January 2012

Exercise, Aromatase Inhibitors, Quality Of Life, And Breast Cancer

Michelle Baglia
Yale University, michelle.baglia@yale.edu

EXERCISE, AROMATASE INHIBITORS, QUALITY OF LIFE, AND BREAST CANCER

By

Michelle Baglia

A Thesis Presented to

The Faculty of the Yale School of Public Health

Yale University

In Candidacy for the Degree of

Master of Public Health

2012

Abstract

Purpose: We conducted a randomized controlled trial of 39 breast cancer survivors who were currently taking aromatase inhibitors and experiencing painful side effects. The purpose of this study was to investigate the role of a 6-month exercise intervention on (1) endocrine-related quality of life and (2) overall quality of life. **Methods:** Eligible women completed self-administered questionnaires at baseline and 6 months including the FACT-B +ES to assess quality of life. The participants were randomized to either an exercise intervention group that met twice weekly with a personal trainer or usual care. T-tests and χ^2 analyses were used to assess differences in endocrine-related quality of life over the 6-month intervention period as well as overall quality of life. The subscales of the FACT-B were examined independently using t-tests. **Results:** The average baseline endocrine-related QOL score was 56.2 for all participants in the study. The average score did not differ by treatment group (p=0.81). Mean 6-month changes from baseline for exercisers for the full QOL endocrine subscale was +3.3 compared to usual care (+1.8). The difference between the two groups was not statistically significant (p=0.32). A significant difference between the exercisers and usual care group for favorable changes in joint pain was observed (p-value = 0.014). A moderately significant effect was also seen for favorable changes on bloating in exercisers as compared to the usual care group (p-value = 0.055). **Conclusion:** In this study, aerobic exercise, such as treadmill walking, and strength training were associated with increases in endocrine-related quality of life. In particular, the intervention was associated with significant decreases in joint pain. These results are encouraging for post-menopausal women who are recommended to take AIs to improve their prognosis.

Acknowledgements

I would like to thank my primary thesis reader and mentor, Dr. Melinda Irwin, and my secondary reader, Dr. Cary Gross, for all of their insight and guidance throughout the thesis process. I am thankful to Dr. Irwin for all of the support and encouragement she provided me as well as the opportunity to use her data for my thesis. Additionally, I would like to thank the members of the HOPE study, Dr. Brenda Cartmel, Yang Zhou, Maura Harrigan, Martha Fiellin, and Scott Capozza, for being available to answer questions and providing support to me. I am grateful to my internship preceptor, Dr. Susan Mayne, for helping me to find such a great opportunity and excellent environment in which to complete my thesis. I am appreciative to the Friends of the Cynthia Barnett Cancer Prevention Fellowship for seeing the value of and helping to fund my summer internship.

Finally, I am especially grateful to my family for always encouraging and believing in me. I would like to thank my husband, Mark, who supported and loved me unconditionally throughout the thesis process as well as my daughter, Carys, who was supportive in ways she will never know. I am grateful to Mark, Carys, and my son, Adrian, for helping me to keep my life in perspective and helping me to realize my full potential.

Table of Contents

List of Tables

Introduction

Breast cancer is the leading cancer diagnosis in women in the United States. Of those diagnosed, approximately 70% present with estrogen receptor positive tumors[1]. Aromatase inhibitors (AIs) have been shown to be the most effective hormonal/endocrine therapy treatment in estrogen receptor-positive breast cancer, and are therefore considered standard of care and generally prescribed for postmenopausal women diagnosed with estrogen-receptor positive breast cancer[1]. Because of their physiological action mechanism, AIs cause lowered levels of estrogen which are associated with menopausal symptoms, such as hot flashes and night sweats, which in turn may impair quality of life[2]. Given the effectiveness of AIs in reducing both risk of recurrence and breast cancer death, and therefore the strong recommendation by clinicians for their patients to take AIs, understanding how to reduce the severity of AI related side effects is necessary.

Numerous studies have examined the relationship between physical activity and well-being, depression, anxiety, physical and emotional functioning, overall quality of life, and other psychosocial factors in breast cancer survivors[3-4]. Exercise has been shown to improve overall quality of life in women diagnosed with breast cancer[5-7]. However, there have not been any studies to date that have explored the impact of exercise on side effects of AIs and on endocrine-related QOL in women taking an AI for early stage breast cancer. QOL in cancer survivors is commonly measured via the Functional Assessment of Cancer Therapy (FACT) questionnaire, with subscales developed for particular cancers, e.g., FACT-Breast (FACT-B) for breast cancer. Furthermore, an endocrine-subscale was recently developed and validated for use with the FACT-B, the FACT-B endocrine subscale or FACT-B-ES, and is comprised of 18 questions[3].

An additional question was added to assess joint pain[8], as this is a common side effect of AIs, making a 19 question endocrine subscale (Table 1). This scale has high validity and reliability making it appropriate for measuring endocrine symptoms in women diagnosed with breast cancer taking AIs[3].

The purpose of this study, entitled the Hormones and Physical Exercise (HOPE) Study, was to examine, in 180 postmenopausal breast cancer survivors who have been taking an AI for at least 6 months and reporting at least mild arthralgias (i.e., joint pain), the effect of a randomized controlled exercise intervention vs. usual care on endocrine-related QOL. We hypothesized that the exercise group would show improved endocrine-related QOL measures as compared to the usual care group. This is a preliminary analysis on the first 39 women who completed 6 months of the intervention.

Materials and Methods

Study Population

Women diagnosed with Stage I-IIIC breast cancer were eligible for the study (see Table 2). AIs are not approved for ductal carcinoma in situ (DCIS), therefore women diagnosed with DCIS were not eligible. Participants must also have been taking an AI for at least 6 months and be currently experiencing side effects of the medication (i.e., at least mild arthralgia, defined as > 3 on the Brief Pain Inventory (BPI) Short Form Questionnaire[9]).

To observe a maximal effect from the exercise intervention, only women reporting less than 90 min/wk of moderate-to-vigorous intensity aerobic exercise and no strength training in the

previous year, as well as low fitness level (< 25 ml/kg/min, as measured by VO_2 max), were eligible to participate. Because a majority of the US population including breast cancer survivors are physically inactive, we anticipated excluding < 25% of the population based on this criteria[10].

Recruitment

We used the Rapid Case Ascertainment (RCA) Shared Resource Service of the Yale Cancer Center to obtain names of women diagnosed with hormone receptor positive breast cancer and treated at one of four hospitals in CT: Smilow Cancer Hospital at Yale-New Haven, St. Raphael's Hospital, Bridgeport Hospital, and Greenwich Hospital. The RCA provides the PI with potential participants' names and their physician's names. Physicians were contacted first for permission to contact the participant. If approved by the physician, we then mailed an invitation letter to the participant, describing the study and telling her that the study manager would call her within a week to tell her about the study and to solicit her interest and eligibility (i.e., screening telephone call). If the participant was eligible and interested, she was scheduled for a baseline visit.

Between April 1, 2010 and October 1, 2011, we completed 555 screening telephone calls. Of the 555 women screened, 25% were ineligible because of discontinuation of AI treatment because of side effects or choosing not to take AIs primarily because of potential side effects, another 38% were ineligible for various reasons, and 25% were not interested. The remaining 12% (n = 65) were enrolled in the study and subsequently randomized to the intervention or

usual care group. Of these 65 women, 39 completed six months of the study as of March 1, 2012, and are included in the analyses.

Data Collection

Data collection for this study involved a screening phone call, clinic visits at baseline and 6-months, and 6 months of the exercise intervention or usual care. Participants completed a QOL questionnaire, a 7-day daily activity log, a physical activity questionnaire, and attended a clinic visit for physical measurements at baseline and 6 months.

Randomization

Participants were randomized to either the exercise group or usual care with equal probability, with blocking on whether taking a bisphosphonate (Y/N) and whether pain started after initiating the AI (Y/N). Those women randomized to the exercise group were scheduled for their first supervised exercise training session at a local health club immediately. Women randomized to the usual care group were contacted by a trained health professional on a monthly basis to discuss relevant health topics so as to maintain study compliance.

Measures

Demographics and medical history. Self-administered questionnaires were completed by the participants for the baseline visit to collect this information.

Endocrine-related QOL. QOL was measured by self-report at baseline and 6 month clinic visits and reviewed by research staff. QOL was measured using the Functional Assessment of Cancer

Therapy-Breast (FACT-B) questionnaire (version 3), together with the endocrine symptom subscale (ES) questionnaire (FACT-B+ES)[11]. The FACT-B is a 36-item questionnaire with six subscales assessing physical, social, emotional, and functional well-being, and additional concerns more specific to women with breast cancer (Appendix 1). The ES was designed for use with the FACT-B and comprises 19 items (e.g., hot flashes, night sweats, weight gain, joint pain (see Table 1)). Participants indicated how true a statement had been for them over the past 7 days using a 5-point scale ranging from 0 (none at all) to 4 (very much). All items received equal weighting for the analysis.

Physical activity. At baseline and 6-months, participants completed a 7-day physical activity log (PAL)[12] and an interviewer-administered physical activity questionnaire[13] to assess physical activity over the past 6 months. For the PAL, women recorded the type and duration of any recreational activity performed on each day. Hours per week spent in moderate-to-vigorous intensity aerobic activity were determined using Ainsworth's Compendium of Physical Activities[14].

Anthropometrics. Height and weight were measured at baseline and 6 months and BMI was calculated. Participants were weighed in light indoor clothing, without shoes, rounding up to the nearest 0.1 kg; height was measured in a standard manner, without shoes, using a stadiometer, rounding up to the nearest 0.1 cm. All measures were performed and recorded twice in succession by the same technician and averaged for data entry.

Exercise Intervention

The exercise intervention group received social and behavioral support and research staff contact time to encourage them to increase their exercise level to include twice weekly strength-training sessions and 150 min of aerobic exercise per week (e.g., three 50-min aerobic exercise sessions or five 30-min sessions) over 6 months. The trainer and participant(s) met at a local gym designated by the study weekly during designated times.

Strength Training Sessions: Each strength training session was ~45 minutes. Six common strength-training exercises were performed using variable resistance machines (for muscles of the chest, back, shoulders, quadriceps, hamstrings, and gluteals, as well as biceps and triceps). We used the protocol developed by Katie Schmitz and colleagues. Their protocol was used in the Physical Activity and Lymphedema (PAL) trial of strength training on lymphedema in breast cancer survivors[15-16].

Aerobic Exercise Intervention: The participants were also required to do aerobic exercise for a total of 150 min/week (the current PA recommendation[17]), whether it be at the health club or in their neighborhood. Participants gradually worked up to exercising 150 min per week within the first two months.

Recording of Strength and Walking Exercise Sessions: Following each strength and aerobic exercise session, subjects completed a physical activity log. The logs were submitted weekly to the Exercise Trainer, who reviewed the log in the presence of the participant. If two days of strength training and 150 min/wk of aerobic exercise were not performed in the previous week, the trainer and

participant discussed the barriers experienced by the participant which prevented the participant from fulfilling the prescribed exercise regimen.

Usual Care

Immediately after randomization, participants in the usual care group were provided written information that emphasized the importance of a healthy lifestyle. Participants were encouraged to follow the NCI and ACS physical activity guidelines. Each month, women randomized to usual care were contacted by a trained health professional to discuss health education topics relevant to breast cancer survivors. Health education sessions that focused on issues relevant to women taking AIs, and breast cancer survivors in general, were included.

Statistical Analysis

Participants were grouped according to the intention-to-treat procedure in which all participants were grouped according to their intervention assignment at randomization regardless of adherence. A sample size of 39 women was used at the time of this preliminary analysis because this was the number of participants who had completed 6-months of the intervention as of March 1, 2012. T-tests and χ^2 analyses were used to assess between-group differences at baseline. The endocrine-related QOL score was calculated by subtracting each individual answer for each question from 4 and totaling the sum from the 19 questions with a total possible score of 0 to 76, with higher scores indicating better QOL. The total summed scores for the exercise and usual care groups were then compared using a t-test. A t-test was also used to test for significant within group differences between baseline and 6 months. Differences in response between the groups on a per question basis were also examined using t-tests. Changes in endocrine-related

QOL by adherence to the intervention were examined in the exercise group only. Changes in the FACT-B by intervention group were also examined by scoring and summing the FACT-B in a similar manner to the endocrine subscale where answers to negative questions were subtracted from 4 and positive questions were scored as the answer on the number scale given. The individual subscales of the FACT-B (physical (7 items, possible score range 0-28 points), social (7 items, possible score range 0-28 points), emotional (6 items, possible score 0-24 points), functional (7 items, possible score range 0-28 points), and breast cancer (9 items, possible score range 0-36 points) subscales) were scored and examined separately. Aggregate scores for the FACT-B (which included the physical, social, emotional, functional, and breast cancer subscales) and FACT-B +ES were calculated as well (possible score range 0-144 and 0-220, respectively). T-tests were used to assess differences between intervention groups at baseline, 6 months, and changes over the intervention period for each subscale separately as well as the aggregate scores for the FACT-B and FACT-B + ES. Additionally, regression analysis was used to build a model to determine if there were any baseline characteristics associated with endocrine-related QOL at baseline. Statistical analyses were performed using SAS software (version 9.2; SAS Institute Inc, Cary, NC).

Results

Baseline characteristics

Baseline demographic and physiologic data in the exercise and usual care groups were similar (Table 2). The average age of study participants was 62.7 years. The majority (87.2%) of participants were non-Hispanic white. The participants were, on average, overweight at baseline

(average BMI 28.8) and averaged 62.9 minutes per week of recreational exercise on the daily activity log. Average time since breast cancer diagnosis was 2.7 years. The average length of time participants had been taking an AI was 2.1 years.

Change in physical activity levels and adherence to the exercise intervention

At baseline, the participants in both groups averaged 71.6 minutes per week of exercise and no strength training over the previous six months as measured by the PAQ. On average, exercisers increased their weekly activity, as measured by the PAQ, by 195.5 minutes per week at six months while the usual care group increased their weekly activity by 39.6 minutes per week ($p=0.0008$). Exercisers increased their weekly strength training by 58.6 minutes compared to controls who increased strength training by 7.4 minutes per week ($p<.0001$).

When examining adherence to the exercise intervention among women randomized to exercise, as measured by the 7-day Physical Activity Log, on average, exercisers completed 135 minutes per week of moderate-to-vigorous intensity exercise over the 6 month study period, and 47.2% reported participating in at least 150 min/wk of exercise. 57.1% reported participating in 120 min/wk of exercise (80% of the goal). Attendance to the twice-weekly in-person/supervised exercise sessions was 83.1%, with 81.0% of the exercisers attending at least 70% of the gym sessions and 61.9% attending at least 80% of the gym sessions (Table 3).

Baseline endocrine-related QOL by treatment group

The average baseline endocrine-related QOL score was 56.2 for all participants in the study. This score was out of 76 possible points with a higher score being indicative of a higher

measure of quality of life. The average score did not differ by treatment group (p=0.81). Each question was broken down individually to detect differences between the treatment groups by question. There were no statistical differences between the groups by question at baseline (all p>0.05). The association between baseline characteristics and baseline endocrine-related QOL was examined. Only age was associated with the measure—as age increased by one year the endocrine-related QOL score increased by 0.74 points.

Effect of exercise vs. usual care on endocrine-related QOL

Mean 6-month changes from baseline for exercisers for the full QOL endocrine subscale was +3.3 compared to usual care (+1.8) (Table 4). The difference between the two groups was not statistically significant (p=0.32). The questions were broken down into four groups by symptom type: vasomotor (hot flashes, cold sweats, night sweats), neuropsychological (lightheaded/dizzy, headaches, mood swings, irritableness), gastrointestinal (weight gain, vomiting, diarrhea, bloating), and gynecological (vaginal discharge, itching, bleeding, dryness, discomfort during intercourse, loss of interest in sex, breast tenderness)—so as to look for differences between groups for different types of symptoms. No significant differences were detected between the two groups. When each item on the endocrine subscale was evaluated independently, a significant difference between the exercisers and usual care group for favorable changes in joint pain was observed (p-value = 0.014). A moderately significant effect was also seen for favorable changes on bloating in exercisers as compared to the usual care group (p-value = 0.055). See Table 5 for complete results.

Effect of exercise on endocrine-related QOL stratified by potential effect modifiers

Several variables were examined as potential effect modifiers on the change in endocrine-related QOL including age, BMI, and time on AI. No effect modification was seen in this sample.

Effect of exercise on endocrine-related QOL stratified by adherence

Participants were classified as high adherers if they attended more than 80% of gym sessions or averaged at least 150 minutes of recreational exercise per week throughout the 6-month intervention. The effect of adherence on endocrine-related quality of life was not significant for percent of gym sessions attended, minutes per week of recreational exercise, or a combination of the two measures. These findings remained even when we defined high adherers differently, e.g., 70% of gym sessions or the median value.

Effect of exercise on endocrine-related QOL stratified by weight loss

On average, participants in the exercise group lost 1.76 pounds over the 6-month intervention period compared with 0.40 pounds lost among participants in the control group. Exercisers who lost weight had higher session attendance than those exercisers who maintained weight (87.1% vs. 78.6%, p=0.12) but reported similar average minutes per week spent doing moderate-to-vigorous aerobic exercise (140.5 vs. 158.9, p=0.51). When exercisers were stratified by weight loss vs. maintaining weight, there was a significant difference in changes in endocrine-related QOL. Exercisers who lost weight averaged a 5.4 increase in endocrine-related QOL whereas exercisers who maintained their weight averaged a 1.0 increase (p=0.049) (Table 6).

Effect of exercise vs. usual care on overall QOL measured by FACT-B

There were no significant differences at baseline between the intervention and usual care groups for overall FACT-B scores or any of the subscales (physical, social, emotional, functional, and breast cancer) (Table 3). Mean 6-month changes from baseline for exercisers for the FACT-B were +10.4 compared to usual care (+3.6). The difference between the two groups was moderately significant (p=0.097). When each subscale was examined separately there were significant differences in changes over 6-months for the physical well-being and social/family well-being subscales. Exercisers increased by 2.5 points on the physical well-being scale and 2.0 points on the social/family well-being scale compared to 0.1 and -0.3, respectively, for the usual care group (p=0.034, p=0.037, respectively). A moderately significant effect was detected for the entire FACT-B-ES 6-month changes between the exercisers and usual care group (p=0.081). The full list of group means and p-values for between group differences for the FACT-B and subscales can be found in Table 4.

Discussion

In this study, aerobic exercise, such as treadmill walking, and strength training were associated with increases in endocrine-related quality of life. In particular, the intervention was associated with significant decreases in joint pain. As joint pain is a significant concern for breast cancer survivors taking AIs, this finding is of particular importance. Adverse events associated with taking AIs are the main reason for treatment discontinuation[18]. These results are encouraging for post-menopausal women who are recommended to take AIs to improve their prognosis.

Due to adverse symptoms and treatment, cancer survivors may have difficulty changing physical activity levels[19]. The breast cancer survivors in this study were all experiencing pain associated with taking an AI for cancer treatment. This intervention was effective in getting these breast cancer survivors to increase their exercise levels indicating that even survivors experiencing moderate to severe adverse treatment-associated symptoms can increase their exercise levels. Furthermore, this increase in physical activity can alleviate pain associated with AI use.

Age was significantly associated with increased baseline endocrine-related QOL scores. This may be due to older women being less bothered by endocrine therapy side effects because of expected age-related declines. Younger women may feel that they are more limited in their abilities or have poorer overall health than their peers compared to older women which may influence the impact of endocrine therapy on quality of life. Other studies have shown that older breast cancer survivors are less affected by treatment over a variety of measures including health-related QOL[20-21].

The improvement in endocrine-related QOL observed among the exercise group was also observed among the usual care group, yet at a lower rate of improvement; thus, the between group differences in change in endocrine-related QOL was not significant. It is possible that this amount of time is not enough to measure favorable changes in many endocrine symptoms related to AI use. However, the intervention described in this study is a 12-month intervention so further results will allow for a potentially more meaningful effect of exercise on endocrine symptoms. The small sample size may also have inhibited us from finding a significant difference between the groups.

There was no effect of adherence on endocrine-related QOL scores. This may be because almost all of the participants attended at least 70% of the gym sessions and exercised recreationally for more than 110 minutes per week. While there were no incentives for attendance, the women were likely motivated to attend due to the free gym membership and personal trainer. With such a small sample size of exercisers it may have been difficult to detect a difference by adherence to the study goals due to low statistical power. However, the HOPE study described is set to enroll approximately 90 exercisers total which will potentially allow for a dose-response relationship with exercise on endocrine-related QOL to be detected. However, when stratified by weight loss, there was a significant difference in endocrine-related QOL. It may be that weight loss is a good predictor of true adherence to the study exercise goals.

A moderately significant effect of exercise was detected on the FACT-B +ES and the FACT-B QOL scales. This suggests that exercise may have an impact on overall QOL in breast cancer survivors. The FACT-B subscales allow for different aspects of QOL to be examined. A significant effect of exercise was seen in particular for the physical well-being and social/family well-being subscales. The participants in our study had normal levels of physical well-being for women taking AIs at baseline and this value increased over the study period to scores much closer to published values for women not undergoing endocrine-therapy[3]. It is well established that exercise is associated with more beneficial physical health outcomes, including better general and health-related QOL[22]. The participants had high levels of social well-being at baseline which increased over the study period for the exercise group. The social subscale may have shown a significant effect of exercise due to the social nature of the exercise-trainer sessions and the interaction between participants at gym sessions. The participants in our study

had high levels of emotional well-being as compared to previous studies of women undergoing various types of endocrine therapy so an increase in this measure may not have been seen due to the ceiling effect[3]. Although the participants in our study had relatively low scores on the breast cancer subscale which increased across the 6 month intervention period, a significant difference was not seen between the two groups (though the increase for the exercise group was 2-fold higher than the usual care group); however, a significant difference may be seen with a larger sample size.

One limitation of this study is that we did not screen on FACT-B-ES so there may be women who already had a high or healthy/normal FACT-B-ES at baseline and therefore no change was able to be observed. However, we did screen on other AI side effects, (i.e., arthralgias, pain/stiffness). Compared to other studies looking at FACT-B and FACT-B-ES QOL scales for breast cancer survivors currently taking AIs, the women in this study had lower scores for both measures[3]. The QOL scores for the women in this study were also lower than published values for breast cancer survivors not undergoing endocrine therapy. The endocrine subscale for women in our study had an average score of 55.2 (S.D. 8.9) at baseline compared to published values of 62.4 (S.D. 7.4) for women taking AIs, but not necessarily experiencing side effects, and 61.1 (S.D. 10.5) for women not taking AIs[3]. Given that this sample does have some adverse AI side effects, it is reasonable and somewhat expected that they had a lower or impaired FACT-B-ES as compared to breast cancer survivors undergoing endocrine therapy with AIs who may or may not be experiencing pain associated with AI use.

This is the first study to examine the effect of exercise specifically on endocrine-related QOL. Other studies have used various approaches to improving endocrine symptoms in breast

cancer survivors including mindfulness-based stress reduction[23], acupuncture[24], physical therapy, and targeted heat[18]. Pharmacological therapies such as use of non-steroidal anti-inflammatory drugs (NSAIDS), cyclooxygenase-2 (COX-2) inhibitors, glucosamine, and narcotic analgesics have also been studied but may be contraindicated or ineffective[18]. None of these non-pharmacological or pharmacological therapies have been shown to sufficiently effective in alleviating symptoms. Therefore, there is a strong need to develop better therapies to improve endocrine symptoms.

New joint symptoms/pain or vasomotor symptoms, which are common with AI endocrine therapy, are an indicator of more beneficial treatment outcomes including breast cancer recurrence[25]. While the reasoning is not fully understood, this provides strong evidence for the need for beneficial interventions that can improve these symptoms which are worse in women who may benefit the most from AI treatment. Further research is needed to better understand why some women experience worse symptoms than others and the role of exercise in alleviating these adverse symptoms to increase adherence to endocrine therapy.

Conclusions

Given the effectiveness of AIs in improving risk of recurrence and breast cancer death, and the resulting strong recommendation by clinicians for their patients to take AIs, understanding how to decrease the severity of AI side effects is necessary. Since side effects associated with AI use are quite common and this is the main reason for treatment discontinuation, this innovative non-pharmacologic intervention could benefit a large number of breast cancer survivors and increase the successful implementation of AIs in breast cancer

treatment. In our study, favorable changes in certain endocrine-related quality of life symptoms were observed. The effect of exercise on these symptoms is promising for breast cancer survivors whose physicians' have recommended AIs for treatment.

References

1. *Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group.* Lancet, 1992. **339**(8784): p. 1-15.
2. Oliveria, S.A., et al., *Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee.* Epidemiology, 1999. **10**(2): p. 161-6.
3. Fallowfield, L.J., et al., *Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B.* Breast Cancer Res Treat, 1999. **55**(2): p. 189-99.
4. Duijts, S.F., et al., *Effectiveness of behavioral techniques and physical exercise on psychosocial functioning and health-related quality of life in breast cancer patients and survivors--a meta-analysis.* Psychooncology, 2011. **20**(2): p. 115-26.
5. Courneya, K.S. and C.M. Friedenreich, *Physical exercise and quality of life following cancer diagnosis: a literature review.* Ann Behav Med, 1999. **21**(2): p. 171-9.
6. Schmitz, K.H., et al., *American College of Sports Medicine roundtable on exercise guidelines for cancer survivors.* Med Sci Sports Exerc, 2010. **42**(7): p. 1409-26.
7. Bicego, D., et al., *Effects of exercise on quality of life in women living with breast cancer: a systematic review.* Breast J, 2009. **15**(1): p. 45-51.
8. Fallowfield, L.J., et al., *Quality of life in the intergroup exemestane study: a randomized trial of exemestane versus continued tamoxifen after 2 to 3 years of tamoxifen in postmenopausal women with primary breast cancer.* J Clin Oncol, 2006. **24**(6): p. 910-7.
9. Wolff, I., et al., *The effect of exercise training programs on bone mass: a meta-analysis of published controlled trials in pre- and postmenopausal women.* Osteoporos Int, 1999. **9**(1): p. 1-12.
10. Das, U.N., *Is obesity an inflammatory condition?* Nutrition, 2001. **17**(11-12): p. 953-66.
11. Nicklas, B.J., et al., *Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial.* Am J Clin Nutr, 2004. **79**(4): p. 544-51.
12. Irwin, M.L., et al., *Influence of demographic, physiologic, and psychosocial variables on adherence to a yearlong moderate-intensity exercise trial in postmenopausal women.* Prev Med, 2004. **39**(6): p. 1080-6.
13. Irwin, M.L., et al., *Recruiting and retaining breast cancer survivors into a randomized controlled exercise trial: the Yale Exercise and Survivorship Study.* Cancer, 2008. **112**(11 Suppl): p. 2593-606.
14. Ainsworth, B.E., et al., *Compendium of physical activities: an update of activity codes and MET intensities.* Med Sci Sports Exerc, 2000. **32**(9 Suppl): p. S498-504.
15. Schmitz, K.H., et al., *Weight lifting in women with breast-cancer-related lymphedema.* N Engl J Med, 2009. **361**(7): p. 664-73.
16. Kelley, G.A. and K.S. Kelley, *Exercise and bone mineral density at the femoral neck in postmenopausal women: a meta-analysis of controlled clinical trials with individual patient data.* Am J Obstet Gynecol, 2006. **194**(3): p. 760-7.
17. Schmitz, K.H., et al., *Strength training and adiposity in premenopausal women: strong, healthy, and empowered study.* Am J Clin Nutr, 2007. **86**(3): p. 566-72.

18. Cella, D. and L.J. Fallowfield, *Recognition and management of treatment-related side effects for breast cancer patients receiving adjuvant endocrine therapy.* Breast Cancer Res Treat, 2008. **107**(2): p. 167-80.
19. Irwin, M.L., *Physical activity interventions for cancer survivors.* Br J Sports Med, 2009. **43**(1): p. 32-8.
20. Ganz, P.A., et al., *Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study.* J Natl Cancer Inst, 2002. **94**(1): p. 39-49.
21. Hopwood, P., et al., *The impact of age and clinical factors on quality of life in early breast cancer: an analysis of 2208 women recruited to the UK START Trial (Standardisation of Breast Radiotherapy Trial).* Breast, 2007. **16**(3): p. 241-51.
22. Penedo, F.J. and J.R. Dahn, *Exercise and well-being: a review of mental and physical health benefits associated with physical activity.* Curr Opin Psychiatry, 2005. **18**(2): p. 189-93.
23. Carlson, L.E., et al., *Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients.* Psychosom Med, 2003. **65**(4): p. 571-81.
24. Crew, K.D., et al., *Pilot study of acupuncture for the treatment of joint symptoms related to adjuvant aromatase inhibitor therapy in postmenopausal breast cancer patients.* J Cancer Surviv, 2007. **1**(4): p. 283-91.
25. Buzdar, A.U., *Medical oncology: Endocrine-therapy-related symptoms and breast cancer.* Nat Rev Clin Oncol, 2009. **6**(6): p. 309-10.

Appendix 1

FACT-B

Below is a list of statements that other people with cancer have said are important to their quality of life. Please indicate the extent to which you have experienced each of the statements during the past 7 days by circling the appropriate number using the following scale.

0	1	2	3	4
not at all	a little bit	somewhat	quite a bit	very much

During the PAST WEEK:

PHYSICAL WELL - BEING					
1. I have a lack of energy.	0	1	2	3	4
2. I have nausea.	0	1	2	3	4
3. Because of my physical condition, I have trouble meeting the needs of my family.	0	1	2	3	4
4. I have pain.	0	1	2	3	4
5. I am bothered by side effects of treatment.	0	1	2	3	4
6. I feel sick.	0	1	2	3	4
7. I am forced to spend time in bed.	0	1	2	3	4
SOCIAL/FAMILY WELL - BEING					
8. I feel close to my friends.	0	1	2	3	4
9. I get emotional support from my family.	0	1	2	3	4
10. I get support from my friends.	0	1	2	3	4
11. My family has accepted my illness.	0	1	2	3	4
12. I am satisfied with family communication about my illness.	0	1	2	3	4
13. I feel close to my partner (or the person who is my main support).	0	1	2	3	4
14. I am satisfied with my sex life.	0	1	2	3	4

During the PAST WEEK:
EMOTIONAL WELL - BEING

15. I feel sad.	0	1	2	3	4
16. I am satisfied with how I am coping with my illness.	0	1	2	3	4
17. I am losing hope in the fight against my illness.	0	1	2	3	4
18. I feel nervous.	0	1	2	3	4
19. I worry about dying.	0	1	2	3	4
20. I worry that my condition will get worse.	0	1	2	3	4

FUNCTIONAL WELL - BEING

21. I am able to work (include work at home).	0	1	2	3	4
22. My work (include work at home) is fulfilling.	0	1	2	3	4
23. I am able to enjoy life.	0	1	2	3	4
24. I have accepted my illness.	0	1	2	3	4
25. I am sleeping well.	0	1	2	3	4
26. I am enjoying the things I usually do for fun.	0	1	2	3	4
27. I am content with the quality of my life right now.	0	1	2	3	4

During the PAST WEEK:

ADDITIONAL CONCERNS

28. I have been short of breath.	0	1	2	3	4
29. I am self-conscious about the way I dress.	0	1	2	3	4
30. My arms are swollen or tender.	0	1	2	3	4
31. I feel sexually attractive.	0	1	2	3	4
32. I have been bothered by hair loss.	0	1	2	3	4
33. I worry about the risk of cancer in my family.	0	1	2	3	4
34. I worry about the effect of stress on my illness.	0	1	2	3	4
35. I am bothered by a change in weight.	0	1	2	3	4
36. I am able to feel like a woman.	0	1	2	3	4

Table 1: Endocrine Subscale for the FACT-B

Please indicate how true each statement has been for you during the past 7 days

Endocrine Symptom Subscale	Not at all	A little bit	Some-what	Quite a bit	Very much
I have hot flushes	0	1	2	3	4
I have cold sweats	0	1	2	3	4
I have night sweats	0	1	2	3	4
I have vaginal discharge	0	1	2	3	4
I have vaginal itching/irritation	0	1	2	3	4
I have vaginal bleeding or spotting	0	1	2	3	4
I have vaginal dryness	0	1	2	3	4
I have pain or discomfort with intercourse	0	1	2	3	4
I have lost interest in sex	0	1	2	3	4
I have gained weight	0	1	2	3	4
I feel lightheaded/dizzy	0	1	2	3	4
I have been vomiting	0	1	2	3	4
I have diarrhea	0	1	2	3	4
I get headaches	0	1	2	3	4
I feel bloated	0	1	2	3	4
I have breast sensitivity/tenderness	0	1	2	3	4
I have mood swings	0	1	2	3	4
I am irritable	0	1	2	3	4
I have pain in my joints	0	1	2	3	4

Table 2: Baseline Characteristics of randomized participants in the HOPE study (N=39)

	Exercisers mean (SD) or %	Usual care mean (SD) or %
N	21	18
Age (y)	63.0 (7.0)	62.4 (6.8)
Ethnicity (%)		
Non-Hispanic white	81.0	94.4
African-American	14.3	0.0
Hispanic	4.8	5.6
Education (%)		
Less than High School graduate	0.0	5.6
High School graduate	9.5	0.0
Some school after high school	38.1	38.9
College graduate +	52.4	55.6
Time since diagnosis (y)	2.6 (1.4)	2.8 (1.2)
Disease stage (%)		
Stage I	52.4	50.0
Stage II	28.6	38.9
Stage III	14.3	5.6
Unknown	4.8	5.6
Treatment (%)		
None	14.3	11.1
Radiation only	33.3	44.4
Chemotherapy only	4.8	11.1
Radiation and chemotherapy	47.6	33.3
Time on AI (y)	2.0 (1.5)	2.3 (1.2)
Weight (kg)	77.1 (17.3)	73.4 (12.6)
BMI (kg/m^2)	29.9 (7.5)	27.9 (5.7)
Physical Activity Questionnaire[1] (min/wk recreational exercise)	76.4 (125.6)	65.9 (73.2)
Daily Activity log[2] (min/wk recreational exercise)	52.1 (72.3)	75.4 (105.7)

No statistically significant differences between exercise and usual care groups at baseline.
[1]Mean min/week of moderate- to vigorous-intensity sports/recreational physical activity as determined from the baseline physical activity questionnaire that assessed activity levels for 6 months prior to study enrollment
[2]Mean min/week of moderate- to vigorous-intensity sports/recreational physical activity at baseline as determined from the 7-dy Daily Activity Log

Table 3: Adherence from baseline to 6-months in the HOPE study (N=39)

	Baseline to 6 Months
Min/week	
Mean (SD)	135 (71.9)
% of goal	90%
% of subjects adhering to	
≥ 150 min/week (100%)	43%
≥ 120 min/week (80%)	57%
≥ 90 min/week (60%)	76%
≥ 60 min/week (40%)	91%
≥ 30 min/week (20%)	100%

Table 4: Change in Fact-B and subscales from baseline to 6-months by randomization group

	Exercisers mean (SD)	Usual care mean (SD)	p-value
Endocrine Subscale			
Baseline	56.5 (9.0)	55.8 (10.1)	0.81
6 months	59.9 (9.4)	57.7 (9.1)	0.46
Change from baseline to 6 months	3.3 (5.2)	1.8 (3.5)	0.32
FACT-B			
Baseline	99.5 (19.6)	101.6 (10.9)	0.68
6 months	109.9 (14.9)	105.1 (15.1)	0.33
Change from baseline to 6 months	10.4 (14.2)	3.6 (10.2)	0.097
Physical Well-Being			
Baseline	21.1 (4.3)	22.6 (2.9)	0.25
6 months	23.6 (2.7)	22.7 (3.6)	0.34
Change from baseline to 6 months	2.5 (3.8)	0.1 (2.7)	0.034
Social/Family Well-Being			
Baseline	21.6 (5.7)	21.1 (5.3)	0.76
6 months	23.7 (4.7)	20.7 (5.3)	0.077
Change from baseline to 6 months	2.0 (3.4)	-0.3 (3.5)	0.037
Emotional Well-Being			
Baseline	18.6 (4.2)	18.9 (2.2)	0.80
6 months	19.9 (4.2)	20.4 (2.6)	0.60
Change from baseline to 6 months	1.2 (2.6)	1.6 (2.9)	0.72
Functional Well-Being			
Baseline	19.8 (5.4)	20.3 (3.4)	0.73
6 months	22.0 (4.4)	21.4 (4.7)	0.66
Change from baseline to 6 months	2.2 (5.7)	1.1 (4.0)	0.47
Breast Cancer Subscale			
Baseline	18.3 (4.9)	18.7 (3.7)	0.77
6 months	20.7 (3.6)	19.9 (4.0)	0.52
Change from baseline to 6 months	2.4 (3.5)	1.2 (2.2)	0.21
FACT-B + ES			
Baseline	156.0 (27.0)	157.4 (17.1)	0.86
6 months	169.8 (21.7)	162.8 (18.3)	0.29
Change from baseline to 6 months	13.7 (16.5)	5.4 (11.6)	0.081

Table 5: Changes in ES for individual questions by randomization group

	Exercisers Mean (SD)	Usual Care Mean (SD)	p-value
Vasomotor			0.58
Hot flashes	0.2500	0.3889	0.72
Cold sweats	0.2381	0.2222	0.97
Night sweats	0.0476	0.3889	0.30
Neuropsycological			0.47
Lightheaded/dizziness	-0.0476	0.2222	0.31
Headaches	0.0476	0.0556	0.97
Mood swings	0.2857	0.5000	0.47
Irritableness	0.3810	0.3333	0.89
Gastrointestinal			0.46
Weight gain	0.5714	0.5556	0.97
Vomiting	0	0	*n/a*
Diarrhea	-0.0952	0.0556	0.39
Bloating	0.5238	0	0.055
Gynecological			0.27
Vaginal discharge	-0.1429	0	0.43
Vaginal itching/irritation	-0.0476	-0.2222	0.52
Vaginal bleeding	0	0	*n/a*
Vaginal dryness	0.2857	-.4444	0.024
Discomfort during intercourse	-0.2000	-0.0588	0.71
Loss of interest in sex	-0.1905	0	0.73
Breast sensitivity/tenderness	0.1429	-0.3333	0.17
Other			
Joint pain	1.0476	0.2778	0.014