Random Control Clinical Trial on the Effects of Aerobic Exercise Training on Erythrocyte Levels During Radiation Treatment for Breast Cancer

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BACKGROUND. Erythrocyte changes from aerobic exercise training were examined during radiation treatment of breast cancer.

METHODS. Twenty sedentary females with breast carcinoma who were ages 35 to 65 years were randomized to aerobic exercise (AE) of walking for 20 to 45 minutes, 3 to 5 times per week, at 50% to 70% of measured maximum heart rates or to placebo stretching (PS) activities 3 to 5 days per week during 7 weeks of radiation treatment. Measures were obtained 1 week before and after the radiation regimen. Serum blood analyses, through complete blood counts, measured red blood cell counts (RBC), hematocrit (HCT), and hemoglobin (HB). Peak aerobic capacity (peak VO_2) was measured by exercise testing with oxygen uptake analysis to assess training. A Wilcoxon Mann-Whitney U test examined changes between groups ($P \leq .05$ for significance).

RESULTS. AE peak VO_2 increased by 6.3% ($P = .001$) and PS decreased by 4.6% ($P = .083$). RBC increased in AE from 4.10 to 4.21 million cells/μL and declined in PS from 4.30 to 4.19 million cells/μL; the between-group differences were significant ($P = .014$). HCT increased in AE from 38.0% to 38.8% and declined in PS from 37.40% to 36.50%; the between-group differences were significant ($P = .046$). HB increased in AE from 12.3 to 12.4 g/dL and declined in PS from 12.25 to 11.77 g/dL; the between-group differences were significant ($P = .009$).

CONCLUSIONS. The results of the current study suggest that moderate intensity aerobic exercise appears to maintain erythrocyte levels during radiation treatment of breast cancer compared with the declines observed in nontraining individuals. These findings suggest a safe, economical method to improve fitness and maintain erythrocytes in women during radiation treatment of breast cancer. ***Cancer*** **2006;107:2490–5.** © *2006 American Cancer Society.*

KEYWORDS: breast cancer, radiation, exercise, aerobic exercise, erythrocyte, hemoglobin, hematocrit, red blood cell count.

Women undergoing radiation treatment for breast cancer commonly experience declines in erythrocyte levels that may last several months after treatment.[1,2] Declines in erythrocyte levels may be associated with radiation treatment complications that include fatigue, anemia, depression, and diminished physical function.[3–5] Reduced erythrocyte levels have also been associated with increased local and regional failure and decreased survival rates in some cancers.[6,7] There is limited evidence that suggests that aerobic exercise training may improve erythrocyte levels, particularly hemoglobin, in individuals during the rehabilitation phase after chemotherapy treatments; however, to our knowledge, the effect of endurance training

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on erythrocyte levels during radiation treatment for women with breast cancer has not been previously explored.[8]

The purpose of this study was to examine whether moderate-intensity aerobic exercise would have a positive effect on hemoglobin (HB), hematocrit (HCT), and red blood cell counts (RBC) compared with those of nontraining females also undergoing radiation treatment of breast cancer. This study also examined whether there was a correlation between changes in physical fitness, using peak aerobic capacity (peak VO_2) measures, and the final erythrocyte measures. This investigation is a secondary analysis of data from a training study that previously examined the effects of aerobic exercise training on peak aerobic capacity, fatigue, and psychological factors in females undergoing radiation treatment of breast cancer.[9]

MATERIALS AND METHODS

Subjects

After receipt of human investigation committee approvals, subjects were recruited through medical and radiation oncologists at a major urban cancer center. Criteria for inclusion were: female gender, age between 20 and 65 years, histologically established breast cancer (AJCC Stage 0 [Tis, N0, M0] to Stage IIIC [T0-4, N3-M0]), and medical clearance through the participant's oncologist and a routine multiple uptake gated scan (MUGA) of heart function, and through stress test results with 12-lead electrocardiographic analysis. Exclusion criteria were erythropoietin treatments, uncontrolled cardiovascular or pulmonary diseases, orthopedic conditions that would limit exercise participation, refusal for randomization, or participation in aerobic exercise training within 3 months before beginning the study.

Individuals who met the inclusion criteria and agreed to participate in the study were given verbal and written information regarding the investigation and provided signed informed consent, and were then randomly assigned by a random number table to either the aerobic exercise training protocol (AE) or a placebo stretching (PS) protocol. Subjects were also informed that participation in the study was voluntary, all data would be confidential, and that they were free to leave the study at any time of their own choosing without incurring changes in their usual cancer treatment or care.

Research Design

This study was a secondary analysis of data from a prospective randomized control clinical trial using a pretest, intervention, posttest design. The experimental intervention was radiation and AE and the control condition was radiation and PS activities.

Tests and Measures

Testing was performed 1 week before and 1 week after a 7-week radiation and activity regimen. Participants were instructed to come to the testing sessions wearing exercise clothing and comfortable shoes and to abstain from food, caffeine, tobacco, or alcohol for at least 4 hours before testing; because testing was performed primarily in the morning, most of the participants fasted overnight. Tests associated with this investigation were serum blood analysis though differential blood counts and a symptom-limited graded exercise treadmill test, using oxygen uptake analysis, to assess AE training effects.

Erythrocyte measures

Differential blood counts through serum blood draws were used to measure RBC, HCT, and HB. Normal values used for women were 4.2 to 5.4 million cells/μL for RBC, 36.1% to 44.3% for HCT, and 12.1 to 15.1 g/dL for HB.[10] Serum blood draws were taken from the antecubital fossa on the side of the nontreated breast by certified technicians with the participant in a seated position. Blood draws were performed primarily in the morning and approximately 90 minutes before the exercise evaluations, with participants in a postprandial state as described earlier.

Physical fitness assessment

Physical fitness was assessed by measuring peak VO_2 during a symptom-limited graded exercise test using the modified Bruce treadmill protocol. Peak VO_2 is the measure of an individual's highest achieved oxygen consumption during the exercise test in mL/kg/min. The individual's peak VO_2 was measured using continuous oxygen uptake analysis through open circuit spirometry and indirect calorimetry of expired gases using an automated metabolic cart (Oxycon-Alpha; Jaeger, Hoechberg, Germany). Peak VO_2 is a clinically accepted measure for an individual's maximal achieved aerobic capacity; this measure can easily be converted into metabolic equivalents (METs) to determine an individual's functional performance capabilities and to develop safe and effective individualized exercise prescriptions.[11] Exercise testing was performed according to the guidelines of the American College of Sports Medicine with onsite physician supervision, and screening and safety factors specific for exercise in individuals with cancer were followed.[11,12]

Interventions

Radiation protocol

All participants in this study underwent breast surgery and then received external beam radiation treatments 5 days per week for 7 weeks. The affected breast and regional lymph nodes were treated with a 4500 to 5000 centigray (cGy) dose in 200-cGy fractions with a boost of 1000 to 1600 cGy delivered to the primary tumor bed.

AE protocol

The results of the initial symptom-limited graded exercise test were used to develop individualized exercise prescriptions for each participant in the AE group. The AE protocol consisted of walking for 20 to 45 minutes 3 to 5 days per week during 7 weeks of radiation, at an intensity of 50% to 70% of each individual's measured maximum heart rate. Participants performed self-monitored walking on home treadmills or in their neighborhoods using heart rate monitors to record exercise duration and intensity. Self-monitored exercise has been determined to be safe and effective for women undergoing radiation or chemotherapy for breast cancer and has been successfully utilized in other studies during cancer treatments.[13,14] Both the AE and the PS participants kept training journals to assist in recording and reporting training compliance and were also contacted weekly to monitor exercise adherence.

Flexibility protocol

Women in the PS group performed a flexibility protocol that included stretching activities for the cervical and thoracic areas as well as the upper and lower extremities. Participants in the PS group were provided with 1 training session by a licensed physical therapist and given written guidelines on proper stretching techniques. Stretching protocols were performed 3 to 5 days per week during the 7-week radiation regimen.

Activity monitoring

The principle investigator communicated with each participant in both the training and nontraining groups weekly either by telephone or in person. The purpose of the weekly communications was to promote compliance, monitor training, answer questions, and oversee safety issues or concerns about the activities. All participants were instructed to contact their physician in the event that they developed any unusual signs or symptoms related to the radiation treatment or to their activity.

Statistical Analyses

Because the sample size was small and data did not meet parametric assumptions, statistical analyses were conducted using nonparametric tests. The Wilcoxon-Mann-Whitney *U* (WMWU) test evaluated between-group differences, the Wilcoxon signed rank test (WSRT) evaluated differences between pretest and posttest measures in each group, and correlations between final erythrocyte measures and changes in peak VO_2 were determined by Spearman rho analyses. Probability for all tests was set at $\leq .05$ and statistical analyses were performed using the Statistical Package for Social Sciences software program (version 10.1; SPSS Inc., Chicago, IL).

RESULTS

Thirty-eight women were referred by their oncologists to take part in this study; 23 individuals agreed to participate, whereas 15 declined. Reasons for declining participation included lack of time, lack of transportation, child care issues, refusal to be randomized, or currently exercising. Twenty-one subjects completed the study: 13 in the AE group and 8 in the PS group. Two participants in the PS group did not return for the final testing session due to conflicts with work schedules and data from 1 subject in the PS group was also eliminated from the final analyses due to marked irregularities in her pretest and posttest physical measures from moderate to severe fluid retention during the initial test session. Participant demographic information appears in Table 1. Participants in the AE group exercised an average of 3.68 $\pm$ 1.4 days per week during the 7-week radiation regimen. Because testing occurred approximately 1 week

TABLE 1
Patient Demographics

	Aerobic exercise group	Placebo-Stretching group
Age, y ± SD	49.4 ± 7.0	51.9 ± 10.0
Cultural groups	7 African-Americans 6 whites	6 African-Americans 2 whites
Surgery only	3	2
Surgery and chemotherapy	10	6
Doxorubicin andcyclophosphamide	9	6
Tamoxifen	1	2
Paclitaxel	1	1
Docetaxel	1	0
Hypertension/meds	3	3
Stage and classifications		
Stage 0: Tis, N0, M0	3	2
Stage I: T1, N0, M0	2	1
Stage IIA: T0-2, N0-1, M0	2	0
Stage IIB: T2-3, N0-1, M0	2	1
Stage IIIA: T-0-2, N1-2, M0	2	2
Stage IIIB: T4, N0-2, M0	2	2

TABLE 2
Median, Interquartile Range, Percent Change, and *P*

Variable	Median	IQR 25th–75th	% Δ	Pre/Post	Between AE and PS
AE RBC					
Baseline	4.10	3.89–4.32	2.68%	$P = .147$	$P = .014$*
Final	4.21	4.03–4.39			
PS RBC					
Baseline	4.30	3.95–4.45	−2.55%	$P = .014$*	
Final	4.19	3.89–4.36			
AE HB					
Baseline	12.30	11.65–12.95	0.81%	$P = .067$	$P = .004$*
Final	12.40	12.25–13.30			
PS HB					
Baseline	12.25	11.90–13.75	−3.91%	$P = .009$*	
Final	11.77†	11.60–13.30			
AE HCT					
Baseline	38.00	36.25–40.10	2.10%	$P = .232$	$P = .046$*
Final	38.80	36.50–39.70			
PS HCT					
Baseline	37.35	36.85–42.13	−2.46%	$P = .045$*	
Final	36.45	35.75–40.05			

IQR indicates interquartile range; % Δ, percent change; Pre/Post, pretest/posttest; AE, aerobic exercise; PS, placebo-stretching group; RBC, red blood cell count in million cells/microliter; HB, hemoglobin in g/dL; HCT, hematocrit %.

* Significant change ($P \leq .05$).

† Below normal clinical values.

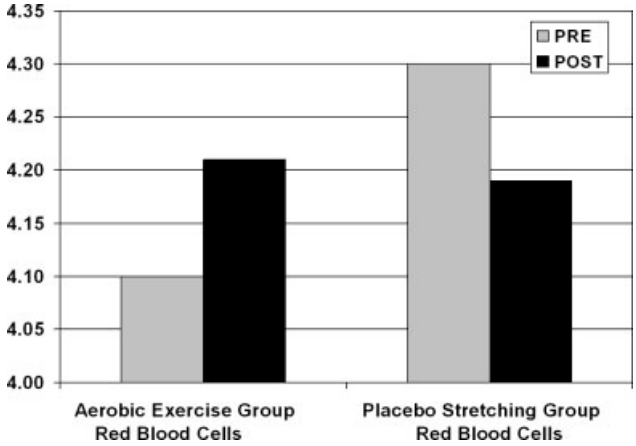

FIGURE 1. Red blood cells, measured in million cells/μL, increased nonsignificantly in the aerobic exercise group by 2.68%, whereas values in the nontraining group declined significantly by 2.55%. PRE/POST indicates pretest/posttest.

before and 1 week after radiation, the average training duration was between 8 and 9 weeks. Individuals in the PS group performed their activity 4.16 ± 1.1 days per week during this same time. Evidence to support an aerobic exercise training effect was the significant improvement in peak VO_2 by a median measure of 6.3% ($P < .001$) in the AE group, whereas the PS group experienced a nonsignificant decline of 4.6% ($P = .083$) during the intervention time.

Statistical Results

WMWU analyses of pretest scores found no significant differences between the AE and the PS groups on all baseline measures for RBC ($P = .164$), HB ($P = .385$), and HCT ($P = .443$). After the intervention, RBC values in the AE group increased nonsignificantly by 2.68% from 4.10 to 4.21 million cells/μL ($P = .147$), whereas RBC values in the PS group declined significantly by 2.55% from 4.30 to 4.19 million cells/μL ($P = .014$). Differences in changes between groups for RBC were statistically significant ($P = .014$).

HB measures in the AE group also increased nonsignificantly after training by 0.81% from 12.30 to 12.40 g/dL ($P = .067$), whereas PS group HB measures decreased significantly by 3.91% from 12.25 to 11.77 g/dL ($P = .009$). Differences between groups for changes in HB values were significant ($P = .009$). HCT measures in the AE group increased nonsignificantly after training by 2.10% from 38.00 to 38.80% ($P = .232$), whereas HCT measures in the PS group declined significantly by 2.46% from 37.35 to 36.45% ($P = .045$). Differences in changes between groups for HCT were statistically significant ($P = .046$). Table 2 and Figures 1 to 3 show a summary of these results.

Spearman's rho analysis of correlations found that changes in peak VO_2 measures were significant and positively correlated to the final measures for RBC ($P = .050$), HB ($P = .013$), and HCT ($P = .015$). Table 3 shows the correlation analyses.

DISCUSSION

A common problem after radiation treatment for breast cancer is a decline in erythrocyte levels that may be associated with negative treatment sequela including fatigue, anemia, depression, loss of physical function, increased risk for local and regional failure, and decreased survival.[1–3,5,14] The current study found that women who performed moderate intensity aerobic exercise during radiation treatment of breast cancer were able to prevent the declines in erythrocyte levels that were experienced by their nontraining peers. This study also found significant positive correlations between changes in peak aerobic capacity and final erythrocyte measures, lending support to the relation between erythrocyte measures and improving physical fitness levels during this time.

Three prior studies were found that examined the effects of aerobic exercise training on erythrocyte measures in individuals with cancer. Dimeo et al.[8]

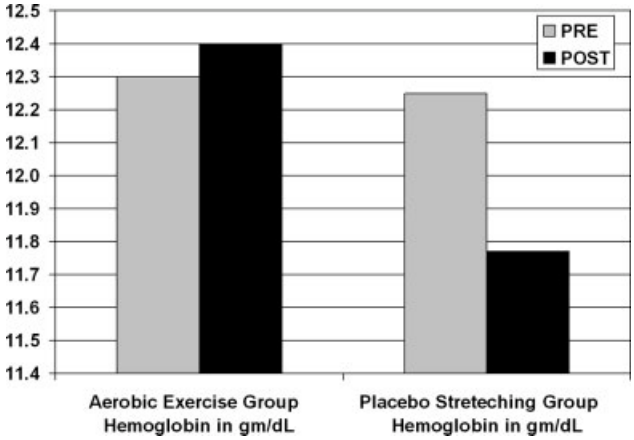

FIGURE 2. Hemoglobin, measured in g/dL, increased nonsignificantly in the aerobic exercise group by 0.81% and decreased significantly by 3.91% in the nontraining group to levels that were below the normal clinical values of 12.1 to 15.1 g/dL. PRE/POST indicates pretest/posttest.

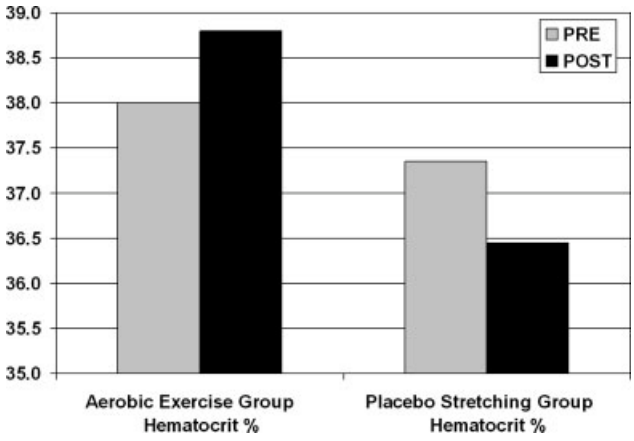

FIGURE 3. Hematocrit percentage increased nonsignificantly in the aerobic exercise group by 2.10% and declined significantly by 2.46% in the nontraining group. PRE/POST indicates pretest/posttest.

examined the effects of 6 weeks of treadmill walking after the completion of high-dose chemotherapy and autologous peripheral stem cell transplantation. After training, maximum walking speed and hemoglobin increased significantly in the training subjects, whereas nontraining subjects' values remained statistically unchanged.

Two subsequent training studies on this topic did not find significant differences in erythrocyte levels between training and nontraining subjects. In the first study, which was performed during high-dose chemotherapy, training intensity (50% of maximum heart rates) and training duration (13–15 days) may not have been sufficient to cause changes in erythrocyte measures.[15] In the second study, which

TABLE 3
Correlations between Peak VO_2 Changes and Erythrocytes

	Red blood cells	Hemoglobin	Hematocrit
Peak VO_2			
Correlation coefficient	.369	.482	.476
Significance (1-tailed)	.050*	.013*	.015*

VO_2 indicates aerobic capacity.
* Significant ($P \leq .05$).

was performed during either conventional or high-dose chemotherapy with stem cell rescue, although participants walked daily on treadmills for 30 ± 10 days, physical performance measures remained unchanged, suggesting that the training intensity or duration may not have been sufficient for training effects to occur.[16]

The major limitation of the current study was the small sample size. Because effect sizes for changes in the AE group for RBC, HCT, and HB were small to moderate (.20, .13, and .38 respectively), this study required 45 to 50 subjects in each condition for adequate statistical power to determine whether improvements in the training group were significant.[17] Therefore, although the AE group experienced modest increases in their erythrocyte levels, subsequent studies using larger samples would be of benefit to support this phenomenon. A second limitation was that although the activity condition was controlled, there was no control of dietary intake during the course of this study, which may also have an impact erythrocyte measures.

Conclusions

The results of the current study suggest that moderate-intensity aerobic exercise performed during radiation treatment may preserve or maintain erythrocyte levels in females being treated for breast cancer compared with declines observed in nontraining peers. This study also found significant positive correlations between changes in peak aerobic capacity and final erythrocyte measures, suggesting an association between fitness and erythrocyte values during radiation treatment of breast cancer. The study results support the potential for moderate aerobic exercise to be a safe, effective, and economical method for improving physical fitness and maintaining erythrocyte levels in females undergoing radiation treatment of breast cancer. Future studies would be of benefit to determine whether improvements in erythrocyte levels from aerobic exercise training have a positive effect of physical function, other health conditions, and

survival rates in women with breast cancer and in other cancer diagnoses and treatments.

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