**Full Title:** Hemoglobin and Aerobic Fitness Changes with Supervised Exercise Training in Breast Cancer Patients Receiving Chemotherapy

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ABSTRACT

Background: Aerobic exercise training is known to increase red blood cell production; however, this has not been evaluated in breast cancer patients undergoing adjuvant chemotherapy (CT). The purpose of this study was to examine the changes in hemoglobin levels in the Supervised Trial of Aerobic versus Resistance Training (START) and to determine its association with changes in VO₂peak. Methods: 242 breast cancer patients initiating CT were randomized to usual care (UC, n=82), resistance exercise (RET, n=82), or aerobic exercise groups (AET, n=78) for the duration of their CT (Median= 17 wks). Supervised exercise was thrice weekly based on standard aerobic and resistance exercise prescriptions. Aerobic fitness (VO₂peak) and hemoglobin concentration ([Hb]) were measured at baseline and end of CT. Results: Regardless of the exercise group, [Hb] declined over the course of CT (13.4 ±10.0 to 11.8 ±11.5 g/dL, P <0.01). Both AET and RET groups had significant, moderate correlations between the change in VO₂peak and [Hb] (AET: r= 0.49, P <0.001; RET: r= 0.39, P = 0.001). Conclusion: The results indicate regular exercise does not protect against the decline in [Hb] associated with CT in breast cancer patients, but resulted in a stronger association between [Hb] and VO₂peak. Impact: Even with the chemotherapy-induced decline in [Hb], breast cancer patients can maintain their aerobic capacity by participating in regular aerobic exercise. Further studies are required to determine safe intensity levels that may stimulate
the maintenance of [Hb] levels in breast cancer patients.
INTRODUCTION

Breast cancer patients undergoing adjuvant therapy commonly suffer from a decline in hemoglobin concentration ([Hb]), which in cancer patients has been related to higher rates of fatigue and depression, combined with a deterioration in physical functioning (1), quality of life (2), and survival (3). Kirshner and colleagues (4) reported a ~40% increase in the incidence of moderate to severe anemia (hemoglobin levels <10 g/dl) in stage II and III breast cancer patients undergoing adjuvant doxorubicin and cyclophosphamide chemotherapy. Treatment of severe anemia may require erythrocyte transfusion, but this carries the risk of transfusion reactions and infectious disease transmission.

Erythropoietic supportive agents (ESAs) are only moderately effective and their use in cancer related anemia increases thromboembolic complications, hypertension, and has been associated with adverse effects on survival (5-7). Furthermore, recent evidence suggesting tumor stimulating effects of ESAs are of particular concern in the curative-intent setting of adjuvant breast cancer chemotherapy (8).

Exercise could be an appropriate non-pharmacological intervention to counteract the decline in [Hb] observed in many breast cancer patients undergoing chemotherapy. Aerobic exercise training is associated with improved haemorheology (see in-depth reviews (9-11)) and can increase blood volume through an increase in plasma volume and red blood cell mass (12). Few studies have evaluated the effect of exercise training on [Hb] in breast cancer patients undergoing adjuvant chemotherapy. Previous studies have reported positive changes in [Hb] with exercise in cancer patients, but the samples were small and clinically heterogeneous, with brief interventions of 6-9 weeks, that occurred
We recently evaluated the relative merits of aerobic and resistance exercise training in moderating these negative side effects caused by chemotherapy in the Supervised Trial of Aerobic versus Resistance Training (START) (15). The START trial was a randomized controlled trial designed to compare the effects of aerobic exercise training (AET) and resistance exercise (RET) training to usual care (UC) in breast cancer patients receiving adjuvant chemotherapy. The results of this study demonstrated that AET was superior to UC for improving self-esteem, preserving aerobic fitness ($\text{VO}_{2\text{peak}}$), and maintaining body fat levels whereas RET was superior to UC for improving self-esteem, increasing muscular strength, adding lean body mass, and facilitating completion of chemotherapy treatment (16). All other outcomes, including the primary endpoint of quality of life, favored the exercise groups over UC but did not reach statistical significance (16).

Although aerobic fitness was preserved in the AET group, it did not improve despite the aerobic exercise training stimulus. One possible explanation for this finding is that changes in peripheral and central adaptations with AET were offset by declines in hemoglobin. We have not evaluated the effect of exercise training during adjuvant chemotherapy on hemoglobin levels. Thus, the purpose of the present study was to examine the changes in hemoglobin concentration with exercise training in breast cancer patients undergoing adjuvant chemotherapy and to determine associations with change in $\text{VO}_{2\text{peak}}$. We hypothesized that the UC and RET groups would show a decline in [Hb] over the course of chemotherapy while the AET group would maintain or increase [Hb].
METHODS

Setting and Participants

Detailed methods of the START trial have been reported elsewhere (16) but we have included a brief summary. Participants were recruited from the British Columbia Cancer Agency (Vancouver, British Columbia), Cross Cancer Institute (Edmonton, Alberta), and the Ottawa Hospital Integrated Cancer Program (Ottawa, Ontario). The trial received ethical approval from all three centers and written informed consent from all participants. English or French speaking, non-pregnant women, ≥18 years old, with stage I–IIIA breast cancer that were initiating first-line adjuvant chemotherapy were eligible to participate. Women were excluded if they had incomplete axillary surgery, transabdominal rectus abdominus muscle reconstructive surgery, uncontrolled hypertension, cardiac illness, psychiatric illness, or were otherwise not approved for participation by their oncologist.

Design and Procedures

The study was a prospective, three-armed, randomized controlled trial. Eligible participants were identified by their treating oncologist prior to chemotherapy. Interested participants completed a questionnaire, physical fitness test, dual x-ray absorptiometry (DXA) scan (added after the first 23 participants were randomized) and had blood drawn for the determination of [Hb]. Charts were reviewed for use of ESAs and blood transfusions in all participants.
Randomization

Participants were stratified by center and chemotherapy protocol (taxane-based versus nontaxane-based) and randomly assigned to either AET, RET, or UC in a 1:1:1 ratio using a computer-generated program. The allocation sequence was generated in Edmonton and concealed from the project directors at each site.

Exercise Training Interventions

Participants exercised three times a week for the duration of their chemotherapy, beginning 1-2 weeks after starting chemotherapy and ending 3 weeks after chemotherapy. The AET group exercised on a cycle ergometer, treadmill, or elliptical trainer, beginning at heart rate that elicited 60% of their VO\textsubscript{2peak} for the first 6 weeks (17). During weeks 7 through 12, women exercised at 70% of their VO\textsubscript{2peak} progressing to 80% beyond week 12. Initial duration was 15 minutes and increased by 5 minutes every 3 weeks until 45 minutes was attained and then maintained. The RET group performed two sets of 8-12 repetitions of 9 different exercises at 60-70% of their estimated 1 repetition maximum (RM) (18) with pre-specified weight progression. Individuals randomized into the UC group were asked not to initiate an exercise program and were offered a one month exercise program after post-intervention assessments.

Assessment of Primary and Secondary Endpoints

Aerobic fitness was assessed at baseline and post-intervention. Aerobic fitness was evaluated using a maximal incremental exercise protocol on a treadmill (19). [Hb] was determined from resting blood samples drawn at the initiation and after the completion of
chemotherapy. Sampling occurred approximately within two weeks of the maximal incremental exercise test.

**Statistical Analyses and Sample Size Calculation**

The sample size calculation was originally based on a change in the FACT-An score (16). Specifically, with 80 participants per group, our trial had .80 power to detect a difference in change scores of 7 points (SD=16) on the FACT-An (20) with a loss-to-follow-up of 10%, a two-tailed alpha <.05, and no adjustment for multiple testing. Mixed-model repeated measures analysis was used to compare the differences in group changes over time. To detect any main effects of chemotherapy regimen (non-taxane vs. taxane based) between groups on percentage difference in VO$_{2\text{peak}}$ and [Hb], a 2x3 between groups analyses was performed. If effects were significant, a follow-up 1x3 between group analyses was performed.

**RESULTS**

Detailed flow of participants through the trial has been reported elsewhere (16). Briefly, we recruited 242 of 736 (33%) eligible participants and obtained follow-up data on over 90% of participants for each outcome. Physical characteristics are contained in Table 1. Further details regarding disease stage, surgical treatment, and chemotherapy protocols have been previously reported (16). The groups were balanced on all variables at baseline including VO$_{2\text{peak}}$ and [Hb]. The median length of the exercise intervention was 17 weeks (95% CI=9 to 24) and adherence was 72.0% and 68.2% in the AET and RET groups, respectively ($P = .41$) (21). No participant received erythrocyte transfusion.
during the course of the study. One patient is suspected to have been administered an ESA.

**Changes in Objectively Measured Outcomes**

Analysis of pre-test scores found no significant differences between groups for VO$_{2\text{peak}}$ ($P = .758$) and [Hb] ($P = .254$). Pre and Post VO$_{2\text{peak}}$ and [Hb] values are presented in Table 2. As previously reported, the AET group maintained VO$_{2\text{peak}}$ ($P = .80$) while both UC and RET showed a significant decline ($P = <.001$ and $P = .002$ respectively) (16).

All groups showed a similar and significant decline in Hb from pre-test to post-test of approximately 14% (AET: 13.4 ±1.2 g/dl to 11.9±1.3 g/dl; $P < .001$, UC: 13.3 ±1.1 g/dl to 11.7 ±1.1 g/dl; $P < .001$, RET: 13.6 ±0.7 g/dl to 11. ±1.18 g/dl; $P < .001$). Of 242 subjects, 102 subjects (33= UC, 38= RET, 31= AET) completed chemotherapy with Hb levels above 12 g/dl, 76 subjects (24= UC, 25= RET, and 27= AET) completed chemotherapy with [Hb] between 11 g/dl and 12 g/dl while 64 subjects (25= UC, 19= RET, and 20= AET) completed chemotherapy with [Hb] less than 11 g/dl.

The between group difference in percent change of VO$_{2\text{peak}}$ from pre- to post-test varied by chemotherapy regime ($P =0.012$). Specifically, breast cancer patients receiving nontaxane-based chemotherapies maintained VO$_{2\text{peak}}$ in the AET group ($P = .613$) whereas both the UC and RET groups showed a significant decline ($P = .002$ and $P = .009$ respectively). Breast cancer patients receiving taxane-based chemotherapies (either docetaxel or paclitaxel) maintained VO$_{2\text{peak}}$ in AET and RET groups ($P = .797$ and $P$
= .113 respectively) while the UC group showed a significant decline ($P = .039$). The decline in [Hb] was similar between chemotherapy regimens ($P = 0.34$).

Both the AET and RET groups had significant, moderate correlations (AET: $r = .49$, $P < .001$; RET: $r = .31$, $P = .007$) between the percentage change in VO$_{2\text{peak}}$ and [Hb] from pre- to post-test (Figure 1). UC had a non-significant, weak correlation between VO$_{2\text{peak}}$ and [Hb] ($r = .17$, $P = .16$).

As the AET group did not significantly improve either VO$_{2\text{peak}}$ or [Hb], we did an ad hoc analysis to determine if failure to meet the prescribed exercise prescription could account for the findings. Overall, subjects in the AET group met the prescribed duration and intensity prescription $69 \pm 30.0\%$ and $63 \pm 29.7\%$, respectively, of the time. For this analysis, we arbitrarily divided the AET group into two groups - those subjects who followed the prescribed duration and intensity prescriptions $\geq 80\%$ of the time and those subjects who did not satisfy this criteria. Although not significantly different, subjects in the AET group that met the intensity prescription $>80\%$ of the time, had a $2.0\%$ (SE 3.5) increase in VO$_{2\text{peak}}$ while those AET subjects that did not follow the intensity prescription had a $3.1\%$ (SE 2.2) decrease in VO$_{2\text{peak}}$ ($P = .195$). Similar results were seen for duration. There was no substantive affects of adherence on [Hb]. Both groups had a similar decline in [Hb] of $\sim 13\%$, $P = .767$.

**DISCUSSION**

This paper examined the relationship between the decline in [Hb] and the changes in...
aerobic capacity in female breast cancer patients, who participated in an exercise intervention during chemotherapy. Contrary to our hypothesis, all breast cancer patients, regardless of group assignment, showed a significant decline in [Hb] over the course of chemotherapy. However, subjects in the aerobic group, even with a chemotherapy-induced drop in [Hb], maintained their aerobic fitness, and for those women who attained their intensity/duration prescriptions greater than 80% of the time, a slight, non-significant rise in VO$_2$ occurred.

Cancer-related anemia can produce an escalating series of side effects that can impair quality of life (2, 22). Specifically, breast cancer patients have demonstrated a significant relationship between anemia and decreased functional capacity (23), quality of life and survival (3, 24, 25). The relationship between chemotherapy-induced anemia and aerobic capacity in breast cancer patients is important. The correlation of the drop in [Hb] with the percent change in VO$_2$ found in the present study is depicted in Figure 1. Exercise mode, length of the intervention and adherence to the exercise prescription may have influenced the results, but further research is required to investigate the mechanisms responsible and the intensity levels, duration or adherence that are necessary to evoke changes in [Hb] in this population.

In healthy individuals, who voluntarily became anemic, a decline in cardiovascular fitness occurred (26–28) such that a 14% drop in [Hb] caused a 10% drop in VO$_2$ (28). Such deteriorations in aerobic capacity can have a significant impact on survival: in a cohort of ~6000 asymptomatic women, a change in 1 MET (3.5 ml/kg/min)
corresponded to a 17% difference in mortality rate (29). However, using aerobic capacity as a prognostic tool has yet to be evaluated in breast cancer patients.

In this study, hemoglobin levels decreased equally (~14%) between the control, resistance and aerobic groups suggesting that the chemotherapy-induced anemia was not prevented with our exercise training stimulus. The results of the present study are similar to those found by Dimeo et al. (1), who investigated [Hb] with endurance training in patients with hematological malignancies during chemotherapy. These authors demonstrated that the patients were able to maintain physical performance, as determined by a submaximal standard stress test, despite a significant decrease in mean [Hb].

Raising [Hb] through exercise is hypothesized to occur following the increase in plasma volume associated with exercise training. This rise creates a relative drop in the [Hb] and oxygen concentration in arterial blood, consequently stimulating erythropoiesis. It may be argued that: 1) neither exercise protocol was sufficient to prevent a decline in [Hb], as there was no significant increase in aerobic capacity, and 2) the myelosuppressive effect of the systemic therapy outweighed the potential exercise stimulus on the erythropoietic system. This suggests that our chosen exercise duration was too short, or the intensity may have been too low to supersede the suppressive effects of the concurrent chemotherapy, thus preventing the maintenance of [Hb]. However, 7 weeks of moderate intensity exercise has been shown to prevent the decline in [Hb] in breast cancer patients undergoing radiation therapy (14) and to improve [Hb] in cancer patients with severe anemia (13).
This study reveals that even with mild to moderate anemia, breast cancer patients who take part in regular, low-to-moderate-intensity aerobic exercise are able to maintain their VO$_2$peak. Maintaining aerobic capacity, even with a chemo-induced decline in [Hb], validates the benefits of implementing an exercise intervention program to counteract the many side effects of breast cancer treatments. We can speculate that the maintenance of aerobic capacity may be explained by peripheral adaptations, rather than central changes in the cardiovascular system. The exercise intervention may have improved red cell deformability and lowered blood viscosity, thus enhancing oxygen transport (30). In addition, adaptations may have occurred at the mitochondrial level, with changes in the number, size or mitochondrial efficiency that compensated for the decrease in [Hb]. It has been reported that non-hemoglobin effects on physical work capacity can occur with training (31), such that an increase in work capacity can occur that is not matched by increases in hemoglobin (32). The moderate correlations depicted in Figure 1 may be explained by these peripheral adaptations. Improvements in tissue oxidative capacity may have allowed the women in this study to maintain their aerobic capacity, thus maintaining the capability to perform day-to-day chores during chemotherapy.

A limitation of this study is that the treatment of anaemia with EPO during the time course of the study was not properly documented in one individual. However, this was a large, randomized controlled trial, thus we expect the impact to be minimal.

In this study, regular exercise did not prevent the decline in [Hb] associated with...
adjuvant chemotherapy in breast cancer patients. However, even with the chemotherapy-induced decline in [Hb], breast cancer patients were able to maintain their aerobic capacity by participating in a supervised exercise program. Further studies are required to determine safe intensity levels that may stimulate the maintenance of [Hb] in breast cancer patients.
References:


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Table 1. Physical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall (N=242)</th>
<th>Usual Care (n=82)</th>
<th>RET (n=82)</th>
<th>AET (n=78)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Mean (range), y</td>
<td>49.2 (25-78)</td>
<td>49.0 (26-78)</td>
<td>49.5 (25-76)</td>
<td>49.0 (30-75)</td>
<td>.946</td>
</tr>
<tr>
<td>Weight Mean, kg</td>
<td>70.6 (14.3)</td>
<td>72.6 (15.2)</td>
<td>69.7 (14.4)</td>
<td>69.4 (13.3)</td>
<td>.282</td>
</tr>
<tr>
<td>BMI Mean, kg/m²</td>
<td>26.6 (5.5)</td>
<td>27.1 (5.4)</td>
<td>26.1 (5.5)</td>
<td>26.7 (5.6)</td>
<td>.518</td>
</tr>
</tbody>
</table>

Data are presented as the mean (standard deviation). RET = resistance exercise training; AET = aerobic exercise training; SD = standard deviation; BMI = body mass index. Adapted from Courneya, K et al: J Clin Oncol 25 (28) 2007: 4396-4404. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.
<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>UC</th>
<th>RET</th>
<th>AET</th>
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<tbody>
<tr>
<td></td>
<td>pre</td>
<td>post</td>
<td>pre</td>
<td>post</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>13.4(1.1)</td>
<td>11.8(1.2)*</td>
<td>13.3(1.1)</td>
<td>11.7(1.1)*</td>
</tr>
<tr>
<td>VO2, ml/kg/min</td>
<td>25.2(6.5)</td>
<td>24.5(6.4)</td>
<td>24.8(6.2)</td>
<td>23.5(5.4)*</td>
</tr>
</tbody>
</table>

Data are presented as the mean (standard deviation); Hb=hemoglobin; VO2=peak volume of oxygen consumed; UC=usual care; RET=resistance exercise training; AET=aerobic exercise training. * Significant difference between post values when comparing to respective pre values, $p < 0.01$. VO2 values adapted from Courneya, K et al: J Clin Oncol 25 (28) 2007: 4396-4404. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.
Figure 1. Correlations between the percent change in hemoglobin (Hb) and the percent change in VO₂ during chemotherapy treatment in the a) controls, b) resistance group and c) aerobic group.
Figure C

Scatter plot showing the relationship between % Change in Hb and % Change in Relative VO2peak. The Pearson correlation coefficient (r) is 0.489, with a p-value of 0.000.
Hemoglobin and Aerobic Fitness Changes with Supervised Exercise Training in Breast Cancer Patients Receiving Chemotherapy


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