records, investigators obtained physician consent to contact women for participation before recruitment letters were mailed. Women were then screened via telephone to determine interest and eligibility for the study. Eligible women who provided informed consent and agreed to enroll were then randomized into either the exercise intervention group or the attention control group.

The primary study location was at Yale Cancer Center (New Haven, CT). Other study sites included Dana-Farber/Harvard Cancer Center (Boston, MA) and Geisinger Health Systems (Danville, PA). Women were also enrolled nationally through self-referral.

**Primary Outcome Measure**

The primary outcome measure within this analysis was change in cognitive function over a six-month time period. Impaired cognitive function in this study was defined as any cancer-related mental fatigue, confusion, lack of concentration, or memory issues, specifically those associated with post-chemotherapy treatment. The FACT-Cog questionnaire was utilized to assess patient-perceived cognitive function. The questionnaire includes responses that address four subscales with their own respective scores. These subscales include Perceived Cognitive Impairments (18 items, Score 0-72), Impact of Quality of Life (4 items, Score 0-16), Comments from Others (4 items, Score 0-16), and Perceived Cognitive Abilities (7 items, Score 0-28). The FACIT Measurement System, which includes FACT-Cog as part of a collection of validated quality of life questionnaires targeted for chronic illness management, recommends that either Perceived Cognitive Impairments (CogPCI) or Perceived Cognitive Abilities (CogPCA) be utilized as the primary score, with more emphasis on using CogPCI. While the assessments for CogPCI and CogPCA are highlighted, scores for all subscales were still calculated and compared, with a higher score indicating better cognitive function.
**Exercise Intervention Group and Attention-Control Group**

Women in the exercise intervention group were recommended to participate in a goal of 150 minutes per week of moderate-intensity aerobic activity, primarily brisk-walking, based on recommendations provided by the American Cancer Society. The intervention was delivered over a period of six months. An ACSM-certified trainer provided weekly individualized counseling sessions through telephone to engage participants in the intervention as well as offered information useful for ovarian cancer survivorship care, including a book that was reviewed one chapter per session. Each participant was also given a heart rate monitor and a target heart rate range, depending on their age and capability of physical activity. Exercises started at 50% of predicted maximum heart rate and were eventually increased to approximately 60-80% of predicted maximum heart rate, according to the American College of Sports Medicine (ACSM) guidelines. Participants self-reported exercise sessions using daily activity logs, which allowed women to report type(s) of exercise, duration, and average heart rate.

Women in the attention control group received standard of care, which included a book containing ovarian cancer survivorship information, and a weekly phone call from a WALC staff member to ensure proper follow-up.

**Statistical Analyses**

All analyses were conducted and adjusted using SAS Software, Version 9.4 (Cary, NC). Descriptive statistics were performed to describe baseline characteristics, including socio-demographic factors and clinically-relevant variables, of the study population (see Table 1). Baseline characteristics between the treatment groups were compared using t-tests for continuous variables and Chi-squared tests for categorical variables. Among the 144 total participants randomized in WALC, only those who completed both the baseline and six-month FACT-Cog
assessments were included in the final statistical analyses, resulting in a final sample size of 111 women. Generalized linear models (GLM) were used to compare change in cognitive function from baseline to 6 months between the exercise intervention group and attention control group and resultant least-squares means were reported. All models were adjusted for respective baseline cognitive function scores and other appropriate variables. Data tables were stratified by baseline FACT-Cog scores and median age (< 57 years and ≥ 57 years) to determine if there were differential effects. The data also stratified women in the intervention group by physical activity level (< 150 minutes and ≥ 150 minutes) to determine a dose-response relationship between adherence to exercise and change in cognitive function.
RESULTS

**Trial Enrollment and Attrition**

A total of 816 ovarian cancer cases were identified during WALC, with 767 of these cases being identified through the Connecticut Tumor Registry and 49 cases who self-referred for the study or were recruited from other sites (*Figure 1*). We received physician consent to contact for 545 women and 510 were screened by telephone. Among the women screened, 235 were ineligible and 131 were not interested in participating in the trial. 144 participants were randomized to a treatment group (28% of women screened) with 74 women randomized to the intervention and 70 women randomized to attention control. Fifty-nine women in the intervention group and 52 women in the attention control group completed cognitive function assessments at both baseline and at six-months, limiting the analyses to 111 participants. Overall, WALC had a 78% compliance rate.\textsuperscript{16}

**Baseline Characteristics**

Participants were 57.5 ± 7.8 (mean ± SD) years old and had a BMI of 29.1 ± 7.0 (*Table 1*). Physical activity at baseline was 30.1 ± 44.8 minutes per week, indicating sedentary lifestyles prior to starting the exercise intervention. A vast majority of women were Non-Hispanic White (94.6%), had no family history of ovarian cancer (84.7%), and had not experienced a recurrence of cancer prior to enrollment (90.1%). Women were 1.7 ± 1.0 years out from their ovarian cancer diagnosis at the time of enrollment into WALC. There were no significant differences for all baseline variables (*Table 1*), including baseline FACT-Cog scores (*Table 2*), between the treatment groups.
**Adherence to Moderate-Intensity Exercise Intervention and Attention Control Group**

For women in the exercise intervention group, the primary measure of adherence was the daily activity logs. The mean duration of exercise recorded was \(166.0 \pm 66.1\) minutes per week. The intervention group had an adherence rate of 65% of women exercising \(\geq 150\) minutes per week of activity and 84% of women exercising \(\geq 120\) minutes per week (met 80% of the recommended goal).\(^{16}\) No adverse events were reported by participants.

Adherence to the weekly telephone calls (25 sessions total) among the exercise intervention group and control group was \(20.4 \pm 5.6\) sessions and \(21.7 \pm 5.5\) sessions, respectively.\(^{16}\) There were no significant differences in adherence to telephone calls between the treatment groups.

**Effect of Exercise Versus Attention Control on Change in Cognitive Function**

Baseline to 6-month change in CogPCI and change in CogPCA were significantly different between the two groups (Table 4). CogPCI improved in the exercise intervention group by \(1.82 \pm 1.0\) (mean \(\pm\) SE) (1.9% change from baseline) while CogPCI was reduced in the attention-control group by \(1.47 \pm 1.0\) (-2.7% change from baseline), \(p=0.025\). CogPCA improved in the intervention group by \(0.76 \pm 0.5\) (4.2% change from baseline) while CogPCA was reduced in the attention-control group by \(1.69 \pm 0.5\) (-8.9% change from baseline), \(p<0.001\). Changes in CogQOL and CogOTH between treatment groups were not found to be significantly different. However, the changes in scores for the intervention group increased for all subscales, whereas changes in scores for the control group declined for all subscales after six months (Table 4).

Age was significantly correlated with three of the four cognitive function scales at baseline (Table 3). Participants were stratified by the median age of 57 years within our study sample. Women \(\geq 57\) years in the exercise intervention group were found to have a \(3.13 \pm 1.1\)
increase in CogPCI and a 0.93 ± 0.6 increase in CogPCA compared with those ≥ 57 years in the control group, who had a 1.48 ± 1.2 decrease in CogPCI and a 1.39 ± 0.6 decrease in CogPCA (group difference in 6-month change; p=0.008 and p=0.013 for CogPCI and CogPCA, respectively) (Table 7). For women < 57 years, women in the exercise group had a 0.51 ± 0.8 increase in CogPCA compared to women in the control group, who had a 1.93 ± 0.8 reduction in CogPCA (p=0.038).

Within the exercise intervention group, women were stratified by physical activity during the study to determine if a dose-response relationship between exercise and cognitive function was present. Change in CogPCA was significantly different, with women exercising < 150 minutes/week experiencing a -0.72 ± 0.8 change and women exercising ≥ 150 minutes/week experiencing a 1.56 ± 0.6 change (p=0.029) (Table 6). A dose-response association was evident within two subscales. Change in CogQOL scores was marginally significant (p=0.051) with women meeting exercise recommendations improving their score by 1.16 ± 0.4 and women exercising less reducing their score by 0.26 ± 0.6.
DISCUSSION

Among women treated for ovarian cancer, a six-month home-based, primarily brisk walking, exercise program was associated with a 1.9%, 5.6%, 8.7%, and 4.2% improvement in perceived cognitive impairments, perceived cognitive impairments on quality of life, comments from others, and perceived cognitive abilities, respectively, among women treated for ovarian cancer. In the subgroup analysis, greater improvements in cognitive function were observed among older women and women meeting recommended amounts of exercise. To our knowledge, this is one of the first studies to examine the impact on cognitive function in women with ovarian cancer in a randomized trial design.

Compared with other exercise trials utilizing FACT-Cog to assess cognitive function, baseline FACT-Cog subscale scores for the ovarian cancer survivors in WALC were similar to the baseline scores reported by Mandelblatt et al. (breast cancer survivors) and Oh et al. (all cancer patients).\(^1\),\(^5\) However, baseline FACT-Cog scores from WALC were much lower than women without cancer (n=350) who were evaluated within the TLC study by Mandelblatt et al., indicating lower cognitive function/quality of life among women with cancer.\(^5\) Compared to the WALC study population, participants in these studies reported by Mandelblatt et al. and Oh et al. were older, ranging from 60-69 years. In addition, Oh et al. included male participants as well as female participants. Of note, other differences include reporting of FACT-Cog. Mandelblatt et al. reported cognitive function as a cumulative score of all the FACT-Cog subscales while Oh et al. excluded the CogOTH subscale in their assessment. Despite these main differences, our study and the studies by Mandelblatt et al. and Oh et al. reported that exercise significantly improved cognitive function.\(^1\),\(^5\) The results from our study support the benefits of a post-diagnosis exercise intervention for improving cognitive function.
There has been much evidence indicating that physical activity is a strong gene modulator that induces functional and structural changes in the brain, influencing neuroplasticity, cognition and wellbeing.\textsuperscript{18} Physical activity has also been shown to be a protective factor for neurodegeneration.\textsuperscript{18} These effects have become a large topic of interest for preventing or minimizing progression of Alzheimer’s disease. However, it is unclear whether the protection against neurodegeneration is through adjustments in biological mechanisms or through better compensation against disease impact.\textsuperscript{18} The most likely explanation is through stimulation of neuroplasticity, which is an important biological feature of the central nervous system (CNS) that allows the brain to form, reorganize, or change synaptic connections.\textsuperscript{19} Over the course of an individual’s lifespan, the brain can engage in synaptic pruning, which is the deletion of certain neural processes that are no longer as useful, in order to support the necessary neural pathways or to compensate for injury and disease. Chemotherapy has been shown to impose neurotoxic effects on the CNS, such as inducing oxidative stress and apoptosis, inhibiting neuronal proliferation, increasing free radicals, and affecting DNA remodeling in the brain.\textsuperscript{6} Some chemotherapy agents have also been found to easily cross the blood-brain barrier, triggering detrimental effects on cognitive function. With researchers from several imaging studies observing brain atrophy after chemotherapy, it has become increasingly clear that more attention is needed to fully understand the nature of chemotherapy-induced cognitive impairments in cancer patients.\textsuperscript{6,20} Due to the CNS being able to modify itself in response to experience and environment, physical activity is considered to be a factor in promoting the neuroplasticity phenomenon and attenuating the effects of chemotherapy. The positive association between physical activity and cognitive function has been found to be related to the sparing of gray matter volume in regions of the brain susceptible to age-related atrophy.\textsuperscript{21,22} A study by Dougherty et
al., which included 91 enrollees at-risk for Alzheimer’s disease, determined that individuals who engaged in exercise levels that met or exceeded recommendations had greater volume of the temporal lobes compared to individuals who had sedentary lifestyles. Similarly, Rovio et al. conducted a cohort study in 2000 participants and found that engaging in active amounts of exercise during midlife was associated with larger total brain and gray matter volume 21 years later. Although the underlying biological mechanisms of different types of exercises are still being reviewed, the current evidence greatly suggests that physical activity has been beneficial in improving aspects of cognitive function and/or counteracting treatment or age-related neurodegeneration.

Some current treatment approaches used by clinicians for chemo brain include pharmacotherapy to combat the neurodegenerative nature of chemotherapeutic agents. A large number of studies have executed pharmacological interventions in controlled trials for their potential in addressing cognitive impairment post-cancer treatment. Among a wide variety of medications, researchers have found erythropoietin, methylphenidate, and modafinil as some of the most promising candidates in reducing impairment for survivors. Although there have been some positive findings, other studies have not confirmed evidence of superiority over a placebo with pharmacological agents, especially with the harmful side effects that may occur. Recently, a new biomarker associated with cancer-related cognitive impairment was identified. Dehydroepiandrosterone (DHEA) and its sulfated form (DHEAS) are a group of neurosteroids involved in regulating brain function and development. The findings from Toh et al. identified that breast cancer patients with higher plasma pre-chemotherapy DHEA(S) levels had lower odds of developing cognitive impairment. The biological and physiological activity of DHEA(S) introduces a new method for objective evaluation for future studies as well as potential to serve
as a pharmacologic intervention. As the research for this biomarker assessing chemo brain is extremely new as of this date, more testing is needed to determine if DHEA(S) supplementation is an appropriate preemptive intervention to reduce cancer-related cognitive impairment as well as how DHEA(S) or other pharmacological compounds might compare to non-pharmacological interventions like WALC. Future studies may want to consider a four-arm trial of pharmacologic treatments for cognitive function, with and without exercise, to determine if there is an additive effect.

**Strengths and Limitations**

Strengths of the WALC study include a prospective, randomized design, high study compliance and high exercise adherence. As one of the largest exercise trials in ovarian cancer survivors, WALC places an emphasis on better understanding the effects of exercise within this understudied patient population. In general, there is a lack of studies assessing quality of life using non-pharmacological interventions within ovarian cancer patients. Even among breast cancer research, which has presented a wider breadth of in-depth investigations compared to ovarian cancer research, exercise trials involving assessments with cognitive function often have small sample sizes, low adherence, high drop-out rates, or an imbalance in baseline characteristics between treatment groups. The moderate-intensity intervention also did not place a large burden on participants who were transitioning from sedentary lifestyles. Expectations for type of exercise, primarily walking, were not unreasonable and were within the scope of what the majority of women felt capable of incorporating on a daily basis. WALC focused on enrolling women who had already undergone cancer treatment, providing the opportunity to translate results and improve discussions surrounding survivorship.
Limitation to the study include a sample primarily of Non-Hispanic white women, although enrollment rates were similar to Connecticut demographics. A total of 33 women (22.9%) did not complete the FACT-Cog questionnaires at both baseline and six-month time points and were not included in the analysis, limiting the study power. No objective assessment of cognitive function was available and level of cognitive function was not an eligibility criteria. In addition, the intervention was of relatively short duration for an exercise trial, which may not have been of sufficient duration to affect a long-term outcome like cognitive health. Cognitive function was also not the primary outcome of WALC, which limited the degree of follow-up with participants regarding their questionnaires as well as implementation of objective cognitive assessments. WALC also enrolled women post-treatment, which is when cognitive decline due to chemotherapy may have already been present. Therefore, trials intervening at diagnosis or before treatment may result in a stronger impact of exercise on preventing and/or treating cognitive decline.

**Future Directions and Translation to Patient Care**

Future exercise trials should aim to enroll patients at diagnosis or prior to active cancer treatment to examine the impact of lifestyle behavioral interventions on preventing treatment-related side effects. Currently, there are very few trials assessing the effect of exercise on cognitive function during chemotherapy. In addition, future studies of cognitive function should incorporate objective assessments, such as neuropsychological exams or memory tests, alongside self-report data assessing cognitive function. However, objective measurements are not commonly proposed, especially among epidemiological studies, due to extensive costs for equipment or training personnel and the complexities in evaluating brain activity that may fluctuate on a daily basis. Epidemiologic studies are generally limited to much briefer tests.
compared to studies involving cognition in other fields.\textsuperscript{32} Samples sizes within existing studies have also been very small and studies have lacked concrete execution or power. For objectively-measured physical activity, the use of accelerometers, pedometers, or FitBits, has increased exponentially over the past decade to reduce limitations of self-report methods.\textsuperscript{33,34}

In conclusion, exercise may benefit cognitive function among ovarian cancer survivors. Further research and robust protocols are still needed to solidify the understanding of type, intensity/rigor, and timing of exercise that can lead to cognitive improvements among cancer survivors. These findings serve to encourage more active lifestyles among ovarian cancer survivors, allow clinicians to tailor physical activity recommendations to a feasible level for older patients, and enhance cancer survivorship care for sustainable health outcomes.\textsuperscript{33}
REFERENCES


27. Fardell JE, Vardy J, Johnston IN, Winocur G. Chemotherapy and cognitive impairment:


Figure 1. Consort Diagram for The Women’s Activity and Lifestyle Study in Connecticut (WALC)

**Ineligible (n= 83)**
- Deceased (n= 41)
- Diagnosed >4 years (n= 22)
- Diagnosis too recent (n= 9)
- Ovarian cancer not invasive (n= 8)
- Age (n= 3)

**Called in or recruited at other sites (Non-CT tumor registry cases) (n= 49)**

**Ovarian cancer cases identified from Connecticut Tumor Registry (n= 767)**

**Contacted physician for consent to participate in clinical trial (n= 684)**

**Physician consent not given (n= 139)**
- Declined consent (n= 77)
- No response (n= 57)
- No consent to exercise (n= 5)

**Unable to contact/screen (n= 84)**
- Voice message (n= 44)
- Disconnected (n= 14)
- Hung up (n= 10)
- No answer (n= 8)
- Wrong number (n= 8)

**Screened via telephone (n= 510)**

**Randomization (n= 144)**

**Not interested in participating (n= 131)**
- No time (n= 47)
- Not interested (n= 44)
- Initially interested but lost to follow-up before randomization (n= 15)
- Declined/vague reason (n= 13)
- Unwilling to participate in activities (n= 9)
- Letter mailed, no response (n= 3)

**Ineligible (n= 239)**
- Too physically active (n= 98)
- On treatment (n= 38)
- Physical illness (n= 35)
- Language barrier (n= 17)
- Not feeling well (n= 17)
- Disease recurrence (n= 7)
- Out-of-state (n= 7)
- Other serious illness (n= 6)
- Could not come to Yale (n= 3)
- Staff impression (n= 2)
- Mental illness (n= 1)
- Finished treatment too recently (n= 1)
- History of heart attack/stroke in past 6 months (n= 1)

**Exercise (n= 74)**

**Attention Control (n= 70)**

**Completed baseline and 6 month FACT-Cog questionnaire (n= 59)**

**Completed baseline and 6 month FACT-Cog questionnaire (n= 52)**
Table 1. Baseline Characteristics of WALC Participants (n=111)

<table>
<thead>
<tr>
<th>Variable of Interest</th>
<th>Study Population (n=111)</th>
<th>Exercise (n=59)</th>
<th>Control (n=52)</th>
<th>P-Value (Between Groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age at Baseline (SD), years</td>
<td>57.5 ± 7.8</td>
<td>57.6 ± 7.9</td>
<td>57.3 ± 7.6</td>
<td>0.868</td>
</tr>
<tr>
<td>Mean Body Mass Index (SD), kg/m²</td>
<td>29.1 ± 7.0</td>
<td>28.9 ± 7.5</td>
<td>29.3 ± 6.6</td>
<td>0.772</td>
</tr>
<tr>
<td>Mean Physical Activity Level (SD), min/wk</td>
<td>30.1 ± 44.8</td>
<td>29.7 ± 48.1</td>
<td>30.7 ± 41.3</td>
<td>0.906</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>105 (94.6)</td>
<td>57 (96.6)</td>
<td>48 (92.3)</td>
<td></td>
</tr>
<tr>
<td>White Hispanic</td>
<td>4 (3.6)</td>
<td>2 (3.4)</td>
<td>2 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Non-White Hispanic</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Mixed Caucasian/African American</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Education Level, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.905</td>
</tr>
<tr>
<td>No GED or equivalent</td>
<td>2 (1.8)</td>
<td>1 (1.7)</td>
<td>1 (2.0)</td>
<td></td>
</tr>
<tr>
<td>GED and some college/Associates</td>
<td>51 (46.0)</td>
<td>26 (44.1)</td>
<td>25 (48.1)</td>
<td></td>
</tr>
<tr>
<td>College graduate or advanced degree</td>
<td>58 (52.3)</td>
<td>32 (54.2)</td>
<td>26 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Employment Status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.710</td>
</tr>
<tr>
<td>Unemployed/retired</td>
<td>51 (46.4)</td>
<td>27 (45.8)</td>
<td>24 (47.1)</td>
<td></td>
</tr>
<tr>
<td>Employed Part-Time (&lt;35 hrs/wk)</td>
<td>36 (32.7)</td>
<td>18 (30.5)</td>
<td>18 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Employed Full-Time (&gt;35 hrs/wk)</td>
<td>23 (20.9)</td>
<td>14 (23.7)</td>
<td>9 (17.7)</td>
<td></td>
</tr>
<tr>
<td>Marital Status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.342</td>
</tr>
<tr>
<td>Single</td>
<td>12 (10.8)</td>
<td>6 (10.2)</td>
<td>6 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Divorced, separated, or widowed</td>
<td>19 (17.1)</td>
<td>13 (22.0)</td>
<td>6 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Married or living with partner</td>
<td>80 (72.1)</td>
<td>40 (67.8)</td>
<td>40 (76.9)</td>
<td></td>
</tr>
<tr>
<td>Family History of Ovarian Cancer, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.314</td>
</tr>
<tr>
<td>Yes</td>
<td>15 (13.5)</td>
<td>8 (13.6)</td>
<td>7 (13.5)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>94 (84.7)</td>
<td>51 (86.4)</td>
<td>43 (82.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1.8)</td>
<td>0 (0.0)</td>
<td>2 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Cancer Stage at Diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.234</td>
</tr>
<tr>
<td>I</td>
<td>26 (23.4)</td>
<td>15 (25.4)</td>
<td>11 (21.2)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>27 (24.3)</td>
<td>10 (17.0)</td>
<td>17 (32.7)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>40 (36.0)</td>
<td>25 (42.4)</td>
<td>15 (29.0)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>17 (15.3)</td>
<td>8 (13.6)</td>
<td>9 (17.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.9)</td>
<td>1 (1.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Mean Time Since Diagnosis (SD), years</td>
<td>1.7 ± 1.0</td>
<td>1.7 ± 0.9</td>
<td>1.7 ± 1.1</td>
<td>0.926</td>
</tr>
<tr>
<td>Cancer Recurrence Prior to Enrollment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.463</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (9.9)</td>
<td>7 (11.9)</td>
<td>4 (7.7)</td>
<td></td>
</tr>
<tr>
<td>No/Unknown</td>
<td>100 (90.1)</td>
<td>52 (88.1)</td>
<td>48 (92.3)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Baseline FACT-Cog Subscales of WALC Participants (n=111)

<table>
<thead>
<tr>
<th>FACT-Cog Subscales</th>
<th>Study Population (n=111)</th>
<th>Exercise (n=59)</th>
<th>Control (n=52)</th>
<th>P-Value (Between Groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Perceived Cognitive Function Score (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CogPCI (Perceived Cognitive Impairments)</td>
<td>53.0 ± 16.0</td>
<td>53.8 ± 14.9</td>
<td>52.0 ± 17.3</td>
<td>0.567</td>
</tr>
<tr>
<td>CogQOL (Perceived Quality of Life)</td>
<td>12.8 ± 4.2</td>
<td>12.7 ± 4.3</td>
<td>12.9 ± 4.2</td>
<td>0.738</td>
</tr>
<tr>
<td>CogOTH (Comments from Others)</td>
<td>15.0 ± 2.4</td>
<td>14.9 ± 2.7</td>
<td>15.1 ± 1.9</td>
<td>0.602</td>
</tr>
<tr>
<td>CogPCA (Perceived Cognitive Abilities)</td>
<td>19.1 ± 6.4</td>
<td>19.0 ± 6.3</td>
<td>19.2 ± 6.5</td>
<td>0.899</td>
</tr>
</tbody>
</table>

Table 3. Pearson’s Correlation Among Baseline FACT-Cog Subscales and Variables of Interest

<table>
<thead>
<tr>
<th></th>
<th>CogPCI</th>
<th>CogQOL</th>
<th>CogOTH</th>
<th>CogPCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age</td>
<td>0.270*</td>
<td>0.219*</td>
<td>0.129</td>
<td>0.272*</td>
</tr>
<tr>
<td>2. BMI</td>
<td>-0.040</td>
<td>-0.081</td>
<td>0.030</td>
<td>-0.012</td>
</tr>
<tr>
<td>3. Education</td>
<td>-0.042</td>
<td>-0.132</td>
<td>-0.168</td>
<td>-0.067</td>
</tr>
<tr>
<td>4. Stage of diagnosis</td>
<td>-0.116</td>
<td>-0.000</td>
<td>-0.083</td>
<td>-0.058</td>
</tr>
<tr>
<td>5. Time since diagnosis</td>
<td>-0.061</td>
<td>-0.160</td>
<td>-0.017</td>
<td>-0.045</td>
</tr>
<tr>
<td>6. Cancer recurrence</td>
<td>0.044</td>
<td>0.030</td>
<td>0.114</td>
<td>0.068</td>
</tr>
</tbody>
</table>

*Significant at 0.05 level
Table 4. Changes in Cognitive Function Between Control Group and Exercise Group (n=111)

<table>
<thead>
<tr>
<th>FACT-Cog Sub-scales</th>
<th>Exercise, $\bar{x} \pm SE$ (n= 59)</th>
<th>Control, $\bar{x} \pm SE$ (n= 52)</th>
<th>P-Value$^a$ (Between Groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 Months</td>
<td>Group $\Delta$ (% Change)</td>
</tr>
<tr>
<td>Perceived Cognitive Impairments (CogPCI)</td>
<td>53.6 ± 1.9</td>
<td>55.3 ± 1.8</td>
<td>1.82 ± 1.0 (1.9%)</td>
</tr>
<tr>
<td>Impact of Perceived Cognitive Impairments on Quality of Life (CogQOL)</td>
<td>12.6 ± 0.5</td>
<td>13.3 ± 3.2</td>
<td>0.64 ± 0.4 (5.6%)</td>
</tr>
<tr>
<td>Comments from Others (CogOTH)</td>
<td>14.9 ± 0.3</td>
<td>16.2 ± 0.6</td>
<td>1.19 ± 0.6 (8.7%)</td>
</tr>
<tr>
<td>Perceived Cognitive Abilities (CogPCA)</td>
<td>19.0 ± 0.8</td>
<td>19.8 ± 0.8</td>
<td>0.76 ± 0.5 (4.2%)</td>
</tr>
</tbody>
</table>

Note: Higher scores on FACT-Cog subscales indicate increased cognitive function

$^a$P-values were adjusted for age, treatment group, baseline scores for respective FACT-Cog subscales, and study sites
Figure 2.
Change in Perceived Cognitive Impairments (CogPCI)

![Graph showing change in CogPCI scores over time for Exercise and Control groups.](image)

- **Δ = 1.9%** (Exercise)
- **Δ = -2.7%** (Control)

*p = 0.028* (Δ between-group)

Baseline | 6 Months
--- | ---

Figure 3.
Change in Perceived Quality of Life (CogQOL)

![Graph showing change in CogQOL scores over time for Exercise and Control groups.](image)

- **Δ = 5.6%** (Exercise)
- **Δ = -3.1%** (Control)

*p = 0.08* (Δ between-group)

Baseline | 6 Months
--- | ---

Figure 4.
Change in Comments From Others (CogOTH)

![Graph showing change in CogOTH scores over time for Exercise and Control groups.](image)

- **Δ = 8.7%** (Exercise)
- **Δ = -2.6%** (Control)

*p = 0.09* (Δ between-group)

Baseline | 6 Months
--- | ---

Figure 5.
Change in Perceived Cognitive Abilities (CogPCA)

![Graph showing change in CogPCA scores over time for Exercise and Control groups.](image)

- **Δ = 4.2%** (Exercise)
- **Δ = -8.6%** (Control)

*p < 0.001* (Δ between-group)

Baseline | 6 Months
--- | ---
Table 5. Changes in Cognitive Function From Baseline to 6 Months Stratified by Median Baseline FACT-Cog Scores

<table>
<thead>
<tr>
<th>Baseline CogPCI Score&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Exercise, $\bar{x} \pm SE$</th>
<th>Control, $\bar{x} \pm SE$</th>
<th>P-Value&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; Median Baseline CogPCI score (n=52)</td>
<td>3.82 ± 1.9</td>
<td>0.61 ± 1.9</td>
<td>0.245</td>
</tr>
<tr>
<td>$\geq$ Median Baseline CogPCI score&lt;sup&gt;d&lt;/sup&gt; (n=59)</td>
<td>0.02 ± 0.9</td>
<td>-3.24 ± 1.0</td>
<td>0.019*</td>
</tr>
</tbody>
</table>

| Baseline CogQOL Score<sup>b</sup> |
|----------------------------------|------------------|------------------|------------------|
| < Median Baseline CogQOL score (n=43) | 3.09 ± 0.6       | 1.40 ± 0.7       | 0.074            |
| $\geq$ Median Baseline CogQOL score (n=68) | -0.78 ± 0.4     | -1.55 ± 0.5     | 0.242            |

| Baseline CogOTH Score<sup>c</sup> |
|----------------------------------|------------------|------------------|------------------|
| < Median Baseline CogOTH score (n=36) | 3.99 ± 1.9       | -0.58 ± 2.1      | 0.129            |
| $\geq$ Median Baseline CogOTH score (n=75) | -0.13 ± 0.1     | -0.20 ± 0.1     | 0.523            |

| Baseline CogPCA Score<sup>d</sup> |
|----------------------------------|------------------|------------------|------------------|
| < Median Baseline CogPCA score (n=55) | 2.23 ± 0.7       | -0.84 ± 0.8      | 0.008*           |
| $\geq$ Median Baseline CogPCA score (n=56) | -0.77 ± 0.6     | -2.51 ± 0.6     | 0.057            |

Note: Higher scores on FACT-Cog subscales indicate increased cognitive function

<sup>a</sup>Median baseline CogPCI score is 57

<sup>b</sup>Median baseline CogQOL score is 14

<sup>c</sup>Median baseline CogOTH score is 16

<sup>d</sup>Median baseline CogPCA score is 20

<sup>e</sup>P-values were adjusted for age, treatment group, baseline scores for respective FACT-Cog subscales, and study sites

* Significant at 0.05 level
Table 6. Changes in Cognitive Function From Baseline to 6 Months Among Exercise Group Stratified by Physical Activity Level

<table>
<thead>
<tr>
<th>FACT-Cog Subscale</th>
<th>&lt; 150 minutes/week, $\bar{x} \pm SE$</th>
<th>$\geq 150$ minutes/week, $\bar{x} \pm SE$</th>
<th>P-Value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$ CogPCI Score</td>
<td>1.44 ± 1.6</td>
<td>1.83 ± 1.1</td>
<td>0.844</td>
</tr>
<tr>
<td>$\Delta$ CogQOL Score</td>
<td>-0.26 ± 0.6</td>
<td>1.16 ± 0.4</td>
<td>0.051</td>
</tr>
<tr>
<td>$\Delta$ CogOTH Score</td>
<td>2.25 ± 1.4</td>
<td>0.73 ± 0.9</td>
<td>0.377</td>
</tr>
<tr>
<td>$\Delta$ CogPCA Score</td>
<td>-0.72 ± 0.8</td>
<td>1.56 ± 0.6</td>
<td><strong>0.029</strong>$^*$</td>
</tr>
</tbody>
</table>

Note: Higher scores on FACT-Cog subscales indicate increased cognitive function.

$^a$P-values were adjusted for age, minutes/week group, baseline scores for respective FACT-Cog subscales, and study sites.
### Table 7. Changes in Cognitive Function from Baseline to 6 Months Stratified by Median Age

<table>
<thead>
<tr>
<th>FACT-Cog Subscale</th>
<th>&lt; 57 years, $\bar{x} \pm SE$ (n=54)</th>
<th>$\geq$ 57 years, $\bar{x} \pm SE$ (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>Control</td>
<td>P-Value$^a$</td>
</tr>
<tr>
<td>$\Delta$ CogPCI Score</td>
<td>0.40 ± 1.6</td>
<td>-1.23 ± 1.8</td>
</tr>
<tr>
<td>$\Delta$ CogQOL Score</td>
<td>0.13 ± 0.6</td>
<td>-0.74 ± 0.7</td>
</tr>
<tr>
<td>$\Delta$ CogOTH Score</td>
<td>0.11 ± 0.3</td>
<td>-0.39 ± 0.3</td>
</tr>
<tr>
<td>$\Delta$ CogPCA Score</td>
<td>0.51 ± 0.8</td>
<td>-1.93 ± 0.8</td>
</tr>
</tbody>
</table>

Note: Higher scores on FACT-Cog subscales indicate increased cognitive function

$^a$P-values were adjusted for treatment group, baseline scores for respective FACT-Cog subscales, and study sites

*Significant at 0.05 level