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# Effect Of Exercise On Vo2max In Breast Cancer Survivors Taking Aromatase Inhibitors: The Hormones And Physical Exercise (hope) Study

Mia Sorkin

*Yale University*, [mia.sorkin@yale.edu](mailto:mia.sorkin@yale.edu)

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**Effect of Exercise on VO<sub>2</sub>max in breast cancer survivors taking aromatase inhibitors:  
The Hormones and Physical Exercise (HOPE) Study**  
**By**  
**Mia Sorkin**

**A Thesis Presented to  
The Faculty of the Yale School of Public Health  
Yale University**

**In Candidacy for the Degree of  
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## **Abstract**

**Purpose:** The purpose of this study was to investigate the effects of a yearlong exercise intervention compared to usual care on cardiorespiratory fitness in sedentary breast cancer survivors who were taking aromatase inhibitors and experiencing arthralgia. **Methods:** Participants were randomized to either an exercise intervention group that met twice weekly with a personal trainer or usual care. Participants completed self-administered questionnaires, including reporting demographic and personal characteristics, and a graded treadmill test using a modified Branching protocol at baseline and at the end of the 12-month study. T-tests and  $\chi^2$  analyses were used to assess change in cardiorespiratory fitness, measured by  $VO_{2max}$ , over the 12 month study period. Potential modifiers of change in cardiorespiratory fitness were examined, these included, disease and treatment characteristics, BMI, and age. **Results:** The average age of the sample was 63.3 years (SD $\pm$  6.2) and women had been taking an AI for an average of 2 years. A majority of women were diagnosed with Stage I breast cancer (54%) and received treatment after surgery of radiation and/or chemotherapy (92%). The average percent change in  $VO_{2max}$  was 5.28 ml/kg/min among exercisers compared to negligible change (0.14 ml/kg/min) among the usual care group (p=0.094). No effect modification was observed among the *a priori* variables; however, a stratified analysis revealed similar trends among age strata, baseline BMI and fitness levels, as well as stage and treatment groups. **Conclusion:** In this study, an exercise intervention including a combination of strength training and aerobic exercise was effective in improving cardiorespiratory fitness among previously sedentary breast cancer survivors taking aromatase inhibitors. These results are encouraging for post-menopausal women who are recommended to take AIs to reduce their risk of cardiovascular and all-cause mortality.

## Background

Breast cancer is the most frequently diagnosed cancer in women, and accounted for 23% (1.38 million) of total new cancer cases and 14% (458,400) of the total cancer deaths in 2011.<sup>1</sup> Approximately two-thirds of women with this malignancy are diagnosed with estrogen-receptor positive tumors.<sup>2</sup> This type of breast cancer is treated with endocrine therapy to prevent cancer recurrence and improve survival. Until the early 2000s, tamoxifen had been the mainstay of endocrine therapy for pre- and post-menopausal women; recently though, several large randomized clinical trials have revealed aromatase inhibitors (AI) as a superior treatment option for postmenopausal women, demonstrating greater disease-free survival, time to recurrence, and overall survival, compared with tamoxifen.<sup>3</sup>

The American Society of Clinical Oncology guidelines recommend that AIs be used as adjuvant endocrine therapy in postmenopausal women with Stage I-III hormone receptor-positive breast cancer, either as initial monotherapy or after 2-5 years of tamoxifen therapy.<sup>3</sup> Currently, there are three third-generation AIs that have been approved by the FDA for adjuvant therapy in postmenopausal women with hormone receptor-positive, early stage breast cancer: anastrozole, letrozole and exemestane. AIs prevent the peripheral conversion of androgens into estradiol, thus lowering circulating estrogen to below detectable levels. Exemestane, a steroidal drug, binds irreversibly to the aromatase enzyme, and the nonsteroidal drugs, letrozole and anastrozole, reversibly bind to the aromatase enzyme. All 3 drugs are used widely at this time.<sup>3</sup>

While AIs are now regarded as the standard of care for adjuvant therapy of hormone receptor positive breast cancer in postmenopausal women, there remains concern regarding the toxicity of these drugs. Cumulative results indicate that arthralgia, defined as pain or stiffness in

the joints, is one of the major adverse events associated with AI therapy, and has been reported in up to 50% of patients, and the most common reason for drug discontinuation<sup>4</sup> Arthralgia has been observed among patients treated with both steroidal (exemestane) and non-steroidal (anastrozole and letrozole) AIs. Spontaneous symptom resolution is rare during therapy, but common after cessation of AI treatment.

Other concerns of AI treatment include their adverse effects on bone health and metabolism, endocrine related quality of life, cognitive ability, and cardiovascular disease (CVD) risk.<sup>4,5,6,7</sup>Of note, CVD mortality is more common among breast cancer survivors than breast cancer-related mortality.<sup>8</sup>

Elevated risk of CVD is likely in part due to low levels of circulating endogenous estrogens caused by AI treatment, resulting in the loss of estrogenic protection.<sup>9</sup> Jones, et al (2007), proposed the “Multiple Hit Hypothesis”, which described a heightened risk of cardiovascular disease among women diagnosed with early breast cancer: preexisting risk factors, such as age, menopause status, and previous chronic disease are compounded by the varying degrees of cardiovascular insults from adjuvant therapies, resulting in an overall greater susceptibility to cardiovascular events among women diagnosed with breast cancer.<sup>10</sup> A recent meta-analysis of randomized trials found that the risk of grade 3 and 4 cardiovascular adverse events was statistically significantly greater among postmenopausal women receiving AI treatment compared to the risk of women receiving tamoxifen (tamoxifen is a selective estrogen receptor modulator, thus not decreasing estrogen levels similarly to the AIs).<sup>11</sup> Moreover, Bell et al (2011) described notable adverse changes in lipid levels (total cholesterol, lipoproteins, and triglycerides) after 3 months of treatment with exemestane and letrozole, serving as surrogate measures of long-term cardiovascular risk.



Cardiorespiratory fitness is an important, yet underused prognostic measure in clinical and research settings. Peak, or maximal, oxygen uptake ( $\text{VO}_2\text{max}$ ) is the gold standard of measuring cardiorespiratory fitness, and can be determined by the amount of oxygen inhaled and carbon dioxide exhaled.<sup>12</sup> This objective measure is obtained through incremental cardiorespiratory exercise (e.g. treadmill walking or bicycle ergometer) to exhaustion or symptom limitation. Studies have demonstrated the association between cardiorespiratory fitness and all-cause mortality and cardiovascular events in healthy individuals.<sup>7,13,14</sup> A recent meta-analysis, conducted by Kodama and colleagues (2009), found that among healthy men and women, the relative risk of all-cause mortality and CVD events were lowered by 13% and 15%, respectively, per 1-MET increase level of  $\text{VO}_2\text{max}$  (RR = 0.87 (95%CI: 0.84-0.90) and 0.85 (95%CI: 0.82-0.88), respectively).<sup>7</sup> Similarly, recent evidence indicates  $\text{VO}_2\text{max}$  provides critical information for predicting cancer-related pre- and post-operative health outcomes and understanding cancer-therapy induced cardiac effects.<sup>15,16,17,18,19</sup> In cross-sectional studies, a notable lower level of  $\text{VO}_2\text{max}$ , measured at diagnosis, has been observed among lung and breast cancer patients, consistently ~30% lower than that of age- and sex-matched sedentary individuals without a history of cancer.<sup>20,21</sup> The fitness level of these patients remained significantly lower or became even further reduced if no exercise interventions were introduced. In a recent meta-analysis, Fong and colleagues reviewed 10 exercise interventions on  $\text{VO}_2\text{max}$  conducted in women diagnosed with breast cancer and found, those randomized to exercise, compared with control, experienced an increased peak oxygen consumption (2.2mL/kg/min, 1.0-3.4,  $p < 0.01$ ) and peak power output (21.0W, 13.0 to 29.1,  $p < 0.01$ ). This improvement in  $\text{VO}_2\text{max}$  is encouraging in regards to improving physical quality of life as well as decreasing CVD risk. However, none of the studies published included a high CVD risk sample of women taking AIs. To our

knowledge there are no studies that focus on the specific effects of exercise on CVD outcomes among patients taking an AI. Thus, the purpose of this study was to examine the effect of a 1-year exercise intervention compared to usual care on cardiorespiratory fitness in 50 postmenopausal women diagnosed with hormone-receptor positive breast cancer who have been taking an AI for at least 6 months.

## **Materials and Methods**

### *Study Population*

The aim of the Hormone and Physical Exercise (HOPE) study was to examine, in 121 postmenopausal breast cancer survivors who have been taking an AI for at least 6 months and are experiencing at least mild arthralgia originating during AI treatment, the yearlong effect of exercise compared to usual care on toxic side effects of AI use, namely arthralgia, bone mass, and endocrine-related quality of life. Women diagnosed with Stage I-IIIc breast cancer were eligible for the study. Participants must 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  $\geq 3$  on the Brief Pain Inventory (BPI) Short Form Questionnaire<sup>22</sup>).

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 were eligible to participate.

### *Recruitment*

The Rapid Case Ascertainment (RCA) Shared Resource Service of the Yale Cancer Center was used to obtain names of women diagnosed with hormone receptor positive breast cancer who were 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 primary investigator with the potential participants' names and their physician's name. Initial contact was made with the physician to request permission to contact the participant regarding the study. If approved, the participant was mailed an invitation letter, describing the study and informing her of the next steps of the study recruitment and enrollment process (i.e., screening telephone call). If at the screening telephone call the participant was deemed eligible and interested, she was scheduled for a baseline visit.

Between April 1, 2010 and December 31, 2012, we completed 1020 screening telephone calls. Of the 1020 women screened, 664 were ineligible, 235 were not interested. The remaining 12% (n = 121) were enrolled in the study and subsequently randomized to the intervention (n=60) or usual care group (n=61). Of these 121 women, 50 completed 12- months of the study as of March 31, 2013, and are included in the analyses (See Figure 1).

### *Data Collection*

At the baseline visit, participants completed questionnaires regarding medical history and health habits, quality of life, as well as a 7-day daily activity log and physical activity questionnaire. Questionnaires and physical measurements (e.g. anthropometric measurements, DEXA scan, blood draw) were repeated during follow up clinic visits at 6 and 12 months. Cardiorespiratory fitness testing was performed at baseline and repeated at the completion of the study, i.e., 12-months.

## **Measures**

*Demographics and medical history:* Information was collected via an interviewer-administered questionnaire at the baseline visit. Information regarding disease stage, hormone receptor status, adjuvant therapy, and surgery was provided by participants and later confirmed by their physician and review of the medical records.

*Physical activity.* At baseline, 6- and 12-months, participants completed a 7-day physical activity log (PAL)<sup>23</sup> and an interviewer-administered physical activity questionnaire (PAQ)<sup>24</sup> to assess physical activity at baseline and at 6 and 12 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 activity were determined using Ainsowrth's Compendium of Physical Activities.<sup>25</sup>

*Anthropometrics.* Height and weight were measured at baseline, 6 and 12 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.

*Cardiorespiratory Fitness:* Research staff, blinded to the participant's randomization group, measured each participant's cardiorespiratory fitness at baseline and 12-months with a VO<sub>2</sub> max treadmill test (including 12-lead ECG). Expired gases were analyzed using a metabolic measurement cart (CPX-D; Medical Graphics, St Paul, MN). Peak oxygen consumption was determined by taking the highest values during a 15-second period. A modified "Branching

Treadmill Protocol” was used: initially, participants began at a normal walking speed (3.0 MPH) and 0% grade, after 2 min the speed was increased to a fast walking speed (3.5 MPH) and 0% grade, and thereafter, only the grade was increased by 3% every 2 min. Oxygen consumption ( $\text{VO}_2$ ), carbon dioxide production ( $\text{VCO}_2$ ), and flow rate was be measured continuously. During each stage, the onsite cardiologist monitored blood pressure and heart rate, and the research staff measured perceived effort using the Borg scale. The test was ended when the participant indicated that she could not continue any further, or if the supervising physician recommended halting the exercise for medical concerns. Maximal heart rate, peak exertion level, and reasons for stopping the test were recorded, and a report of the cardiorespiratory measures ( $\text{VO}_{2\text{max}}$ ,  $\text{VCO}_{2\text{max}}$ , respiratory exchange ratio [RER], and metabolic equivalent for task [MET]) was obtained.

### *Randomization*

Participants were randomized to either the exercise group or usual care with equal probability, with blocking on whether taking a bisphosphonate and whether arthralgia/joint pain started after initiating the AI. Those women randomized to the exercise group were scheduled for their first supervised exercise training session 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.

### *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 12 months. The HOPE study trainer and participant(s) met at a local gym designated by the study during designated weekly times.

*Strength Training Sessions:* Each strength training session was ~30 minutes. Seven common strength-training exercises were performed for three sets and 8-12 repetitions using variable resistance machines (e.g., leg press, leg extension, bench press, lat pull down, seated row) .<sup>26,27</sup>

*Aerobic Exercise Intervention:* The participants were also required to do moderate- to vigorous-intensity aerobic exercise for a total of 150 min/week (the current PA recommendation).

Participants wore heart rate monitors during each workout, with heart rate electronically monitored with high/low pulse rate alarms individually set for each subject. Exercise started at 50% of predicted maximal heart rate ( $220 - \text{age}$ ) and was gradually increased in accordance with American College of Sports Medicine guidelines to approximately 60-80% of predicted maximal heart rate. Following each exercise session, participants recorded the type, duration, perceived intensity of activity, and average heart rate during exercise in physical activity logs. The aerobic exercise consisted primarily of treadmill walking, although participants could choose to meet the exercise goal through other forms of aerobic activity.

*Recording of Strength and Aerobic Exercise Sessions:* Following each strength and aerobic exercise session, participants completed a physical activity log. The logs were submitted weekly to the Exercise Trainer, who reviewed the log in the presence of the participant.

### *Usual Care*

Immediately after randomization, participants in the usual care group were provided written information that emphasized the importance of a healthy lifestyle. Each month, women randomized to usual care were contacted by a trained health professional to discuss health education topics relevant to women taking AIs and breast cancer survivors in general. Examples of topics were benefits of AIs, bone health, and lymphedema.

### *Statistical Analysis*

Participants were grouped according to the intent-to-treat approach (ITT), in which all participants were analyzed according to their intervention assignment at randomization, regardless of adherence. A sample size of 50 women had completed baseline and 12-month treadmill examinations at the time of this preliminary analysis. T-tests and  $\chi^2$  analyses were used to assess between-group differences at baseline. A t-test was also used to test for significant differences in cardiorespiratory fitness parameters between exercise and control groups at baseline and 12-months. The percent change in cardiorespiratory fitness was also compared between groups using t-tests.  $P < 0.05$  was considered statistically significant.

We also explored potential effect modification by *a priori* variables that were potentially associated with change in cardiorespiratory fitness, identified based on previous studies and on observations of the study staff and included: treatment, disease stage, time since diagnosis, baseline fitness level, and baseline BMI. Intervention effects were evaluated by the differences in the mean percent change at 12-months between the intervention and usual care groups using the generalized estimating equation modification to linear regression models to account for the longitudinal nature of the data.

Adherence, assessed from weekly 7-day physical activity logs, was defined as the average min/week of moderate-intensity aerobic exercise performed from baseline to 12-months. Good adherence was defined as 80% of the exercise prescription (or 120 min of the 150 min/week goal). For exerciser only, we examined changes in cardiorespiratory fitness by adherence. Statistical analyses were performed using SAS software (version 9.3; SAS Institute Inc, Cary, NC).

## ***Results***

### *Baseline characteristics*

Baseline demographic and physiological factors for women randomized to exercise vs. usual care were not significantly different (Table 1). The average age of study participants was 62.6 years. The majority of women in our sample were non-Hispanic white and highly educated; 91.6% achieving a college degree or greater. Sixty-eight percent of the participants were classified as overweight (BMI $\geq$ 25) at baseline (BMI= 28.45  $\pm$  6.25). The average time since breast cancer diagnosis was 2.9 years and women had been taking an AI for 2 years prior to enrollment in the study. The majority of participants were diagnosed with Stage I breast cancer (54%) and received treatment after surgery (radiation and/or chemotherapy) (92%).

### *Adherence to Exercise Intervention*

The mean attendance rate to the twice-weekly yearlong supervised gym sessions (that included aerobic and resistance exercise) was 80.3%. When examining adherence to aerobic exercise, women participated in moderate- to vigorous-intensity aerobic exercise for 148.0  $\pm$



75.17 min/week (99% of the prescribed 150 min/week). More than half (57.7%) of the exercisers exceeded the goal of 150 min/week over the 12 months (Table 2).

#### *Baseline cardiorespiratory fitness by treatment group*

The average baseline  $VO_2$ max for all participants in the study was 23.45 ml/kg/min and did not vary by treatment group (Table 3). Vigorous-intensity exercise is defined as greater than 6.0 metabolic equivalents (METs). The average METs achieved during the baseline cardiorespiratory exam among all participants was 6.71 METs. There was no significant difference in baseline METs ( $p=0.932$ ) and peak heart rate ( $p=0.626$ ) between women randomized to exercise vs. usual care. The average respiratory exchange ratio (RER), a confirmatory measure of peak oxygen uptake and a maximal test being achieved, for all participants was 1.09.

#### *Effect of exercise vs. usual care on $VO_2$ max*

The average cardiorespiratory fitness level after the 12-month intervention among exercisers was 24.75 ml/kg/min compared to 23.50 ml/kg/min in the control group ( $p=0.429$ ). There was a borderline statistically significant difference in percent change in cardiorespiratory fitness pre- and post-intervention among the exercise group (5.28 ml/kg/min) compared to that of the usual care group (0.14 ml/kg/min) ( $p=0.0944$ ). There were no significant differences in peak heart rate or peak RER among treatment groups at the 12-month assessment; however, the exercise group demonstrated an average 4.56% increase in METS from baseline to 12-months compared to a 4.85% decline in METS in the usual care group ( $p=0.0796$ ).

### *Effect of exercise on cardiorespiratory fitness stratified by potential modifiers*

Age, disease stage, treatment received, time on aromatase inhibitors, baseline body mass index, and baseline cardiorespiratory fitness did not modify the effect of exercise on percent change in cardiorespiratory fitness. However, stronger effects of exercise on percent change in cardiorespiratory fitness were observed among women with greater baseline BMI and lower baseline fitness levels (Table 4).

### *Effect of exercise on cardiorespiratory fitness stratified by attendance*

Women who had greater attendance to gym sessions (greater than 80% attendance) demonstrated greater percent change in cardiorespiratory fitness (7.11%) compared to those with poor attendance (-0.46%,  $p=0.0822$ ).

## ***Discussion***

In our study, an exercise regime of moderate- to vigorous-intensity aerobic exercise and resistance training was associated with a borderline statistically significant increase in cardiorespiratory fitness among breast cancer survivors taking aromatase inhibitors. The HOPE exercise intervention protocol was feasible from the standpoint of efficacy and implementation, and well accepted by the participants.

Our findings are consistent with previous research investigating exercise interventions in breast cancer survivors, showing a significant increase in cardiorespiratory fitness in women enrolled in the exercise prescription. McNeely et al (2006) concluded that participating in aerobic exercise during and after cancer treatment has been effective in improving functional capacity, as measured from symptom limiting graded exercise testing 3.39 ml/kg/min; CI: 1.67 to

5.1). Our results are also in accordance with the data presented in the meta-analysis performed by Fong and colleagues (2012), demonstrating a significant association between physical activity and increase peak oxygen consumption among survivors of lung, colorectal, and breast cancer (2.2 ml/kg/min,  $p < 0.01$ ).

Whereas other studies have examined the cardiorespiratory effects of aerobic and resistance exercise on breast cancer survivors, only the study conducted by Rogers and colleagues (2009) have shown an increase in  $VO_2\text{max}$  among 30 survivors taking aromatase inhibitors. Participants engaged in a 12-week physical activity behavior change intervention, which included 12 individual supervised exercise sessions and received counseling on home-based exercise programs. The authors examined the physiological effects of exercise among women taking AIs for at least 8 months, but did not represent a high risk population: women did not report arthralgia or AI-associated side effects. Rogers and colleagues reported a non significant but moderate-to-large increase in  $VO_2\text{max}$ ; however, cardiorespiratory fitness was measured using a submaximal treadmill protocol and the duration of the intervention was only 3 months. Whereas, the HOPE study uses a maximal exercise testing protocol (modified Branched), which provides a more accurate estimate of peak  $VO_2\text{max}$ , and measures changes in fitness after a yearlong exercise intervention.

Attendance to twice-weekly resistance training sessions was 80% among exercisers. Approximately 92.3% of exercisers achieved 90-minutes per week of moderate- to vigorous-physical activity, which is 60% of the national recommendation of 150 minutes/week.

According to ACSM guidelines, for women between the ages 60-65, a  $VO_2\text{max}$  between 23.0 and 34.0 ml/kg/min is defined as normal cardiorespiratory fitness. At baseline, the average  $VO_2\text{max}$  among participants was 23.45 ml/kg/min, indicating relatively low fitness levels.

Similarly, Burnett et al (2013) reported relatively low fitness levels in a cohort of breast cancer survivors with a mean VO<sub>2</sub>max ( $25.4 \pm 5.3$  mL.kg<sup>-1</sup>.min<sup>-1</sup>), which was similar to the 20th percentile threshold value (25.1 mL.kg<sup>-1</sup>.min<sup>-1</sup>) for age and gender group matched normative values. Cardiorespiratory capacity is often compromised in breast cancer survivors because of the pathology of disease, therapeutic regimes, and subsequent weight gain and physical inactivity as a result of treatment. The detrimental effects of poor cardiorespiratory fitness have been well documented in variety of subpopulations, particularly among cancer patients.<sup>23,28</sup>

A concern when conducting an incremental treadmill tests is that a participant may not achieve maximal oxygen uptake. The respiratory exchange ratio (RER) is used as evidence of a definitive plateau of the VO<sub>2</sub>. The literature suggests a criterion value of RER between 1.0 and 1.15 indicates maximal exertion.<sup>29</sup> The average RER among our participants was 1.09, which provides evidence that maximal testing of cardiorespiratory fitness is feasible among breast cancer survivors. Moreover, the average metabolic equivalents (METs) achieved for both treatment groups during baseline and 12-month testing was greater than 6 METs, signifying vigorous-intensity physical activity was achieved during the treadmill test. The exercise group achieved greater METs during 12-month follow-up, meaning women that participated in the exercise intervention were capable of performing higher intensity activity to achieve maximum oxygen uptake compared to the control group. METs and heart rate can be used to explain a woman's functional capacity; an inability to exercise for more than 6 minutes is associated with an ability to increase heart rate to >85% of maximum predicated heart rate. These are significant indicators of increased risk of coronary events. Participants that experience an excessive rise in heart rate during the test and reach 85% of maximum heart rate in the beginning stages

demonstrate limited exercise capacity. This rapid rise is primarily a result of reduced stroke volume caused by physical deconditioning, cardiac disease or arrhythmias.<sup>30</sup>

At the end of the 12-month intervention, the average  $\text{VO}_2\text{max}$  among exercisers increased to 24.75 ml/kg/min ( $\% \Delta = 5.28 \pm 10.59$ ); whereas women randomized to usual care demonstrated negligible or no change in cardiorespiratory fitness at 12-months (23.5 ml/kg/min -  $\pm 5.34$ ;  $\% \Delta = 0.14 \pm 10.73$ ). Research in older age healthy cohorts has shown that adults can achieve the same 10 to 30 percent increase in  $\text{VO}_2\text{max}$  in response to exercise training as their younger counterparts.<sup>31</sup> Improved peak oxygen consumption after exercise training is associated with increase cardiac output and greater arteriovenous oxygen content difference (a- $\text{VO}_2$  diff).<sup>32</sup> There is biological plausibility to suggest that this mechanism is responsible for the physiological changes observed in this study.

While we did not observe statistically significant effect modification by our *a priori* covariates, stronger effects of exercise on cardiorespiratory fitness were observed by baseline BMI status and fitness status. Irrespective of BMI (obese vs. not obese), women in the exercise group experienced a similar improvement in cardiorespiratory fitness over the course of the study; however, controls with who were obese experienced a drastic decline in cardiorespiratory fitness ( $-6.36\text{ml/kg/min} \pm 3.69$ ) over the 12-month study. These results suggest that women with greater baseline BMI levels ( $\geq 30 \text{ kg/m}^2$ ) can receive the greatest cardiorespiratory fitness benefit from a 12-month exercise protocol. Women with lower cardiorespiratory fitness at baseline (stratified by the median value of 24 ml/kg/min) experienced larger improvements in  $\text{VO}_2$  max compared to their fitter counterparts, as participating in the amount of exercise recommended was able to improve their  $\text{VO}_2\text{max}$ . The more fit women at baseline may have needed more exercise to increase their  $\text{VO}_2\text{max}$  more so than less fit women.

AIs offer an effective strategy for breast cancer survivors to reduce the risk of recurrence, particularly in early stage hormone-sensitive breast cancer. While AI treatment is generally well tolerated, it is important to consider the long-term health impacts of hormone therapy on other health outcomes, especially in postmenopausal women. The cardiovascular risks of estrogen deprivation experienced in postmenopausal women are exacerbated by endocrine therapy with AIs; long-term effects on the cardiovascular system are especially relevant, because CVD is a common cause of death among breast cancer patients.<sup>33,34</sup> High aerobic functional capacity has been associated with beneficial health outcomes, such reductions in all-cause mortality and cardiovascular events, and improvements in health-related quality of life.<sup>7,35</sup> As demonstrated in the present study, appropriate exercise protocols serve an important role in the management of cardiovascular risk in this population; aerobic physical activity can reverse the cardiac stresses of hormone therapy and previous sedentary lifestyle.<sup>7</sup>

Strengths of The HOPE study was its methodologically strong design, population-based recruitment strategy, randomization to study groups, a physical activity prescription that met national guidelines, detailed measurement of physical activity and adherence, gold standard assessment of cardiorespiratory fitness, and long study duration. However, the sample evaluated in these analyses is small with implications for compromised statistical power with regard to some stratified analyses. Our sample was predominantly non-Hispanic white and highly educated.

In conclusion, there is promising evidence that supervised resistance training, coupled by adequate aerobic exercise, compared with usual care, is associated with improvements in cardiorespiratory fitness for breast cancer survivors undergoing aromatase inhibitor treatment. As new treatment therapies are developed and breast cancer survivorship improves, cardiac

health will continue as a major concern among this population as cardiovascular disease mortality is more common among breast cancer survivors than breast cancer-related mortality.<sup>8</sup> In a study of a demographically similar population of older cardiac patients, Keteylan and colleagues (2008) concluded that a 1 ml/kg/min improvement in  $\text{VO}_2\text{max}$  is associated with 15% decrease risk for all-cause mortality and CVD-specific mortality demonstrating relatively small average changes in cardiorespiratory fitness at the population level could have great implications for longevity in breast cancer survivors.

As we transition into the era of “personalized medicine” in oncology, it will be critical to identify exercise prescriptions that are suitable for the clinical and treatment characteristics of a patient subgroup.<sup>36</sup> Future studies examining physical activity interventions among breast cancer survivors will help generate guidelines for safe and efficacious exercise protocols. Moreover, future trials should investigate the effects of exercise on other objective CVD measures. Measuring B-type natriuretic peptide (BNP) and troponin T (TnT), biomarkers of cardiac injury, can provide more information about the effects of aromatase inhibitor on cardiovascular health and quantify the impact of exercise interventions on these measures.

**Table 1: Baseline characteristics of randomized participants in the HOPE study (N=50).**

|   | <b>Exercisers<br/>Mean (SD) or<br/>N (%)<br/>(n=26)</b> | <b>Usual Care<br/>Mean (SD) or<br/>N (%)<br/>(n=24)</b> |
|---|---|---|
| Age (years)                             | 63.3 ± 6.2  | 62.5 ± 7.1  |
| Ethnicity (%)                           |   |   |
| White (Non-Hispanic)                    | 23 (88.5%)  | 21 (87.5%)  |
| Black or African American               | 3 (11.5%)   | 2 (8.3%)  |
| Asian or Pacific Islander               | (0%)  | 1 (4.17)  |
| Education (%)                           |   |   |
| Less than high school degree            | 2 (7.7%)  | 2 (8.3%)  |
| High school diploma or GED              | 8 (30.8%)   | 8 (33.3%)   |
| College graduate or professional school | 16 (61.5%)  | 14 (58.3%)  |
| Weight (kg)                             | 79.9 ± 19.0   | 71.73 ± 15.0  |
| BMI (kg/m <sup>2</sup> )                | 30.4 ± 7.2  | 26.9 ± 4.6  |
| Time since diagnosis (months)           | 36.3 ± 28.3   | 34.0 ± 19.9   |
| Time on AI (months)                     | 23.9 ± 12.27  | 26.1 ± 16.0   |
| Disease Stage                           |   |   |
| Stage I                                 | 14 (53.8%)  | 13 (54.2%)  |
| Stage II                                | 8 (32.0%)   | 7 (31.8%)   |
| Stage III                               | 3 (11.5%)   | 1 (4.2%)  |
| Unknown                                 | 1 (3.58%)   | 1 (4.2%)  |
| Treatment after surgery                 |   |   |
| None                                    | 1 (3.8%)  | 3 (12.5%)   |
| Radiation only                          | 0 (0%)  | 3 (12.5%)   |
| Chemotherapy only                       | 12 (46.2%)  | 9 (37.5%)   |
| Radiation and chemotherapy              | 13 (50.0%)  | 9 (37.5%)   |

No statistically significant differences between exercise and usual care groups at baseline (p<0.05).



**Table 2: Adherence from baseline to 12-months in HOPE study (n= 26)**

|  | <b>Exercisers</b> |
|--|-------------------|
| Attendance to gym sessions (strength training)                           | 80.3% ± 14.83%    |
| Moderate- to vigorous-intensity aerobic exercise (min/week) <sup>1</sup> |                   |
| Mean (SD)  | 148.0 ± 75.17     |
| % of subjects adhering to  |                   |
| ≥ 150 min/week (100% of goal)  | 57.7%             |
| ≥ 120 min/week (80% of goal)   | 69.2%             |
| ≥ 90 min/week (60% of goal)  | 92.3%             |
| ≥ 60 min/week (40% of goal)  | 96.1%             |
| ≥ 30 min/week (20% of goal)  | 100.0%            |

<sup>1</sup> Mean min/week of moderate- to vigorous-intensity aerobic activity from baseline to 12-months determined from the Daily Activity Logs

**Table 3: Unadjusted comparison of cardiorespiratory fitness levels between women randomized to exercise vs. usual care in the HOPE study.**

|  | <b>Exercisers<br/>Mean (SD) (n=26)</b> | <b>Usual Care<br/>Mean (SD) (n=24)</b> | <b>P-<br/>value</b> |
|--|--|--|---------------------|
| <b>VO<sub>2</sub>max (ml/kg/min)<sup>1</sup></b> |  |  |                     |
| Baseline   | 23.51 ± 4.78                           | 23.38 ± 4.20                           | 0.915               |
| 12-months  | 24.75 ± 5.74                           | 23.50 ± 5.34                           | 0.429               |
| %Δ   | 5.28 ± 10.59                           | 0.14 ± 10.73                           | 0.0944              |
| <b>Peak RER<sup>2</sup></b>                      |  |  |                     |
| Baseline   | 1.09 ± 1.06                            | 1.09 ± 0.06                            | 0.855               |
| 12-months  | 1.09 ± 0.07                            | 1.02 ± 0.24                            | 0.256               |
| <b>Peak HR</b>                                   |  |  |                     |
| Baseline   | 156.60 ± 12.45                         | 154.30 ± 19.97                         | 0.626               |
| 12-months  | 155.9 ± 13.73                          | 152.3 ± 19.57                          | 0.454               |
| <b>MET<sup>3</sup></b>                           |  |  |                     |
| Baseline   | 6.72 ± 1.37                            | 6.69 ± 1.22                            | 0.932               |
| 12-months  | 6.98 ± 1.71                            | 6.38 ± 2.04                            | 0.285               |
| %Δ   | 4.56 ± 10.97                           | -4.85 ± 22.91                          | 0.0796              |

<sup>1</sup> Normal cardiorespiratory fitness is defined as a VO<sub>2</sub>max between 23 ml/kg/min and 34 ml/kg/min. Low fitness levels is defined as a VO<sub>2</sub>max < 13.

Source: Preventive Medicine Center, Palo Alto, Calif., and a survey of published sources.

<sup>2</sup> Respiratory exchange ratio (RER) = (CO<sub>2</sub> production/ O<sub>2</sub> uptake) serves as an indirect measure of muscle oxidative capacity to get energy

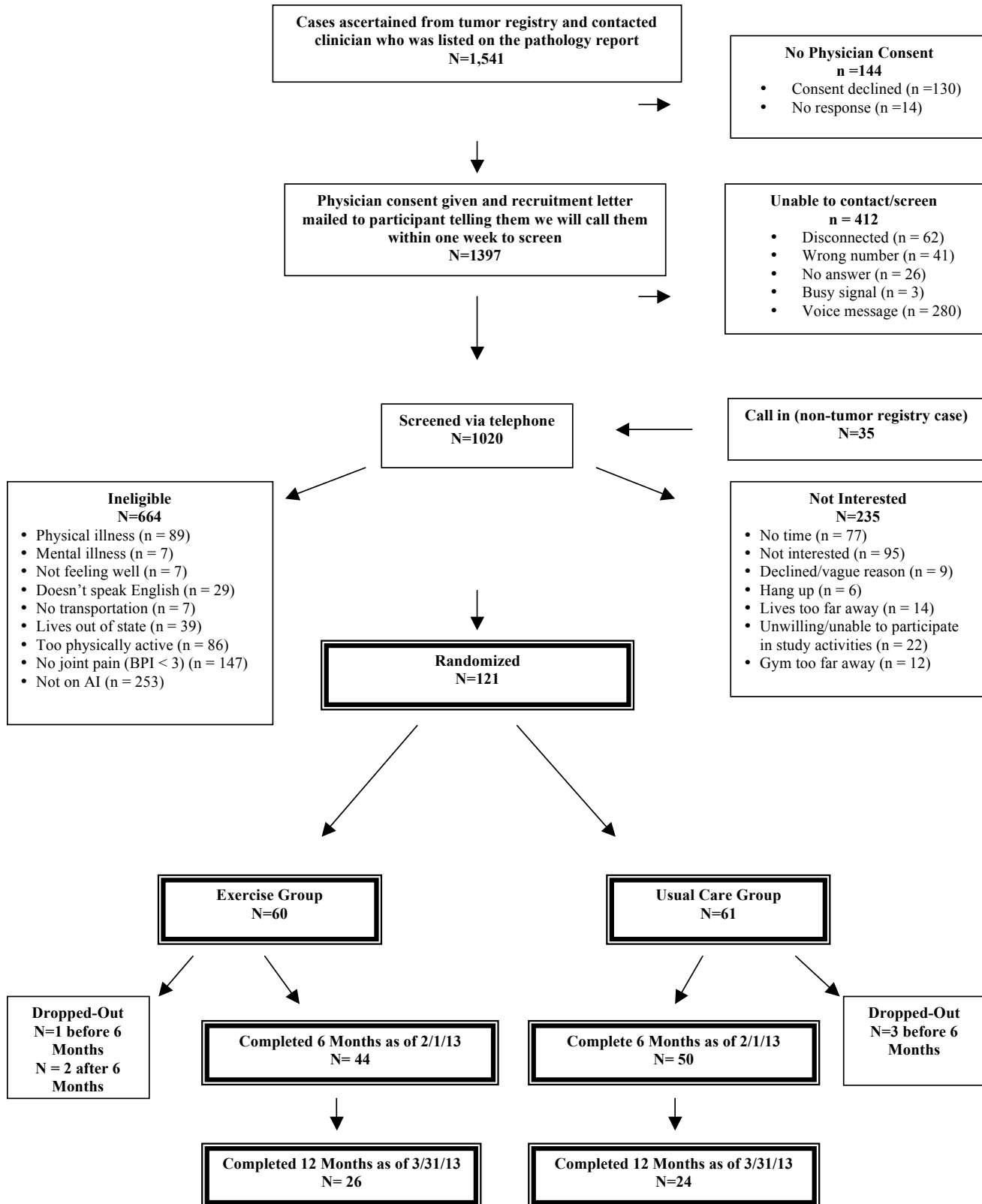
<sup>3</sup> Metabolic equivalent (MET) is a unit used to estimate the amount of oxygen used by the body during physical activity. Activity that burns 3 to 6 METs is considered moderate-intensity physical activity. Activity that burns greater than 6 METs is considered vigorous-intensity physical activity.

**Table 4: Stratified analysis of change in cardiorespiratory fitness between women randomized to exercise vs. usual care in the HOPE study.**

|  | % $\Delta$ VO <sub>2</sub> max | P-value |
|--|--------------------------------|---------|
| Age $\leq$ 63y                                       |                                |         |
| Exercisers n=14                                      | 6.22 (2.96)                    | 0.113   |
| Controls n=15  | -0.51 (2.86)                   |         |
| Age > 63y  |                                |         |
| Exercisers n=12                                      | 4.20 (3.04)                    | 0.7113  |
| Controls n=9   | 2.39 (3.7)                     |         |
|  |                                | 0.4442* |
| BMI <sub>b</sub> < 30 kg/m <sup>2</sup>              |                                |         |
| Exercisers n=16                                      | 5.10 (2.78)                    | 0.471   |
| Controls n=18  | 2.31 (2.62)                    |         |
| BMI <sub>b</sub> $\geq$ 30 kg/m <sup>2</sup>         |                                |         |
| Exercisers n=10                                      | 5.59 (2.86)                    | 0.0226  |
| Controls n=6   | -6.36 (3.69)                   |         |
|  |                                | 0.1682* |
| Disease Stage  |                                |         |
| Stage I  |                                |         |
| Exercisers n=14                                      | 4.98 (2.15)                    | 0.370   |
| Controls n=13  | 1.47 (2.15)                    |         |
| Stage II and III                                     |                                |         |
| Exercisers n=11                                      | 6.69 (3.54)                    | 0.189   |
| Controls n=10  | -0.30 (3.71)                   |         |
|  |                                | 0.582 * |
| Time since diagnosis $\leq$ 35 months                |                                |         |
| Exercisers n=13                                      | 5.76 (3.00)                    | 0.743   |
| Controls n=13  | 4.36 (3.00)                    |         |
| Time on since diagnosis > 35 months                  |                                | 0.070   |
| Exercisers n=12                                      | 4.20 (2.88)                    |         |
| Controls n=10  | -3.97 (3.15)                   | 0.270*  |
| Time on AI $\leq$ 23 months                          |                                |         |
| Exercisers n=12                                      | 3.71 (3.47)                    | 0.640   |
| Controls n=10  | 6.16 (3.80)                    |         |
| Time on AI > 23 months                               |                                |         |
| Exercisers n=11                                      | 7.73 (2.47)                    | 0.00420 |
| Controls n=9   | -4.3 (2.73)                    |         |
|  |                                | 0.0304* |
| VO <sub>2</sub> max <sub>b</sub> < 24 ml/kg/min      |                                |         |
| Exercisers n=14                                      | 6.13 (2.55)                    | 0.0159  |
| Controls n=11  | -3.89 (2.88)                   |         |
| VO <sub>2</sub> max <sub>b</sub> $\geq$ 24 ml/kg/min |                                |         |
| Exercisers n=12                                      | 4.31 (3.29)                    | 0.871   |
| Controls n=13  | 3.56 (3.17)                    |         |
|  |                                | 0.1280* |
| Received treatment (Radiation and/or chemotherapy)   | 5.29 (2.09)                    | 0.944   |



**Figure 1. Flow of participants through the HOPE Study**



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