Moderator Effects in a Randomized Controlled Trial of Exercise Training in Lymphoma Patients

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Abstract

Background: **The Healthy Exercise for Lymphoma Patients trial showed that aerobic exercise training improved important health outcomes in lymphoma patients. Here, we examine potential moderators of the exercise training response.**
Methods: **Lymphoma patients were stratified by major disease type and current treatment status and randomly assigned to usual care (*n* = 62) or aerobic exercise training (*n* = 60) for 12 weeks. Endpoints were quality of life, cardiovascular fitness, and body composition. Moderators were patient preference for group assignment, age, sex, marital status, disease stage, body mass index, and general health.**
Results: **Patient preference did not statistically moderate the effects of exercise training on quality of life (*P* for interaction = 0.36), but the interaction effect of 7.8 points favoring patients with no preference was clinically meaningful. Marital status (*P* for interaction = 0.083), general health (*P* for interaction = 0.012), and body mass index (*P* for interaction = 0.010) moderated the effects of aerobic exercise training on quality of life with better outcomes for unmarried versus married patients, patients in poor/fair health versus good-to-excellent health, and normal weight/obese versus overweight patients. Disease stage (*P* for interaction = 0.056) and general health (*P* for interaction = 0.012) moderated the effects of aerobic exercise training on body composition with better outcomes for patients with advanced disease versus early disease/no disease and patients in good health versus very good-to-excellent health. No variables moderated intervention effects on cardiovascular fitness. Findings were not explained by differences in adherence.**
Conclusions: **Clinically available variables predicted quality of life and body composition responses to aerobic exercise training in lymphoma patients. If replicated, these results may inform future randomized trials and clinical practice.** (Cancer Epidemiol Biomarkers Prev 2009;18(10):2600–7)

Introduction

Lymphoma is the fifth most common cancer in the United States and Canada, with 89% of cases being non-Hodgkin's lymphomas and 11% being Hodgkin's lymphomas (1, 2). The 5-year relative survival rate is 63% for non-Hodgkin's lymphoma and 85% for Hodgkin's lymphoma. Lymphoma patients are often treated with successive courses of chemotherapy, radiation therapy, and/or biological therapy interspersed with active surveillance. These diseases and their repeated treatments can produce side effects that result in physical deconditioning and diminished quality of life (3-6). Few interventions have been shown to improve these outcomes in lymphoma patients. We previously reported results from the Healthy Exercise for Lymphoma Patients (HELP) trial showing aerobic exercise training improved important patient-rated outcomes, cardiovascular fitness, and body composition compared with usual care (7).

Clinical trial experts have recommended that subgroup analyses be conducted in randomized controlled trials (8, 9). Such analysis can provide important information for future clinical trials and clinical practice (9). Moderators (or effect modifiers) identify for whom or under what conditions an intervention works or works best. Moderators may influence eligibility or stratification decisions in future randomized controlled trials and identify which patients might benefit the most in clinical practice. We previously reported that the improvements in health outcomes in the HELP trial were not moderated by our stratification variables of major disease type (non-Hodgkin's lymphoma versus Hodgkin's lymphoma) or current treatment status (receiving chemotherapy versus off treatment; ref. 7). Here, we report the effects of other prespecified and exploratory moderators to determine if selected subgroups of lymphoma patients responded differently to aerobic exercise training.

We selected moderators for the HELP trial based on the results of our Supervised Trial of Aerobic versus Resistance Training (START) in breast cancer patients receiving chemotherapy (10, 11). In that trial, patient preference for group assignment and marital status moderated the effects of exercise training on quality of life (11). Moreover, age predicted cardiovascular fitness response, and disease stage predicted body composition effects (11). Based on these results, we hypothesized that aerobic exercise training would produce a larger quality of life response in lymphoma patients with no preference for group assignment

Received 5/26/09; revised 7/17/09; accepted 7/30/09; published online 10/8/09.

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doi:10.1158/1055-9965.EPI-09-0504

and in unmarried patients. We also hypothesized that younger patients would obtain a better cardiovascular response. Finally, we expected better body composition outcomes for patients with advanced disease. Because of the mixed-sex sample and the greater heterogeneity in health status of lymphoma patients, we also explored sex, general health, and body mass index (BMI) as potential moderators.

Materials and Methods

Details of the HELP trial have been reported elsewhere (7). Briefly, the study was a single-center, two-armed randomized controlled trial. Ethical approval was obtained from the Alberta Cancer Board and the University of Alberta, and written informed consent was obtained from participants.

Setting and Participants. Participants were recruited from the Cross Cancer Institute in Edmonton, Canada. Eligibility criteria were English speaking, ≥18 y old, histologically confirmed Hodgkin's lymphoma or non-Hodgkin's lymphoma, and receiving chemotherapy or off treatments. Eligible patients were identified in clinic by oncologists and through a mailed invitation using the Alberta Cancer Registry.

Randomization. Participants were stratified by major disease type (Hodgkin's lymphoma, indolent non-Hodgkin's lymphoma, aggressive non-Hodgkin's lymphoma) and current treatment status (chemotherapy, off treatments) and randomized to aerobic exercise training or usual care using a computer-generated program with concealed allocation sequence. Fitness assessors were not blinded to group assignment but were trained in standardizing the testing procedures.

Exercise Training Intervention. Participants randomized to aerobic exercise training received a supervised exercise program consisting of cycling on an upright or recumbent ergometer thrice per week for 12 wk. Intensity began at 60% of the peak power output that corresponded with baseline peak oxygen consumption ($\text{Vo}_{2\text{peak}}$) and was increased 5% each week to 75% by week 4. Duration began at 15 to 20 min for the first 4 weeks and increased by 5 min per week until 40 to 45 min in week 9, resulting in a total volume of 120 to 135 min of vigorous exercise per week. Adherence was facilitated with behavioral techniques, including flexible hours, booked exercise sessions, telephone follow-up after missed sessions, positive reinforcement from staff, and paid parking/transportation. Usual-care participants were asked not to change their exercise and were offered 4-wk supervised exercise after postintervention assessments.

Assessment of Endpoints Included in the Moderator Analyses. Endpoints for the trial were assessed at baseline and postintervention. Our primary endpoint was patient-rated physical functioning assessed by the Trial Outcome Index–Anemia scale (12), which ranges from 0 to 136 and includes items such as "I have energy" and "I am able to do my usual activities." Secondary endpoints were cardiovascular fitness and body composition. Cardiovascular fitness was assessed by a maximal graded exercise test (13) and followed American Thoracic Society guidelines (14). Metabolic data were averaged over 15 s, with the highest 15-s Vo_2 value recorded as $\text{Vo}_{2\text{peak}}$. For analyses, $\text{Vo}_{2\text{peak}}$ values were normalized for age and sex based on the formula of Jones et al. (15). Dual X-ray absorptiometry assessed lean body mass and percent body fat (General Electric LUNAR EXPERT).

Assessment of Moderators. Patient preference for group assignment was assessed in the baseline questionnaire before randomization by the question: "If I had my choice, I would prefer…." Options were (*a*) to exercise over the next 12 wk, (*b*) not to exercise over the next 12 wk, and (*c*) either one is fine with me, I have no preference. Demographic data were collected by self-report, and medical data were abstracted from records. Marital status was divided into "married" (married, common law) versus "unmarried" (never married, separated, widowed, divorced). Age was divided into <50 versus ≥50 y. Disease stage was divided into no evidence of disease, stage I/II, and stage III/IV. BMI was assessed by objectively measured body weight and height and divided into normal weight (<25 kg/m^2), overweight (25 to 29.9 kg/m^2), and obese (≥30 kg/m^2). General health was assessed by the single item from the SF12 asking respondents to rate their current health from poor to excellent and was divided into poor/fair, good, and very good/excellent (16).

Statistical Analyses. We used linear mixed-model analysis to assess effect modification of the intervention by each hypothesized moderator in the form of an interaction test (17). Each outcome measure was modeled to compare changes over time across intervention-moderator groups. Our primary analyses were adjusted for baseline value of the outcome, age, sex, disease stage, major disease type, current treatment status, and recent exercise (except when a covariate was tested as the moderator). For all analyses, we used the intention-to-treat principle. We examined patient preference and marital status for quality of life only because there was no biological plausibility for how these moderators might affect objective responses to exercise training. Age, sex, disease stage, BMI, and general health were examined for all four endpoints. This strategy resulted in 22 tests of interactions. We made no adjustment for multiple comparisons because our trial was not originally powered to detect interactions and we considered these analyses to be exploratory (hypothesis generating) rather than hypothesis testing (18). Moreover, given the underpowered nature of these analyses, we report quality of life interaction effects that exceed the minimally important difference on the Trial Outcome Index–Anemia of 6.0 points (12), regardless of statistical significance.

Results

Flow of participants through the trial has been reported elsewhere (7). Briefly, we recruited 9% (122 of 1,306) of screened patients and 26% (122 of 474) of eligible patients. We obtained postintervention quality of life data, cardiovascular fitness data, and body composition data on 96% (117 of 122), 89% (108 of 122), and 91% (111 of 122) of participants, respectively. Groups were balanced on the moderators at baseline except for general health wherein patients in the usual-care group had borderline significant ($P = 0.054$) better health (Table 1). Given that only two participants selected a preference not to exercise over

Table 1. Baseline distribution of proposed moderators, overall and by group assignment

Variable	Overall (*N* = 122)	Usual care (*n* = 62)	AET (*n* = 60)	*P*
Patient preference				0.34
No preference	18 (14.8%)	11 (17.7%)	7 (11.7%)	
Preferred AET	104 (85.2%)	51 (82.3%)	53 (88.3%)	
Age, y				0.89
<50	42 (34.4%)	21 (33.9%)	21 (35.0%)	
≥50	80 (65.6%)	41 (66.1%)	39 (65.0%)	
Sex				0.55
Male	72 (59.0%)	35 (56.5%)	37 (61.7%)	
Female	50 (41.0%)	27 (43.5%)	23 (38.3%)	
Marital status				0.44
Married	94 (77.0%)	46 (74.2%)	48 (80.0%)	
Unmarried	28 (23.0%)	16 (25.8%)	12 (20.0%)	
Disease stage at study entry				0.78
No evidence of disease	34 (27.9%)	18 (29.0%)	16 (26.7%)	
SI/II	43 (35.2%)	23 (37.1%)	20 (33.3%)	
SIII/IV	45 (36.9%)	21 (33.9%)	24 (40.0%)	
General health				0.054
P/F	19 (15.6%)	7 (11.3%)	12 (20.0%)	
GD	47 (38.5%)	20 (32.3%)	27 (45.0%)	
VG/EX	56 (45.9%)	35 (56.5%)	21 (35.0%)	
BMI				0.35
<25.0	38 (31.1%)	23 (37.1%)	15 (25.0%)	
25.0-29.9	48 (39.3%)	22 (35.5%)	26 (43.3%)	
≥30.0	36 (29.5%)	17 (27.4%)	19 (31.7%)	

NOTE: Data are in *n* (%).
Abbreviations: AET, aerobic exercise training; SI/II, stage I/II; SIII/IV, stage III/IV; P/F, poor/fair; GD, good; VG/EX, very good/excellent.

the next 12 weeks, these two participants were combined with the 16 participants selecting no preference. The aerobic exercise training group attended a mean of 77.8% and a median of 91.7% of their supervised sessions.

Moderators of Quality of Life Response. Patient preference did not statistically moderate the effects of aerobic exercise training on quality of life (*P* for interaction = 0.36), but the interaction effect of 7.8 points favoring the no-preference group was clinically meaningful (Fig. 1A). Specifically, aerobic exercise training resulted in a 13.0-point benefit in the no-preference group (*P* = 0.093) compared with a 5.3-point benefit in the preference group (*P* = 0.11). Adherence to aerobic exercise training was 77% and 87% in the preference and no-preference groups (*P* = 0.42), respectively (Table 2).

Marital status was a borderline significant moderator of the effects of aerobic exercise training on quality of life (*P* for interaction = 0.083), with the interaction effect of 12.8 points favoring unmarried patients (Fig. 1B). Specifically, aerobic exercise training resulted in a 17.1-point advantage in the unmarried group (*P* = 0.010) compared with a 4.3-point advantage in the married group (*P* = 0.19). Adherence to aerobic exercise training was 82% in unmarried patients and 77% in married patients (*P* = 0.64).

General health was a significant moderator of the effects of aerobic exercise training on quality of life (*P* for interaction = 0.012) with the interaction effect favoring the poor/fair health group over the good health group by 27.1 points (*P* = 0.003) and over the very good/excellent health group by 20.8 points (*P* = 0.022; Fig. 1C). Specifically, aerobic exercise training resulted in a 27.7-point advantage in the poor/fair health group (*P* < 0.001) compared with a 0.6-point advantage in the good health group (*P* = 0.89) and a 6.9-point advantage in the very good/excellent health group (*P* = 0.12). Adherence to aerobic exercise training was 81%, 73%, and 83% in patients in poor/fair, good, and very good/excellent health, respectively (*P* = 0.49).

BMI was a significant moderator of the effects of aerobic exercise training on quality of life (*P* for interaction = 0.010), with the interaction effect favoring the normal weight and obese patients over the overweight patients by 21.4 points (*P* = 0.003) and 13.7 points (*P* = 0.059), respectively (Fig. 1D). Specifically, aerobic exercise training resulted in an 18.2-point advantage in normal weight patients (*P* = 0.001) compared with a 10.5-point advantage in obese patients (*P* = 0.061) and a 3.2-point disadvantage in overweight patients (*P* = 0.47). Adherence to aerobic exercise training was 89%, 79%, and 68% in normal weight, overweight, and obese patients (*P* = 0.12), respectively. Age, sex, and disease stage did not moderate the quality of life response (all *P*s for interactions > 0.20).

Moderators of Cardiovascular Fitness Response. Age, sex, disease stage, BMI, and general health did not moderate the effects of aerobic exercise training on cardiovascular fitness response (all *P*s for interactions > 0.20).

Moderators of Body Composition Response. Disease stage was a borderline-significant moderator of the effects of aerobic exercise training on lean body mass (*P* for interaction = 0.056), with the interaction effect favoring patients with stage III/IV disease over patients with no disease by 1.8 kg (*P* = 0.025) and over patients with stage I/II disease by 1.4 kg (*P* = 0.070; Fig. 2A). Specifically, aerobic exercise training resulted in a 1.8-kg advantage in lymphoma patients with stage III/IV disease (*P* = 0.001) compared with a 0.4-kg advantage in patients with stage I/II disease (*P* = 0.43) and no difference in patients with no disease (*P* = 0.96). Adherence to aerobic exercise training was 86%, 69%, and 80% in patients with no disease, stage I/II disease, and stage III/IV disease (*P* = 0.22), respectively. Age, sex, BMI, and general health did not moderate the lean body mass response (all *P*s for interactions > 0.20; Table 3).

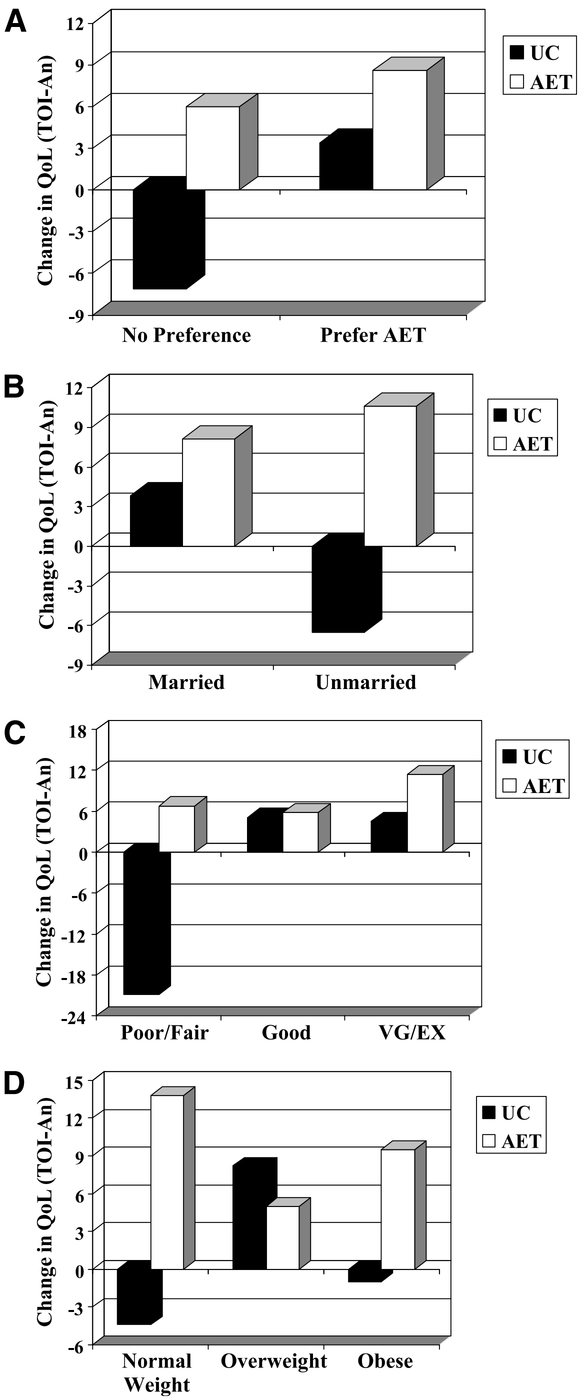

Figure 1. Change in quality of life by patient preference for group assignment (**A**), marital status (**B**), general health (**C**), and BMI (**D**). QoL, quality of life; TOI-An, Trial Outcome Index–Anemia; VG/EX, very good/excellent; UC, usual care; AET, aerobic exercise training.

General health was a statistically significant moderator of the effects of aerobic exercise training on percent body fat (*P* for interaction = 0.012), with the interaction effect favoring the good health patients over the very good/excellent health patients by −2.5% (*P* = 0.012; Fig. 2B). Specifically, aerobic exercise training resulted in a −2.2% advantage in lymphoma patients in good health (*P* = 0.002) compared with −0.4% advantage in patients in poor/fair health (*P* = 0.76) and a 0.3% disadvantage in patients in very good/excellent health (*P* = 0.67). As noted previously, adherence to aerobic exercise training was 81%, 73%, and 83% in patients in poor/fair, good, and very good/excellent health, respectively (*P* = 0.49). Age, sex, disease stage, and BMI did not moderate the percent body fat response (all *P*s for interaction > 0.20).

Discussion

Previous randomized controlled trials of exercise in cancer patients have been too small to test for moderators properly (19, 20). Some trials have presented stratified subgroup analysis (21, 22) but have not conducted a formal test of the interaction (8, 9, 18). Other trials have conducted formal tests of interactions but have had limited power (23-26) or have examined only baseline functioning scores (27). The START trial was one of the largest exercise trials in cancer patients to conduct formal tests of interactions.

In the HELP trial, we did not observe a statistically significant moderation of the quality of life response by patient preference but the interaction effect of almost 8 points exceeds the minimally important difference of 6 points on the Trial Outcome Index–Anemia. This finding is consistent with the START trial that compared aerobic exercise training and resistance exercise to usual care in breast cancer patients receiving chemotherapy. In that three-armed trial, patients who preferred resistance exercise had a better quality of life response when assigned to resistance exercise, consistent with a patient preference effect. Conversely, patients who preferred aerobic exercise training did not have a better quality of life response when assigned to aerobic exercise training. Rather, patients with no preference responded better to aerobic exercise training, consistent with the present trial.

One important difference between the two trials is the no-preference option in the HELP trial was for exercising versus not exercising, whereas it was unclear in the START trial if the no-preference option meant no preference for aerobic exercise training versus resistance exercise or no preference for exercising versus not exercising. Despite this difference, the same pattern of results emerged for the no-preference and aerobic exercise training–preference groups. To the best of our knowledge, the HELP trial is the first trial to ask about a preference for group assignment in an exercise trial with only one active intervention arm. Although only two patients preferred not to exercise (that is, preferred usual care), 16 patients reported no preference, suggesting that not all patients in an exercise trial with a no-exercise arm prefer the exercise intervention. Nevertheless, the small number of patients in the no-preference group may have affected our ability to detect a statistically significant interaction.

There are several explanations for a "no-preference effect" in exercise trials. First, patient preference may influence the emotional response to group assignment. We actually assessed emotional response to group assignment in the 6-month follow-up survey by asking participants to recall how they felt about their group assignment on a 7-point scale ranging from extremely disappointed to extremely pleased. χ^2 Analysis indicated a significant interaction between patient preference and group assignment ($P < 0.001$). Specifically, participants who preferred aerobic exercise training had a universally positive response when assigned to aerobic exercise training but a largely negative response when assigned to usual care (Fig. 3A). Conversely, participants with no preference responded well emotionally to either group assignment (Fig. 3B). These data suggest that a preference for the active exercise arm results in a negative emotional response when assigned to the no-exercise arm (that is, usual care). Intuitively, however, this pattern of emotional response would seem to favor a larger quality of life response in the preference group. Nevertheless, future trials should examine emotional responses to group assignment to determine its implication for exercise response even if the comparison arm is a no-exercise arm.

It is also possible that participants who preferred aerobic exercise training were more likely to exercise during the randomized controlled trial despite being assigned to usual care (that is, a cross-over effect) than those with no preference. Again, we have some data to address this question, albeit self-report. At postintervention, we asked participants to report any exercise done outside the trial during the 12-week intervention. Participants that preferred aerobic exercise training were no more likely to report regular exercise if assigned to usual care (22.5%) than participants with no preference (18.2%; $P = 0.75$). Consequently, greater contamination in the usual-care group does not seem to explain the smaller effect in the aerobic exercise training–preference group. Conversely, however, a slightly higher adherence to aerobic exercise training of about 10% by participants with no preference may partly explain the better quality of life outcome. More research is needed about the effects of patient preference in unblinded exercise trials, as well as the mechanisms for any effect.

Consistent with our START trial (11), marital status was an important moderator of the effects of exercise training on quality of life with the interaction effect of 13 points favoring unmarried patients. In both trials, unmarried cancer patients experienced significant declines in quality of life when assigned to usual care that were not experienced by married patients. The decline among unmarried patients was completely reversed with aerobic exercise training. The effect does not seem to be explained by differences in exercise adherence. One possible explanation is that unmarried patients may have less social support at home than married patients (28) and consequently benefit more from the social aspects of the exercise program. Research on psychosocial interventions has shown that cancer patients with the least support tend to benefit the most from psychosocial interventions (29). Although our

Table 2. Moderators of quality of life response to exercise training in lymphoma patients

	Baseline M (SD)	Posttest M (SD)	Adjusted M change, M (95% CI)	Adjusted subgroup difference in M change, M (95% CI); *P*	Adjusted interaction effect, M (95% CI); *P*
Patient preference					
Preferred AET					
UC	106.5 (20.3)	108.1 (20.5)	3.4 (−1.3 to 8.0)	5.3 (−1.3 to 11.8); 0.11	
AET	99.9 (21.6)	109.6 (18.9)	8.6 (4.2 to 13.0)		7.8 (−9.0 to 24.5); 0.36
No preference					
UC	98.9 (24.6)	93.5 (25.3)	−7.1 (2.7 to −16.8)	13.0 (−2.2 to 28.3); 0.093	
AET	101.9 (26.1)	107.3 (18.7)	6.0 (−5.9 to 17.8)		
Marital status					
Married					
UC	104.0 (21.6)	106.3 (20.6)	3.8 (−0.9 to 8.4)	4.3 (−2.3 to 10.9); 0.19	
AET	100.7 (21.9)	109.1 (19.6)	8.1 (3.5 to 12.6)		12.8 (−1.7 to 27.2); 0.083
Unmarried					
UC	108.3 (20.1)	102.7 (26.3)	−6.5 (2.0 to −15.0)	17.1 (4.2 to 29.9); 0.010	
AET	98.0 (22.7)	110.1 (15.1)	10.6 (1.1 to 20.1)		
Baseline general health					
P/F					
UC	73.4 (10.3)	70.4 (16.2)	−20.9 (−8.4 to −33.4)	27.7 (12.7 to 42.7); <0.001	P/F vs GD
AET	81.2 (15.2)	105.8 (20.4)	6.8 (−3.3 to 16.9)		27.1 (9.3 to 44.8); 0.003
GD					
UC	110.4 (14.1)	111.5 (16.4)	5.1 (−1.9 to 12.1)	0.6 (−8.6 to 9.9); 0.89	GD vs VG/EX
AET	100.3 (20.0)	105.1 (17.6)	5.8 (−0.3 to 11.8)		−6.3 (6.6 to −19.1); 0.33
VG/EX					
UC	108.5 (20.8)	109.2 (19.3)	4.5 (−0.9 to 10.0)	6.9 (−1.9 to 15.6); 0.12	P/F vs VG/EX
AET	110.7 (21.0)	116.7 (17.8)	11.4 (4.4 to 18.4)		20.8 (3.1 to 38.6); 0.022
Baseline BMI					
NW					
UC	104.8 (22.6)	100.5 (26.1)	−4.4 (2.2 to −11.0)	18.2 (7.7 to 28.7); 0.001	NW vs OW
AET	100.7 (23.5)	113.3 (16.1)	13.8 (5.8 to 21.8)		21.4 (7.4 to 35.4); 0.003
OW					
UC	104.7 (21.6)	111.4 (15.2)	8.2 (1.5 to 14.9)	−3.2 (−12.2 to 5.8); 0.47	OB vs OW
AET	101.7 (23.0)	107.4 (21.4)	5.0 (−1.1 to 11.1)		13.7 (6.6 to −19.1); 0.059
OB					
UC	106.3 (19.5)	104.1 (22.9)	−1.0 (−9.0 to 7.0)	10.5 (−0.5 to 21.4); 0.061	NW vs OB
AET	97.5 (20.0)	108.6 (17.1)	9.5 (2.0 to 17.0)		7.7 (−7.3 to 22.8); 0.31

NOTE: Mean (SD) at posttest are based on available data ($n = 117$). Adjusted mean change, adjusted subgroup difference in mean change, and adjusted interaction effect are estimated based on mixed model analysis adjusted for baseline value of the outcome, age, sex, disease stage, major disease type, current treatment status, and recent exercise (a covariate was excluded if tested as a moderator).

Abbreviations: UC, usual care; M, mean; 95% CI, 95% confidence interval; NW, normal weight; OW, overweight; OB, obese.

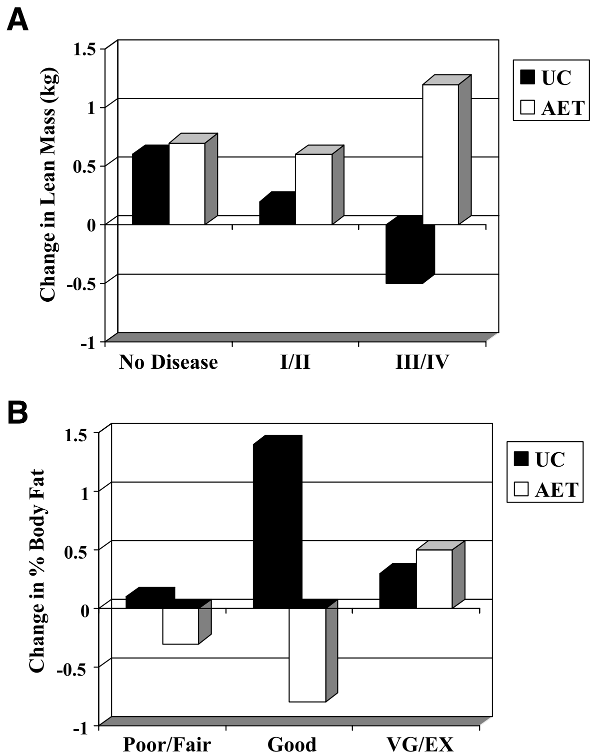

Figure 2. Change in body composition by disease stage (**A**) and general health (**B**).

exercise intervention was not designed as a psychosocial intervention, there was significant interaction with the exercise trainers and among trial participants.

General health was a significant moderator of the effects of exercise training on quality of life, with the interaction effect favoring patients in poor/fair health over those in good health and very good/excellent health by a substantial 21 to 27 points, or 3 to 4 times the minimally important difference for this scale. The effect seems to have resulted primarily from a significant decline in quality of life for patients in poor/fair health assigned to usual care that was completely reversed with aerobic exercise training. Lymphoma patients with poor/fair health typically experience more treatment toxicities (30), which may explain the large decline in quality of life in the absence of exercise. Interestingly, however, patients in poor/fair health did not achieve a better health-related fitness response, suggesting that the same magnitude of improvement in health-related fitness may lead to greater quality of life benefits for patients at the lower end of the health continuum than at the higher end. Given the magnitude of this effect, future exercise trials with cancer patients may consider stratification by general health status.

BMI was a significant moderator of the effects of exercise training on quality of life, with the interaction effect favoring the normal weight and obese patients over the overweight patients by a substantial 21 and 14 points, respectively. It is unclear why overweight lymphoma patients would not improve quality of life with aerobic exercise training. Adherence to aerobic exercise training was slightly higher in normal weight patients compared with overweight patients (89% versus 79%) but was actually lower in obese patients (68%). Previous cross-sectional research has shown a positive association between physical activity and quality of life in cancer survivors, regardless of BMI category (31). Perusal of the data show that overweight patients assigned to usual care fared quite well, making it more difficult to show a benefit with aerobic exercise training. Some data are available to suggest that being overweight might be protective for some health outcomes, especially in patients with chronic diseases. Nevertheless, given the exploratory analysis and the unexpected

Table 3. Moderators of body composition response to exercise training in lymphoma patients

	Baseline M (SD)	Posttest M (SD)	Adjusted M change M (95% CI)	Adjusted subgroup difference in M change: M (95% CI); *P*	Adjusted interaction effect M (95% CI); *P*
Disease stage on lean body mass, kg					
ND					
UC	52.1 (9.8)	51.8 (9.5)	0.6 (−0.2 to 1.5)	0.0 (−1.1 to 1.2); 0.96	SI/II vs ND
AET	50.6 (11.0)	50.4 (11.3)	0.7 (−0.2 to 1.5)		0.4 (−1.2 to 2.0); 0.61
SI/II					
UC	48.1 (9.8)	48.4 (10.1)	0.2 (−0.5 to 0.9)	0.4 (−0.6 to 1.5); 0.43	SIII/IV vs SI/II
AET	55.0 (11.6)	55.1 (12.2)	0.6 (−0.2 to 1.4)		1.4 (−0.1 to 2.8); 0.070
SIII/IV					
UC	49.9 (10.4)	49.7 (10.5)	−0.5 (−1.3 to 0.2)	1.8 (0.8 to 2.8); 0.001	SIII/IV vs ND
AET	51.5 (10.3)	51.2 (11.0)	1.2 (0.5 to 2.0)		1.8 (0.2 to 3.3); 0.025
Baseline general health on body fat, %					
P/F					
UC	31.7 (7.7)	33.9 (6.4)	0.1 (−1.9 to 2.1)	−0.4 (−2.8 to 2.1); 0.76	GD vs P/F
AET	38.0 (7.6)	38.2 (8.2)	−0.3 (−1.7 to 1.1)		−1.8 (1.0 to −4.6); 0.19
GD					
UC	33.9 (11.2)	35.3 (10.6)	1.4 (0.4 to 2.4)	−2.2 (−0.8 to −3.6); 0.002	GD vs VG/EX
AET	33.3 (11.9)	32.9 (12.0)	−0.8 (−1.7 to 0.1)		−2.5 (−0.5 to −4.4); 0.012
VG/EX					
UC	32.0 (11.5)	31.8 (11.0)	0.3 (−0.5 to 1.0)	0.3 (−1.0 to 1.6); 0.67	P/F vs VG/EX
AET	28.8 (6.5)	29.4 (6.6)	0.5 (−0.5 to 1.6)		−0.6 (2.2 to −3.5); 0.64

NOTE: Mean (SD) at posttest are based on available data (n = 111). Adjusted mean change, adjusted subgroup difference in mean change, and adjusted interaction effect are estimated based on mixed model analysis adjusted for baseline value of the outcome, age, sex, disease stage, major disease type, current treatment status, and recent exercise (a covariate was excluded if tested as a moderator).
Abbreviation: ND, no disease.

nature of this interaction, this finding may have resulted by chance and needs to be replicated before it can be considered reliable.

Contrary to our hypothesis, age did not moderate the effects of aerobic exercise training on cardiovascular response. This finding is not consistent with our START trial results in breast cancer patients receiving chemotherapy, but it is consistent with our REHAB trial, wherein we reported no effects of age (<60 versus ≥60 years) on aerobic fitness gains in 52 breast cancer survivors (24). In the START trial, however, we did not normalize cardiovascular fitness responses for age. In the general literature it has been established that, despite lower baseline values, older individuals typically have the same relative improvement in maximal aerobic capacity given the same exercise prescription (32). Interestingly, no age differences emerged despite the fact that adherence was 15% lower in the younger age group compared with the older age group (68% versus 83%). Additional research on age effects in exercise trials with cancer patients is warranted.

Consistent with the START trial, disease stage was a borderline-significant moderator of the effects of aerobic exercise training on lean body mass, with the interaction effect favoring patients with stage III/IV disease over patients with no disease or stage I/II disease. The effect seems to have resulted from a combination of a greater loss of lean body mass in patients with advanced disease assigned to usual care, as well as a greater response to training in those patients. Lymphoma patients with more advanced disease typically receive more anticancer therapy (33), which may explain the greater loss in lean body mass for advanced disease stage patients assigned to usual care. This fact was verified in our own data set, with stage I/II patients averaging 5.2 cycles of chemotherapy compared with 6.9 cycles for stage III/IV patients (P = 0.001). Adherence to aerobic exercise training was slightly higher in patients with no disease (86%) compared with patients with stage III/IV disease (80%), although it was lower in patients with stage I/II disease (69%). Given the replication of this finding from our START trial, disease stage may be an important variable to consider in future exercise trials wherein body composition endpoints are of interest.

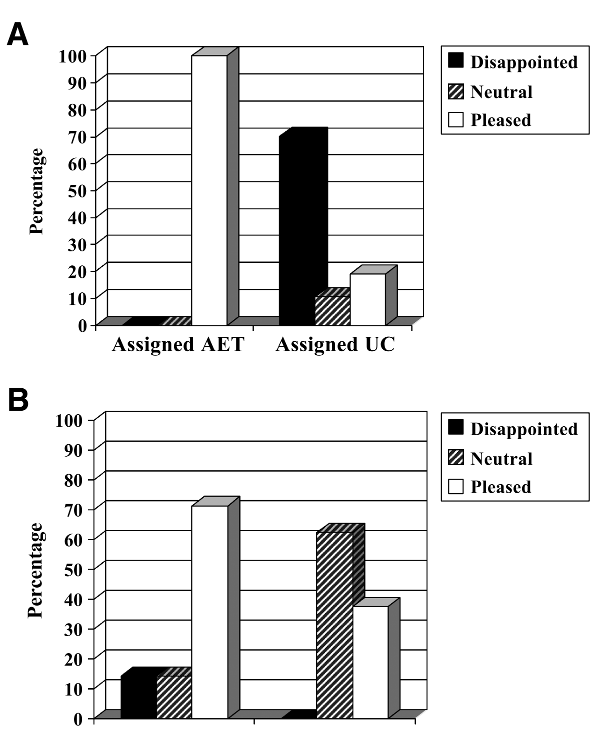

Figure 3. Emotional response to group assignment for patients that preferred aerobic exercise training (**A**) and had no preference (**B**).

General health was a statistically significant moderator of the effects of exercise training on percent body fat, with an interaction effect favoring the good health patients over the very good/excellent health patients by −2.5%. One possible explanation is that patients in very good/excellent health may have had less body fat to lose, although we did statistically control for the baseline value in our analysis. Given the unexpected nature of this interaction, additional research is warranted before conclusions should be drawn.

The overall strengths of our trial have been noted elsewhere (7). Additional strengths of the present report include our prespecified moderator analyses based on a previous trial, our selection of prerandomization characteristics as moderators, the clinical utility of our selected moderators, assessment of patient preference before randomization, use of the intention-to-treat population, direct tests of interactions, replication of several interaction effects previously observed with breast cancer patients on chemotherapy, and biological or psychosocial plausibility for most of our findings (8). The overall limitations of our trial have also been noted elsewhere (7). Additional limitations of the present report include our limited statistical power to detect interactions, our failure to obtain a measure of the emotional response to group assignment at the time of randomization, and the 22 interaction tests, which would likely result in one false discovery if all tests were null.

In summary, our moderator analyses suggest that quality of life and body composition responses to aerobic exercise training in lymphoma patients may be partly predicted by readily available clinical variables. It seems that greater quality of life benefits from aerobic exercise training are achieved by lymphoma patients that have no preference for exercise, are unmarried, have normal weight or are obese, or are in poor/fair health. The largest gain in lean body mass is obtained by patients with more advanced disease, and the largest fat loss is achieved by patients in good health. Nevertheless, it is important to note that all subgroups of lymphoma patients achieved at least some benefit from aerobic exercise training. Moreover, although we replicated several interaction effects from the START trial, we view our findings as hypothesis generating rather than hypothesis testing (18) and in need of replication (8). Future trials should continue to examine patient preference, marital status/social support, age, disease stage, and general health as potentially important moderators of exercise training responses in cancer patients, and use larger sample sizes with more power to detect meaningful differences. Until then, exercise and cancer care professionals may consider our results when designing future exercise trials and/or recommending exercise to lymphoma patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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Cancer Epidemiol Biomarkers Prev 2009;18:2600-2607.