January 2015

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ABSTRACT

Purpose: Despite effective therapies and treatments, breast cancer survivors often suffer from distressing side effects which may increase depressive symptomatology. Aromatase inhibitors (AI) are widely used as adjuvant treatment in breast cancer patients, but are associated with side effects such as joint pain that may impact quality of life. We conducted, in 121 breast cancer survivors receiving an AI, a yearlong randomized trial of exercise versus usual care on depressive symptomology.

Methods: Eligibility criteria included taking an AI for at least 6 months, reporting < 90 minutes per week of exercise and no strength training, and reporting $\geq$ 3 on a scale of 10 for worst joint pain on the Brief Pain Inventory (BPI). Participants were randomly assigned to exercise (150 minutes per week of aerobic exercise and supervised strength training twice per week) or usual care. The Centers for Epidemiological Studies: Depression Scale (CES-D) was completed at baseline and 6- and 12 months. Intervention effects were evaluated using generalized linear models, comparing change at 6- and 12 months.

Results: Over 12 months, a 4.7 point (36%) decline in CES-D score was seen for women randomly assigned to exercise (n = 60) versus a 0.3-point (2%) decline among those receiving usual care (n = 60; $p < 0.05$). In secondary analysis, women that scored above the generally accepted CES-D score cutoff of 16 (indicating depressive symptomatology), had a 12.6 ($\pm$2.6) point (50%) decrease (mean$\pm$SD) in CES-D score, significantly greater than those in this category who were assigned to usual care, 5.5 ($\pm$2.8) point decrease (29%). Women with later stage breast cancer, those who had taken AIs for a longer period of time, and those who had attended more supervised exercise sessions showed a greater decrease in CES-D scores compared to their counterparts.

Conclusion: Exercise led to favorably reductions in CES-D scores in previously inactive breast cancer survivors taking AIs. Exercise programs should be implemented for breast cancer survivors in an effort to reduce depressive symptoms.

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INTRODUCTION

There are approximately 3.1 million breast cancer survivors in the United States, a result in part of improved treatments.[1] With survival rates increasing, researchers are increasingly looking at side effects that affect quality of life in breast cancer survivors. Cancer survival can be accompanied by adverse physiological and psychological side effects, such as weight changes, decreased strength and flexibility, and depression and anxiety. [2-6]

Depression is a relatively common side effect of cancer and cancer treatment and its prevalence varies by cancer site.[7] Depression is characterized by feelings of sadness, hopelessness, changes in sleep and appetite, psychomotor retardation, and withdrawal from social contact.[7] Cancer survivors may experience fear of death, disease relapse, and body image changes that can contribute to a reduced quality of life and impaired social and occupational functioning. Depression in cancer survivors is often correlated to various comorbities, such as obesity, diabetes, and the development of cardiovascular disease.[8]

Breast cancer survivors are at an increased risk for depression, due to the side effects of cancer treatment. The prevalence of depression among breast cancer survivors ranges widely from 1.5 to 46 percent, dependent on variables such as age, treatment, number of children at home, and socioeconomic status .[9] Current treatments for depression in cancer survivors include pharmacologic interventions and psychotherapy. For many, these treatments are safe, effective, and provide significant benefit. For others, they may have limited usefulness because of personal, behavioral, or biological factors.[7]

Additionally, other breast cancer treatment-related side effects may increase depression symptomatology. Agents such as steroids and estrogen depleting interventions, which can alter serotonin levels, are associated with the development of depression.[10] Aromatase inhibitors (AI) are widely used as adjuvant treatment for postmenopausal women with estrogen receptor-positive breast cancer and act through estrogen depletion. Arthralgia (i.e., joint pain) is one of

the major complaints of breast cancer patients undergoing AI treatment, and may be associated with worse overall quality of life and psychological well-being.[11]

Exercise has been identified as a treatment that may provide symptom relief for depression, as well as improve physical health outcomes in cancer survivors.[12] Accumulating evidence suggests exercise after diagnosis of cancer may improve functional capacity, muscular strength, and reduce cancer-related fatigue. Trials of exercise among breast cancer survivors have generally had small sample sizes and have varied widely in quality and in specifics such as exercise prescription, time since diagnosis, and choice of patient-reported outcomes. Recent systematic reviews and meta-analyses have reported clear benefits of physical activity for cardiovascular fitness in breast cancer survivors, but report only generally modest or inconsistent effects for outcomes like depression.[13] No large-scale randomized controlled trial assessing the effect of exercise on depression in breast cancer survivors, in particular, those taking AIs, has been conducted.

We recently completed a randomized trial, the Hormones and Physical Exercise (HOPE) Study, which examined the effect of an exercise intervention vs. usual care on AI side-effects in breast cancer survivors. The purpose of this paper was to evaluate how the HOPE exercise intervention vs. usual care impacted depression scores in women taking AIs and experiencing arthralgia.

METHODS

The HOPE Study was a yearlong, randomized control trial, which evaluated the effect of an exercise intervention vs. usual care (control) on AI side-effects. All study procedures, including written informed consent, were approved by the Yale School of Medicine Human Investigation Committee and Connecticut Department of Public Health and Human Investigation Committee.

Study Participants and Recruitment

Breast cancer survivors were recruited between June 1, 2010 and December 30, 2012 from 5 hospitals in Connecticut through the Rapid Case Ascertainment Shared Resource of the Yale Cancer Center (RCA), a field arm of the CT Tumor Registry. Detailed recruitment methods are described elsewhere.[14]

Eligible participants were physically inactive (<90 min/wk of physical activity in the past six months and no strength training in the past year), postmenopausal women, diagnosed 0.5-4.0 years prior to enrollment with hormone receptor positive Stage I to III breast cancer, who had taken an AI for at least six months prior to enrollment. Participants had to be experiencing arthralgia for at least two months prior to enrollment that was a minimum of mild in severity, defined as a score of at least 3 out of 10 on the worst pain item of the Brief Pain Inventory.[15] Women were eligible if arthralgia started after initiation of an AI or if they had pre-existing join pain as long as the pain or stiffness was exacerbated by AI use.

Primary Outcome Measures

Depression: Depression was assessed with the Centers for Epidemiological Studies – Depression Scale[16] (CES-D). The CES-D is a 20-item scale designed to measure current level of depressive symptomatology, with emphasis on the affective component, depressed mood. The 20 items are divided into four domains: Somatic Retarded Activity (7 items), Depressed Affect (5 items), Positive Affect (4 items), and Interpersonal Affect (2 items), and 2 single items that complete the total score.[17] The possible range of scores is zero to 60, with higher scores indicating more symptoms, weighted by frequency of occurrence during the past week.[16] The construct validity and internal consistency of the CES-D are good.[17] The positive predictive value is 54.5% for the cut-off score of 16 in head and neck cancer patients,[17] which was also used as the cutoff score for this population. A group with a high average score may be interpreted to be “at risk” of depression or in need of treatment. The scale is a valuable tool to

identify such high-risk groups and the relationships between depressive symptoms and other variables.

Secondary Outcome Measures and Covariate Measures

An interviewer-administered questionnaire at the baseline visit was used to assess disease stage, type of surgery, adjuvant therapy, and comorbidities. Stage was self-reported, and was subsequently verified using medical records. Additionally, we collected information on participants' race/ethnicity, education level, time since diagnosis, time on AI, and height and weight. Height and weight were measured at baseline, 6-, and 12 months. Participants were weighed on a digital scale in light clothing, without shoes. Height without shoes was measured using a stadiometer. All measurements were taken twice and averaged. Exerciser trainers were responsible for recording attendance to the supervised exercise training sessions. Physical activity was recorded at baseline, 6-, and 12 months, via an interviewer-administered physical activity questionnaire, assessing the past 6 months of recreational activity including the type, frequency, and duration of 20 activities.[18]

Exercise Intervention

To comply with current exercise recommendations for cancer survivors,[19] the yearlong exercise intervention was a combination of a twice-weekly supervised exercise training program consisting of resistance and aerobic exercise (under supervision of an American College of Sports Medicine certified cancer exercise trainer) at a local health club and additional aerobic exercise on their own (at home or the gym), for a total of 150 min/wk of aerobic exercise. Detailed information about the intervention protocol has been previously reported.[14] Following each exercise session, participants recorded the type of duration, and average heart rate during exercise, in physical activity logs.[20] Participants returned logs to the exercise trainers at the end of each week. Exercise trainers also recorded attendance to the supervised exercise session.

The aerobic exercise intervention consisted primarily of brisk walking, either on a treadmill or outside, although participants were allowed to choose other aerobic exercise

training, such as stationary bicycling or using the elliptical machine. Exercise started at 50% of maximal heart rate (determined from VO_2 max testing) and gradually increased over the first month to 60-80% of maximal heart rate for the duration of the study. The strength training protocol consisted of six exercise: bench press, latissimus pull down, seated row, leg press, leg extension, and leg curl. Each of these exercises were performed for 8-12 repetitions for three sets. A standard progressive resistance training approach was used in which participants progressed up to three sets per exercise over the first month of training. After two sessions during which a participant lifted the same weight 12 times during each set, the weight was then increased by the smallest possible increment.

Usual Care Group

Women were instructed to continue with their usual activities. Participants were not discouraged from exercise on their own but were not given any exercise instruction. Both the exercise and usual care groups were provided with an educational booklet prepared for the HOPE study, which addressed breast cancer topics such as lymphedema and fatigue. These topics were discussed monthly over the phone for the usual care group, or at an exercise session for the exercisers. Participants in this group were called monthly by research staff to determine AI adherence. In addition, AI adherence was assessed in the usual care group at the monthly phone call. At the completion of 12 months, women were offered a supervised exercise session and exercise handouts.

Statistical Analyses

Descriptive statistics were used to describe the study population based on socio-demographic and clinically relevant indicators according to study randomization. Participants were analyzed using the intention-to-treat principle. For those women who did not have six-month questionnaires, the change in CES-D was imputed as 0. Generalized linear models (GLM) were used comparing women randomized to the exercise intervention arm and women randomized to the usual care group on depressive symptomatology. Potential covariates

included baseline CES-D score, cancer stage, age, time since diagnosis, and time on AI. Only 14 women reported previous diagnosis of depression, and 11 of those women reported taking antidepressants at baseline. Because of the small number, the effect was assumed to be very small and this was not included in analysis. In looking at attendance using the average minutes per week, a t-test was performed to analyze if changes were significant from baseline.

Owing to the relatively low CES-D score observed at baseline, secondary analyses were conducted to determine the effect of exercise on CES-D by the baseline CES-D cutoff of 16. We also examined effect modification by disease stage and time on AI. Analysis was performed using SAS version 9.3 (Cary, NC). Statistical significance was set at $p<0.05$ using 2-sided tests.

RESULTS

A total of 1,537 breast cancer survivors were identified through the Rapid Case Ascertainment (RCA) Shared Resource of the Yale Cancer Center (Figure 1). Screening phone calls were completed with 1016 women. Of these 1016 women screened, 253 women had already stopped taking an AI because of side effects or chose not to take and AI because of potential side effects. A total of 121 women were randomized. One woman did not complete the baseline CES-D, and was subsequently removed from statistical analysis resulting in an analytic sample of 120. Given funding cuts, the last 25 of the 121 women recruited were enrolled into a 6-month rather than a 12-month trial. Thus, their study adherence and attrition is based on 6-month data. Study attrition was low, with 58 of 61 exercisers (95%) and 49 of 60 usual care women (82%) completing 6-month measures, and 45 of 48 exercisers (94%) and 39 of 48 usual care women (81%) completing 12-month measures.

Women randomly assigned to exercise reported their exercise prospectively in daily activity logs and reported and average 119 minutes per week of exercise, with an average of 70% of strength training sessions completed. There were no adverse events associated with the exercise program. [14]

Baseline Characteristics

The average age of participants was 61 years (Table 1). The majority of the study population were white (88%) and diagnosed with Stage I breast cancer (59%). A large portion of the study participants had a lumpectomy or partial mastectomy (65%) and had an average time between diagnosis and enrollment of 2.0 years. All baseline characteristics were similar for both arms ($p > 0.05$).

Effect of Exercise on CES-D

At baseline, CES-D scores were similar in both groups (12.3$\pm$1.3 exercise group and 12.5$\pm$1.3 usual care; $p = 0.89$) (Table 2). Thirty-five individuals (29%) scored a 16 or greater on the CES-D, indicating a higher level of depressive symptomatology. At the 6-month follow-up, CES-D scores decreased by 3.5 ($\pm$0.8) points (28%) in women randomized to exercise compared to a 0.6 ($\pm$0.8) decrease (5%) in women randomized to usual care (difference = 2.9; $p = 0.018$) Table 2. Adjustment for age, time since diagnosis, time on AI, race, education, stage, surgery, treatment, BMI, BPI, and baseline CES-D scores did not affect the results (results not shown).

Stratified analyses examining the effect of the intervention specifically within those participants who reported CES-D $\geq$16 scores at baseline. At baseline, 18 study participants (15%) randomized to the exercise arm and 17 study participants (14%) randomized to the usual care group scored at or above the generally accepted cutoff of 16, suggesting a potentially elevated rate of depressive symptoms. In looking at those who scored at or above 16 on the baseline CES-D, participants baseline CES-D score averaged 23.7 $\pm$ 7.9 and 26.8 $\pm$ 8.8 for exercisers and usual care, respectively ($p = 0.272$) (Table 3). At 6 months, CES-D scores decreased 12.06 ($\pm$2.0) points (48%) in women randomized to exercise verse 5.23 ($\pm$2.1) points (22%) in women randomized to usual care (difference = 6.83 $p=0.025$).

Similar findings were observed when measuring mean difference of CES-D scores in comparison to stage of breast cancer at diagnosis. Individuals diagnosed with stage 0 and I

had averaged baseline CESD scores of 11.4 ± 8.8 and 12.9 ± 11.6 for exercisers and usual care (p=0.39) (Table 4). Those diagnosed with later stage II or III breast cancer had averaged baseline CESD scores of 14.9 ± 11.3 and 13.6 ± 9.6 (p =0.40). At 12 months, the CES-D change among those in the exercise intervention at both earlier and later stages was significantly greater than those in the usual care group. Furthermore, for those with later stage breast cancer, their depressive symptom scores decreased by 6.0 points compared to those of the same stage randomized to usual care group, whose scores increased by 1.7 (difference = 7.7; p = 0.006).

Baseline CES-D scores were comparable for participants taking an AI for less than 20 months and greater than 20 months (p = 0.781 and p = 0.558) (Table 4). Significant decreases in CES-D scores can be seen in those have been on an AI for a longer period of time. Over 12 months, CES-D scores decreased by 5.1(±1.1) points in women randomly assigned to exercise, versus a 2.2 (±1.2) increase in women randomly assigned to usual care (difference = 7.3; p = <0.001). Adjusting for age, stage, race, surgery, treatment, and BMI did not affect the results. Attendance was examined by using the median of 82 minutes per week. Twenty-nine women averaged more than 82 minutes per week, decreased their CES-D score by 6.2 (±1.3) at 12 months, compared to the 31 women who averaged less than 82 minutes per week and loss approximately 3.4 (±1.4) points. CES-D scores in both high and low attendance groups decreased significantly compared to baseline (p=<0.001) (Table4). Similarly, significant decreases in CES-D scores over time were seen for both attendance groups at the 6-month time point.

DISCUSSION

In this exercise intervention trial in women receiving AI therapy for breast cancer, we found depressive symptomatology decreased significantly more in those in the exercise intervention versus usual care. Baseline scores were comparable to other published research looking at the quality of life, using the CES-D in breast cancer survivors,[9 21 22] On average,

depression scores in women randomly assigned to exercise decreased from moderate at baseline to mild at the end of the intervention period (ie, CES-D score of approximately moderate score of 12 to mild score of 7). To our knowledge, this is the strongest methodological study, given the randomized design, large sample size, and 12-month intervention period, that has examined the effect of exercise on depression in breast cancer survivors on AI therapy.

The largest effects of depression changes in cancer survivors have been found in those who participated in programs in which all or majority of the exercise was supervised, as compared with those exercising in the home.[7] This suggests caution in how exercise programs are implemented for breast cancer survivors if reduction in depression is a goal. The majority of exercise interventions designed for cancer survivors, including HOPE, are not likely designed to target depressive symptoms. Research has shown that duration of exercise session was not a significant moderator of the effect of exercise on depression,[7] but frequency of exercise was an important factor, an exercise frequency of 5 times per week was reported as being significantly more effective than 2 to 4 days of activity.[23] Future research could compare the effect of a variety of exercise intensities and varying lengths of exercise sessions on depression so that evidence based recommendations can be made about the appropriate exercise prescription for breast cancer survivors with regard to reducing depression.

Our study has some limitations. Participants in the HOPE study were primarily non-Hispanic white, well educated, and diagnosed with Stage I breast cancer; therefore do not constitute a representative sample of the overall population of breast cancer survivors. Women with breast cancer who have lower socioeconomic status (SES) have an increased risk of developing depression; with symptom burden differing by race and SES.[24] Ideally future studies will include larger numbers of breast cancer patients from ethnic minorities and those who have low SES; giving a clearer view of potential moderator variables. Additionally, although most of the participants were recruited from tumor registries, given the sizable time commitment, it is

very possible that those women who elected to enroll in the study were higher functioning than breast cancer survivors, in general. Most participants in HOPE scored within a "normal" range on the CES-D, lower than a score of 16. In observing a significantly greater decrease in depressive symptomatology among those in the exercise arm, future studies could use depression symptomatology as an entry criterion.

Strengths of the HOPE study include the randomized design, high adherence to exercise, and a focus on women experiencing arthralgia resulting from AI use. Studies looking into AI-induced arthralgia are mostly small (<59 participants), uncontrolled, and of short duration.[14] However, depression was not the primary outcome of the HOPE trial and as a result limited information was collected about the participant's history of depression, ongoing treatment for depression, length of current depressive symptoms, or additional psychologic comorbities. With more specific information about onset, persistence, and treatment for specific depression bouts, potential moderators could be examined in more detail.

Furthermore, a final strength of this study was a focus on a sample of women at higher risk for depression because of treatment side effects. AIs are often well tolerated with very few serious adverse events, but common side effects include joint pain, loss of bone mineral density, hot flashes, night sweats, and vaginal dryness.[25] These side effects are the primary cause of discontinuation and often responsible for exacerbating depressive feelings and could be a reason for higher baseline CES-D scores. Women in the HOPE study had reported the side effect of arthralgia prior to enrollment. Improvement in arthralgia potentially stands as a potential mediator of improving depression or vice versa. For instance, exercise was shown to improve depressive symptomatology, which may in turn improve the side effect of joint pain, or the psychological factors associated with pain. Appropriate management of AI side effects is of critical importance for overall quality of life and to ensure adherence.

In conclusion, the HOPE exercise intervention improved depressive symptomatology as measured by the CES-D. However, further research is necessary using a more diverse

population and targeting at risk populations. With more women surviving breast cancer, it becomes important to understand their experiences in survivorship and to give clinicians treating them realistic expectations about the prevalence of psychological difficulties.

References:

1. Breast Cancer Facts and Figures: 2013-2014. 2013.
2. Irwin ML MA, Baumgartner RN, et al. Changes in body fat and weight after a breast cancer diagnosis: influence of demographic prognostic, and lifestyle factors J Clin Oncol 2005;**4**(23):774-82.
3. Galvao D NR. Review of exercise intervention studies in cancer patients. J Clin Oncol 2005;**23**:899-909.
4. Burgess C CV, Love S, et al. . Depression and axiety in women with early breast cancer: Five-year observational cohort data. BMJ 2005;**330**:702-05.
5. Ganz PA KL, Staton AL et al. Quality of life at the end of primary treatment of breast cancer: first results from the moving beyond cancer randomized trial. . J Natl Cancer Inst 2004;**96**(5):376-87.
6. Irwin ML CD, McTiernan A, et al. . Physical activity levels before and after a diagnosis of breast cancer carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. Cancer 2003;**97**(7):1746-57.
7. Craft LL VE, Helenowski IB, et al. . Exercise effects on depressive symptoms in cancer survivors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2012;**21**:3-19.
8. Somerset W SS, Miller AH, Musselman D. Breast Cancer and depression. Oncology 2004;**18**:1021-34.
9. Deshields T. TT, Fan Ming-Yu, Taylor M. Differences in patterns of depression after treatment for breast cancer Psycho-oncology 2006(15):398-406.
10. Fann JR TRA, Katon WJ, Cowley D, Pepping M, McGrogor BA, et al. Major depression after breast cancer: a review of epidemiology and treatment. Gen Hosp Psychiatry 2008;**30**:112-26.
11. Denysschen CA BH, Ademuyiwa F, et al. Exercise intervention in breast cancer patients with aromatase inhibitor-associated arthralgia: a pilot study. Eur J Cancer Care 2013;**23**(4):493-501.
12. SB. F. Treatment of symptom clusters: pain, depression, and fatigue. J Natl Cancer Inst Monogr 2004:119-23.
13. Schmitz KH HJ, Courneya KS, Masse LC, Duval S, Kane R. Controlled physical activity trials in cancer survivors: a systematic review and meta analysis. Cancer Epidemiol Biomarkers Prev 2005;**14**(7):1588-95.
14. Irwin ML. CB, Gross Cary., Ercolano E., et al. Randomized excersize trial of armatase inhibitor-induced arthalgia in breast cancer survivors`. JCO 2014;**33**((11)).
15. Cleeland CS RK. Pain assessment: Global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994(23):129-38.
16. L. R. The CES-D Scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977(1):385-401.
17. Van Wilgen CP DP, Stewart RE, Ranchor AV, Roodenburg JN. Measuring somatic symptoms with the CES-D to assess depression in cancer patients after treatment: Comparison among patients with oral/oropharyngeal, gynecological, colorectal, and breast cancer. Psychosomatics 2006;**47**(6):465-70.

18. Kriska AK, W. LaPorte, R. et al. Development of a questionnaire to examine the relationship of physical activity and diabetes in Pima Indians. Diabetes Care 1990(13):401-11.
19. Schmitz KH CK, Matthews C, et al. . American college of sports medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;**42**(7):1409-26.
20. Blair S HW, Ho P, et al. Assesment of habitual physical activity by a seven day recall in a community survey and controlled experiements. Americal Journal of Epidemiology 1985(122):794-804.
21. Andrykowski MA ea. Psychosocial adjustment and quality of life in women with breast cancer and benign breast problems: a controlled comparison. J Clin Epidemiol 1996;**49**(8):827-34.
22. Ganz PA ea. Life after breast cancer: udnerstanding women's health-related quality of life and sexual functioning. J Clin Oncol 1998;**16**(2):501-14.
23. Rethorst CD WB, Landers DM. The antidepressive effects of exercise a meta-analysis of randomized trials. Sports Med 2009(39):491-511.
24. Fu OS CK, Jacobson JS, Greenlee H, et al. Ethnicity and persistent symptom burden in breast cancer survivors. J Cancer Surviv 2009;**3**(4):241-50.
25. Dent SF GR, Kissner M, Pritchard Kl. Aromatase inhibitor therapy: toxicities and management strategies in the treatment of postmenopausal women with hormone-sensitive early breast cancer. Breast Cancer Res Treat 2011;**126**(2):295-310.

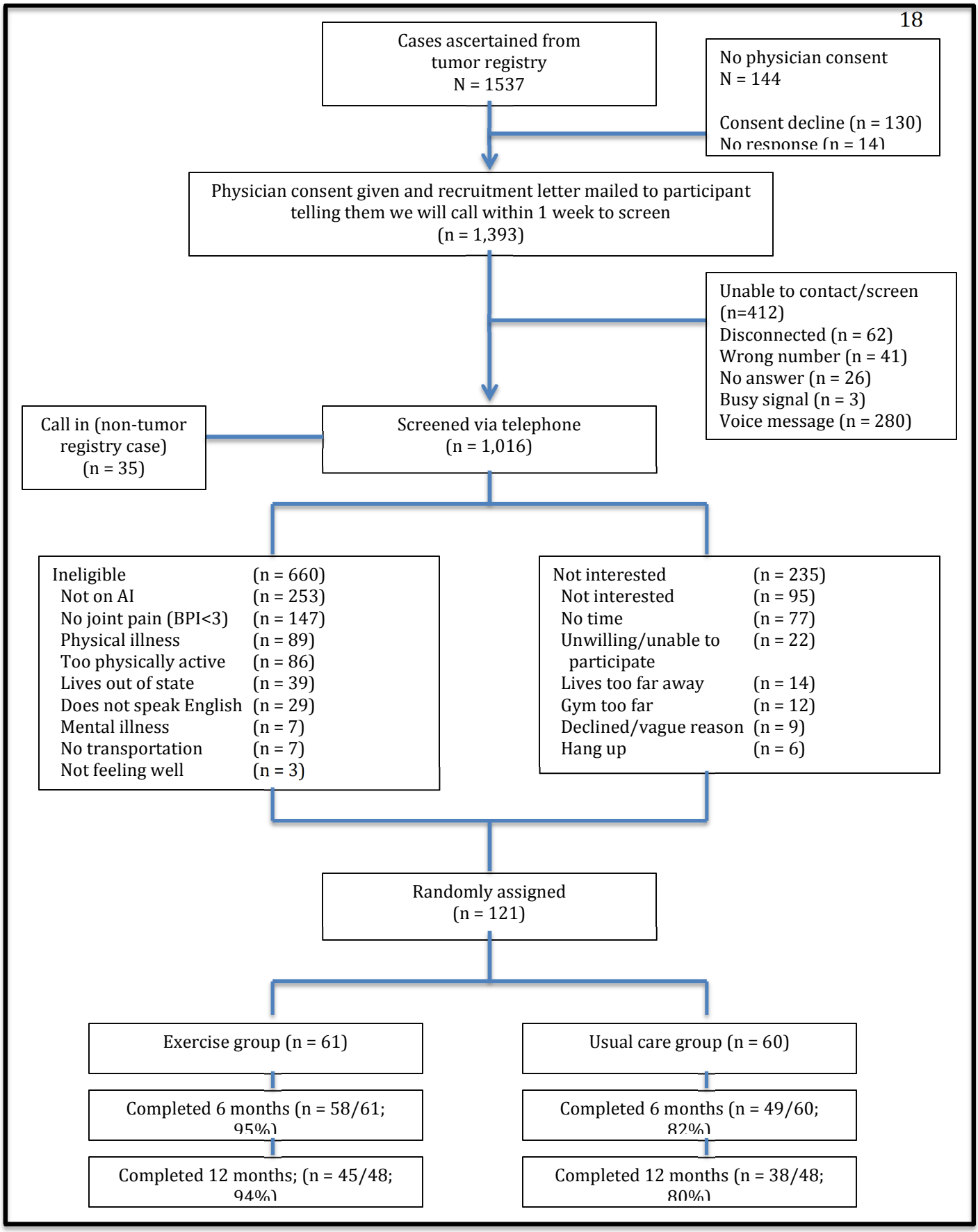

Fig 1. Flow of participants through Hormones and Physical Exercise study.

Table 1. Baseline Characteristics (n=120)[a]

Characteristic	Exercise (n=60)[b]	Usual Care (n=60)[b]	p[c]
Age (years)	62.0 ± 7.0	60.5 ± 7.0	0.245
Body mass index (kg/m^2)	30.0 ± 6.8	28.7 ± 5.5	0.275
Time on AI	1.9 ± 1.9	1.8 ± 1.3	0.888
Race/Ethnicity (%)			0.846
Non-Hispanic White	86.9	88.3	
Hispanic	1.6	5.0	
African American	9.8	6.7	
Asian/Pacific Islander	1.6	1.7	
American Indian	0.0	1.67	
Education (%)			0.290
High school graduate	9.8	15.0	
Some school after high school	32.8	41.7	
College graduate +	57.4	43.3	
Stage (%)			0.909
Stage 0 (in situ) and Stage I	60.7	61.7	
Stage II and Stage III	39.3	38.3	
Surgery (%)			0.796
Lumpectomy or partial mastectomy	70.5	65.0	
Unilateral mastectomy	16.4	18.3	
Bilateral mastectomy	13.1	16.7	
Treatment (%)			0.633
Chemotherapy	6.6	8.33	
Radiation	36.1	40.0	
Chemotherapy and Radiation	45.9	35.0	
Surgery Only	11.5	16.7	
Time Since Diagnosis	2.7 ± 3.1	3.3 ± 3.9	0.303

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

Table 2. Effect of exercise vs. usual care on depression changes at baseline, 6-, and 12 months[a, b]

	Exercise (n=60)	**Usual Care (n=60)**	**p-value**
Baseline	12.3 (1.3)	12.5 (1.3)	0.885
6 Month	8.9 (1.1)	11.9 (1.1)	0.054
Change	-3.5 (0.8)	-0.6 (0.8)	0.018
	Exercise (n=45)	**Usual Care (n=38)**	
12 Month	7.9 (1.2)	12.5 (1.4)	0.011
Change	-4.7 (1.0)	0.3 (1.1)	0.001

[a] Numbers are change in CES-D using least-square mean (SE)

[b] Model controls for baseline CES-D score and study arm

Table 3. Mean depression scores and changes of those above and below CES-D score of 16 at baseline, 6-, and 12 months.[a]

		Exercise (n=60)	**Usual Care (n=60)**	**P-value**
CESD ≥ 16 (n=35)	**Baseline**	23.7 (7.9)	26.8 (8.8)	0.272
	6 Month	12.3 (7.7)	20.9 (11.2)	0.012
	Change	-12.06 (2.0)	-5.23 (2.1)	0.025
	12 Month	11.9 (9.7)	19.1 (10.3)	0.084
	Change	-12.6 (2.5)	-5.5 (2.8)	0.073
CESD < 16 (n=85)	**Baseline**	7.4 (4.5)	6.9 (4.21)	0.599
	6 Month	7.4 (5.6)	8.3 (6.6)	0.513
	Change	0.1 (0.8)	1.3 (0.8)	0.308
	12 Month	6.1 (5.8)	9.9 (6.4)	0.021
	Change	-1.3 (1.0)	2.9 (1.0)	0.005

[a] Numbers are change in CES-D using least-square mean (SE)

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

	Change in CES-D Exercise Intervention LSMEAN (SE)	Change in CES-D Usual Care LSMEAN (SE)	p
Stage O and I (n=75)			
6 month	-2.5 (1.1)	-1.2 (1.1)	0.370
12 month	-4.0 (1.1)	-0.2 (1.2)	0.027
Stage II and III (n=45)			
6 month	-4.8 (1.4)	0.3 (1.4)	0.013
12 month	-6.0 (1.8)	1.7 (1.9)	0.006
AI < 20 months (n= 59)			
6 month	-3.3 (1.2)	0.1 (1.2)	0.054
12 month	-4.6 (1.7)	-1.4 (1.8)	0.198
AI ≥ 20 months (n = 59)			
6 month	-4.0 (1.3)	-1.0 (1.2)	0.097
12 month	-5.1 (1.1)	2.2 (1.2)	<0.001
Attendance < 82 (n = 29)[b]			
Min per week 6 month	-3.2 (1.2)	N/A	<0.001
12 month	-3.4 (1.4)	N/A	<0.001
Attendance ≥ 82 (n = 31)[b]			
Min per week 6 month	-4.2 (1.0)	N/A	<0.001
12 month	-6.2 (1.3)	N/A	<0.001

[a] Numbers are change in CES-D using least-square mean (SE)

[b] P-value is for t-test