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Symptom Management and Supportive Care

Effectiveness of Oncologist-Referred Exercise and Healthy Eating Programming as a Part of Supportive Adjuvant Care for Early Breast Cancer

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Key Words. Breast neoplasms • Exercise • Drug therapy • Quality of life

Abstract

Background. Randomized trials have established efficacy of supervised exercise training during chemotherapy for breast cancer for numerous health outcomes. The purpose of this study was to assess reach, effectiveness, maintenance, and implementation of an evidence-based exercise and healthy eating program offered within an adjuvant care setting.

Subjects, Materials, and Methods. Women receiving adjuvant chemotherapy for breast cancer were given a prescription by their oncologist to participate in the Nutrition and Exercise during Adjuvant Treatment (NExT) program. The NExT program consisted of supervised, moderate-intensity, aerobic and resistance exercise three times a week during adjuvant therapy, followed by a step-down in supervised sessions per week for 20 additional weeks, plus one group-based healthy eating session. Usual moderate-to-vigorous physical activity (MVPA) and health-related quality of life (HRQoL) were assessed by questionnaire at baseline, program completion, and one year later, along with measures of satisfaction and safety.

Results. Program reach encompassed referral of 53% of eligible patients, 78% uptake ($n = 73$ enrolled), and 78% retention for the 45.0 ± 8.3-week program. During the program, MVPA increased (116 ± 14 to 154 ± 14 minutes per week, $p = .014$) and HRQoL did not change. One year later, MVPA (171 ± 24 minutes per week, $p = .014$) and HRQoL (44 ± 1 to 49 ± 1, $p < .001$) were significantly higher than baseline. Exercise adherence was 60% ± 26% to three sessions per week during treatment. No major adverse events occurred and injury prevalence did not change relative to baseline. Participants were highly satisfied.

Conclusion. This oncologist-referred exercise and healthy eating supportive-care program for breast cancer patients receiving chemotherapy was safe, successful in reaching oncologists and patients, and effective for improving MVPA and maintaining HRQoL. ***The Oncologist*** 2018;23:105–115

Implications for Practice: Despite evidence that exercise is both safe and efficacious at improving physical fitness, quality of life, and treatment side effects for individuals with cancer, lifestyle programming is not offered as standard of cancer care. This study describes an oncologist-referred, evidence-based exercise and healthy eating program offered in collaboration with a university as supportive care to women with breast cancer receiving chemotherapy. The program was well received by oncologists and patients, safe, and relatively inexpensive to operate. Importantly, there was a significant positive impact on physical activity levels and health-related quality of life lasting for 2 years after initiation of therapy.

Introduction

There is compelling evidence from randomized controlled trials that exercise is safe for women diagnosed with breast cancer during treatment and that it improves the side effects of cancer treatment, quality of life, and overall health of cancer survivors [1–5]. However, cancer survivors report unique barriers to exercise adoption and maintenance, including concerns about safety, desire for guidance from trained professionals with experience working with cancer survivors, and physical limitations related to treatment side effects [6–8]. In addition, it is now advocated that support for healthy eating and weight

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management is integrated into clinical oncology care [9]. Currently, however, access to registered dietitians is limited within cancer care, and resources are typically prioritized to tumor sites at high risk for malnutrition and for management of acute symptoms (e.g., head and neck, gastrointestinal).

Women with newly diagnosed breast cancer may increase exercise when referred by their oncologist [10, 11]. However, cancer survivors in the U.S. and Canada have little access to appropriate exercise programming outside of research studies, especially during adjuvant treatment when the need may be greatest. There exists a gap between the scientific evidence and clinical practice in the management of breast and other cancers with respect to exercise and healthy eating programming [12]. Potential reasons for this gap in knowledge translation include concern among clinicians regarding safety, lack of clinician exercise experience/education [13], and lack of established referral pathways to exercise professionals with cancer experience, as well as inadequate registered dietitian staffing.

With efficacy and safety established by randomized trials, the Nutrition and Exercise during Adjuvant Treatment (NExT) study was designed to assess effectiveness of a supervised exercise and healthy eating program offered as part of supportive care in a real-world setting. New breast cancer patients who were receiving adjuvant chemotherapy were referred to the program by medical oncologists using a prescription to facilitate with patient screening and enhance enrollment. The program was evaluated using the RE-AIM framework to report on reach, effectiveness, maintenance, and implementation [14]. Our primary aim was to assess the reach of the program (referral rate, uptake, and retention). The secondary aim was to assess effectiveness of the program on physical activity levels and health-related quality of life (HRQoL), and maintenance of these changes. The tertiary aim was to assess implementation (adherence, cost, participant satisfaction, and safety). Goals for successful referral rate (50%), uptake (70%), retention (70%), and adherence (70%) were chosen a priori by study authors. Based on previous efficacy trials, we hypothesized that physical activity levels and HRQoL would improve by the completion of the program, and that given the length of the program, changes would be maintained 1 year later.

Subjects, Materials, and Methods

Design

The NExT study was a prospective, single-arm intervention program. As a study assessing effectiveness, it focused on a design that would be feasible to put into practice, in contrast to previous randomized trials that tested a similar intervention under the ideal circumstances of a well-controlled research environment with an expectation of adherence to the protocol (i.e., an efficacy trial) [15–18]. The British Columbia Cancer Agency (BCCA) Research Ethics Board approved the study. Participants provided written informed consent.

Patients

English-speaking adult women with newly diagnosed stage I–IIIA breast cancer who were scheduled to receive adjuvant chemotherapy (with or without radiation) were invited to enroll within the first half of their chemotherapy treatments. Exclusion criteria were conditions requiring closer monitoring of exercise supervision (e.g., uncontrolled or unstable cardiovascular disease or diabetes mellitus), body mass index >40 kg/m^2, use of mobility aids, and stage IV/metastatic disease.

Recruitment

Recruitment took place via medical oncologist referral at the Vancouver center of the BCCA. Referrals via word of mouth were also accepted for patients treated at this center. A core team of eight medical oncologists completed and signed a prescription for eligible patients to participate in NExT (Fig. 1). The oncologist gave one copy to their patient and another copy to study staff for referral. The prescription form included documentation of comorbid health conditions and medications and provided clearance to exercise (Fig. 1). The Physical Activity Readiness Questionnaire [19] was administered by study staff via telephone to identify any additional concerns, which were discussed with the oncologist via e-mail. If an individual contacted the study directly, a prescription was requested from their oncologist.

Sample Size

The goal was to open recruitment for 12 months as a measure of yearly intake for a potential clinical program. However, additional funding allowed recruitment to be extended to a total of 15 months, from August 5, 2013, to October 31, 2014.

Exercise Intervention

The exercise component was managed by a local university, and included aerobic and resistance training based on the benefits established in past trials [15, 16] and recommendations for cancer survivors [20]. Supervised exercise took place at a stand-alone fitness facility used for individuals with cancer or other chronic diseases located near the cancer treatment center. The goal of the combined supervised and home-based prescription was to meet the recommendations for cancer survivors of 150 weekly minutes of moderate-intensity aerobic exercise, and whole-body resistance training two to three times per week [20]. The exercise program was divided into three phases: treatment (length of chemotherapy, plus radiation if received), post-treatment (10 weeks), and maintenance (10 weeks). The latter two phases were designed to step-down the amount of supervised sessions offered, and increase the amount of home-based exercise encouraged (Table 1).

Nutrition Intervention

The healthy eating component consisted of a singular 2-hour, group-based healthy eating education session led by a registered dietitian with breast cancer experience; topics are described in Table 1. The session was offered monthly within the cancer treatment center, and the goal was to attend at least once near the start of the program.

Outcome Measures

Reach

A comprehensive electronic master list of patients scheduled for breast medical oncology consultation appointments at the Vancouver BCCA during the study recruitment dates was used to accurately assess referral rate. A trained staff member identified patients who were referred to the study, then carefully reviewed the medical records of patients who were not

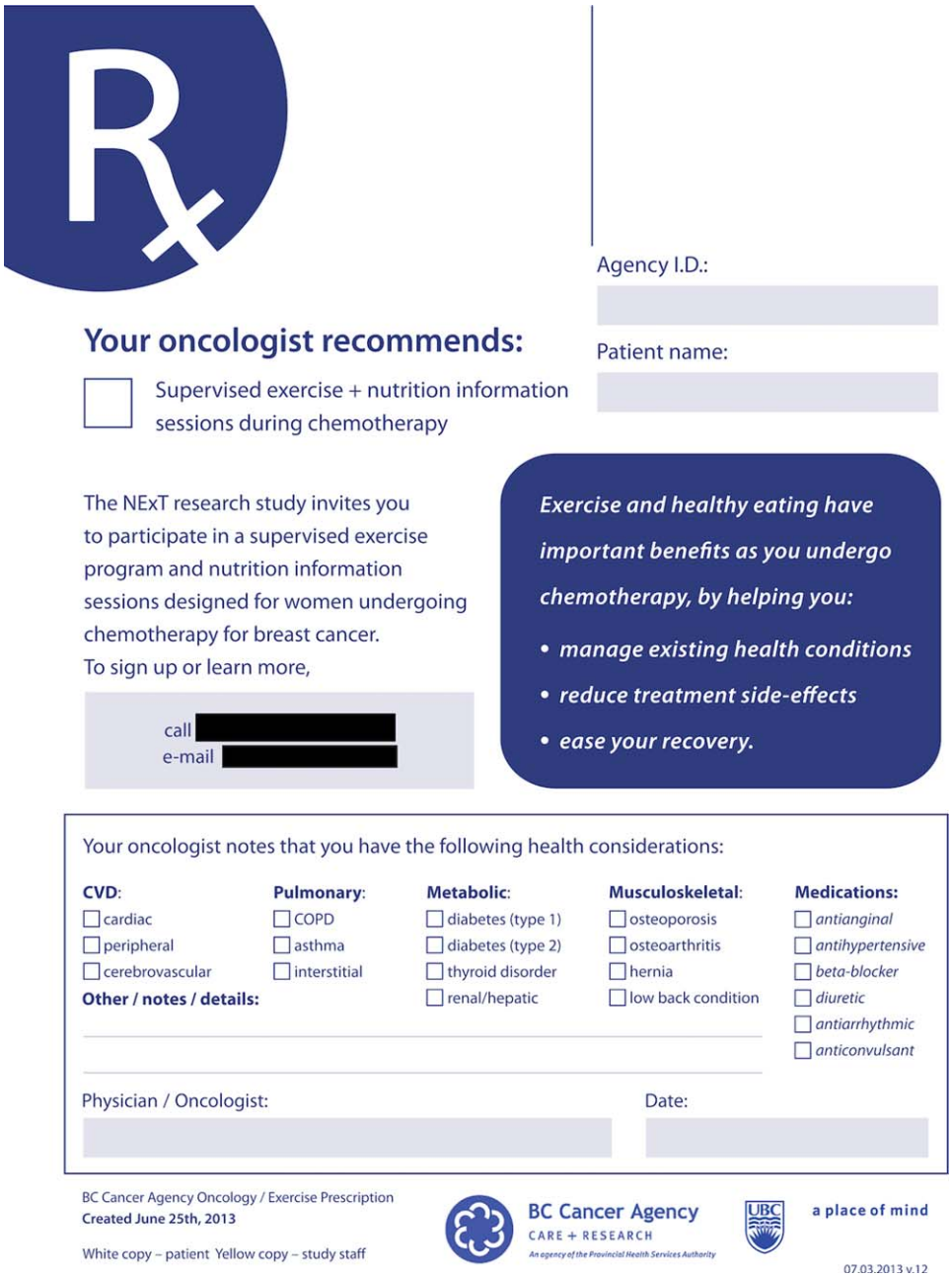

Figure 1. Exercise and nutrition program prescription form.

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; NExT, Nutrition and Exercise during Adjuvant Treatment.

referred to ascertain eligibility and specific reasons for noneligibility. Referral rate was calculated as the percentage of eligible patients included in the master list that were referred to the program. Uptake was calculated as the percentage of eligible, referred patients who enrolled. Retention was calculated as the percentage of participants who did not request withdrawal from the study. Representativeness was assessed by age of the study sample relative to those who were eligible but were not referred. This was the only characteristic available for comparison in the electronic list of new patients.

Effectiveness

Physical activity levels were assessed using a modified version of the Minnesota Leisure Time Physical Activity Questionnaire [21] administered by interview with reference to the 6 months prior to baseline, the end of the program (including supervised and home-based exercise), and at 1 year after program completion. A metabolic equivalent (MET) score [22] was used to estimate the intensity of each activity. Average moderate-to-vigorous physical activity (MVPA) was calculated as the average weekly minutes of aerobic activities with a MET score $\geq$3.0. The average resistance training performed was calculated as the average weekly minutes of "weight lifting" reported.

Exercise behavior correlates were assessed by questionnaires, including a single rating on a 5-point Likert scale for exercise enjoyment [23], a 5-item, 11-point Likert scale for exercise self-efficacy [24], and a 21-item, 5-point Likert scale for perceived barriers to exercise [23].

Table 1. Summary of exercise and healthy eating programming offered in the Nutrition and Exercise during Adjuvant Treatment trial

	Exercise programming description		
	Treatment phase	**Post-treatment phase**	**Maintenance phase**
Timing	Enrollment to end of chemotherapy ± radiation	Immediately after treatment phase + 10 wks	Immediately after post-treatment phase + 10 wks
Supervised aerobic and resistance frequency prescribed	3x per wk	2x per wk	1x per wk
Supervised aerobic modes	Treadmill, elliptical, upright or recumbent cycle ergometer		
Supervised aerobic intensity prescribed	• Progressive from 50% to 70% of APMHR HRR over wks 1–8 • 70%–75% for wks 9+	• 1x: 70%–75% of APMHR HRR • 1x: intervals (4x [4 mins at 75%–85% + 4 mins at 40%–65% VO_2R/HRR]) [43,44]	Choice of 1x/week: • 70%–75% of APMHR HRR, or • Intervals (4x [4 mins at 75%–85% + 4 mins at 40%–65% VO_2R/HRR]) [43,44]
Supervised aerobic duration prescription	• Progressed from 20 to 25 mins over wks 1–3 • 30 mins for wks 4+	• 30–32 mins	• 30–32 mins
Supervised aerobic exercise prescription modifications	Prescribed intensity was reduced by 10 percentage points (e.g., 60%–65% HRR became 50%–55% HRR) when participant reported severe treatment symptoms, or missed 1–2 wks		
Supervised resistance exercise types	Leg press, leg curls, calf raises, chest press, and seated row on resistance machines; triceps extensions and biceps curls using dumbbells; two core-strengthening exercises		
Supervised resistance intensity	• Chest and leg press: 50% estimated 1-RM [45] • Similar RPE for all other exercises • Weights were progressed[a] every 4 wks up to 75% of 1-RM	• 75% of most recent 1-RM	• 75% of most recent 1-RM
Supervised resistance duration	• 1 set of 10 repetitions for wk 1 • 2 sets of 10–12 repetitions for wks 2+	• 2 sets of 10–12 repetitions	• 2 sets of 10–12 repetitions
Supervised resistance prescription modifications	• The upper-body exercises were only initiated once full shoulder range of motion was regained following surgery • Modifications to weights and exercises were made as needed, and exercises were paused if any potential lymphedema symptoms were noted and restarted after the participant received approval from their care team[20]		
Suggested home-based aerobic exercise	• None for wks 1–2 • 1x: 15–20 mins per wk for wks 3–4 • 2x: 20–25 mins per wk for wks 5–8 • 2x: 20–30 mins per wk for wks 9+ • RPE of 12–13 for all sessions	• 3x: 30 mins per wk • RPE of 12–15 for all sessions	• 4x: 30 min per wk • RPE of 12–15 for all sessions
Suggested home-based resistance exercise	None	None	Choice of 1x per wk: • Supervised prescription at own gym or • Resistance band program at home
Healthy eating programming description			
• Singular, 2-hour, group-based session offered once monthly by a registered dietitian for participants upon enrollment • Topics: nutritional management of treatment side effects, achieving adherence to Canada's Food Guide's gender- and age-specific guidelines, the Dietary Reference Intakes for Canadians, and the Canadian Cancer Society diet and cancer prevention guidelines aimed at chronic disease risk reduction and weight maintenance			

[a]Weights were progressed by the minimal possible amount (i.e., 10 lbs for lower body, 2–5 lbs for upper body).
Abbreviations: 1-RM, one repetition-maximum; APMHR, age-predicted maximal heart rate; HRR, heart rate reserve; min, minute; RPE, rating of perceived exertion (Borg 6–20 scale); VO_2R, volume of oxygen consumption reserve; wk, week; x, times (number of sessions).

Health-related quality of life was assessed by the physical component summary of the Medical Outcomes Survey RAND-36, the higher-ordered cluster based on the physical health variance in common among the eight multi-item scales [25]. This scale relating to the physical components of quality of life was chosen because it is most likely to respond to interventions

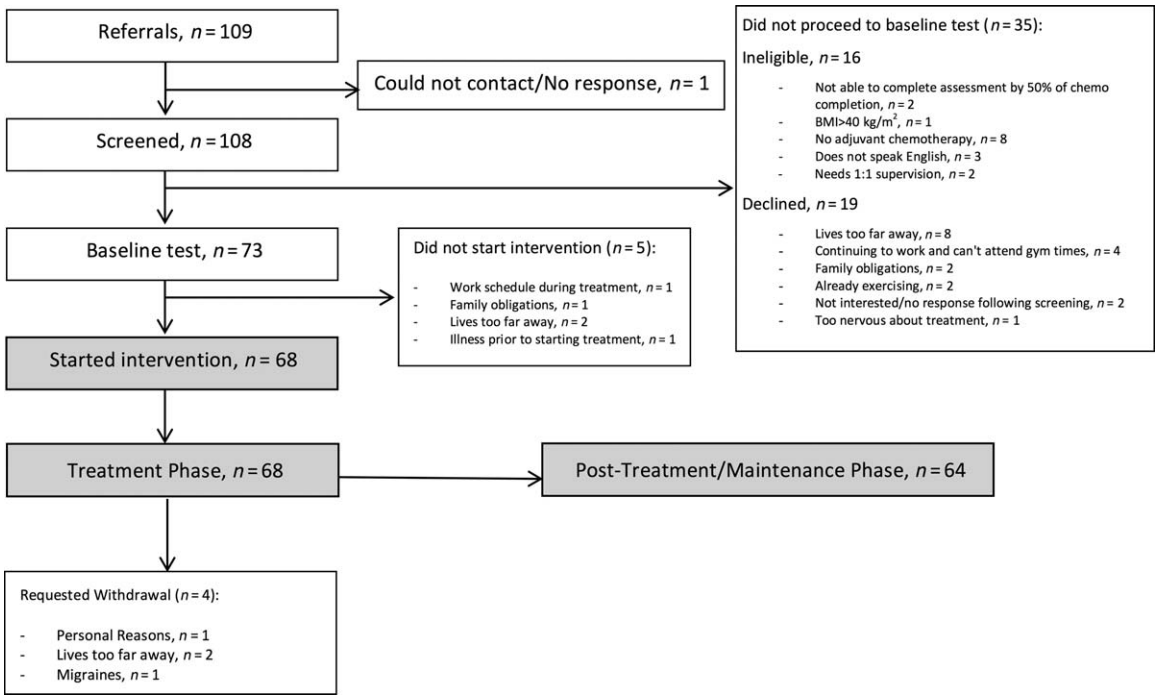

Figure 2. Flow through study.
Abbreviation: BMI, body mass index.

that change physical morbidity like exercise [26]. The minimally clinically important difference (MCID) is considered 3–5 points [27].

All of the above measures were assessed at baseline, end of program, and 1-year follow-up to end of program, and correlates of exercise behavior and HRQoL were also assessed following completion of treatment.

Implementation

Adherence was calculated as the number of exercise and healthy eating sessions attended out of the number of prescribed sessions for all participants who started the program. Participants were encouraged to attend as many exercise sessions as they could, and were asked to call or e-mail if they could not attend. If no notice was provided, or if 2–4 consecutive sessions were missed (determined at the discretion of the gym staff on a case-by-case basis), the participant was called or e-mailed and encouraged to return. The gym was open Monday, Wednesday, and Friday mornings and afternoons except for statutory holidays.

Cost was estimated for running the NExT trial as a clinical program affiliated with a university, and does not include research costs. The personnel costs allow exercise supervision by one lead trainer with a bachelor's degree in Kinesiology to oversee the program, with additional supervision by graduate students in kinesiology or physical therapy, and both paid and volunteer undergraduate kinesiology students to maintain a 1:4 staff to participant ratio. The dietitian costs are to deliver the group session once monthly. The costs do not include leasing of space or major exercise equipment because these costs will vary by location, and there is opportunity to run this program out of an existing public or clinical (e.g., cardiac rehabilitation) facility.

Participant satisfaction was assessed by a researcher-developed questionnaire. Safety was assessed by tracking injuries and adverse events using a musculoskeletal injury questionnaire [28] completed by the participants at baseline, end of treatment, and end of study, and case reporting forms, respectively. Adverse events were defined as serious medical events (i.e., cardiac, fractures) that occurred at the exercise facility or were attributed to the intervention, and were monitored on an ongoing basis.

Statistical Analysis

A generalized linear mixed model was used to analyze the questionnaire data due to missing data at various time points, and non-normal distribution of residuals. A random intercept was used with participant as the random factor to control for the nonindependence of measurements within a participant, and time point was included as a repeated and fixed effect. Main effects for time with $p \leq .05$ were further interpreted with contrasts between time points using a Bonferroni correction for multiple pairwise comparisons. The assumption of normality of residuals was not met regardless of the model/method used for resistance training; the consistent general findings with all models tested are reported. The McNemar's test was used to compare the prevalence of participants meeting the MVPA guidelines ($\geq$150 minutes per week) and injuries at baseline relative to end of study, as well as MVPA maintenance between end of study and 1-year follow-up. A p value of .05 was used to interpret the McNemar's test results.

Results

Reach

The program referral rate was 53% (82 of 154). The master list generated 938 patients who attended a medical oncology

Table 2. Participant baseline characteristics

Characteristics	*n* (%)
Demographics	
Age (years), mean ± SD (min-max)	50.8 ± 10.6 (29–77)
Marital status[a]	
Married/common-law	49 (71)
Divorced/separated/widowed	8 (11)
Single	11 (16)
Ethnicity[a]	
White	44 (64)
Asian	22 (32)
Other	3 (4)
Education[a]	
High school diploma/college	23 (33)
Some university	8 (12)
Bachelor's degree	17 (25)
>Bachelor's degree	21 (30)
Working status during treatment	
Working	11 (15)
Not working	55 (75)
Working part-time/casual	7 (10)
Medical history	
Menopausal status at baseline	
Post-menopausal	33 (45)
Peri-menopausal	12 (16)
Menopausal	28 (38)
Comorbidities	
Hypertension	12 (16)
Mental illness	11 (15)
Arthritis/osteoporosis	8 (11)
Asthma/lung disease	7 (10)
Cardiovascular disease/arrhythmias	5 (7)
Metabolic disease	3 (4)
Previous cancer	3 (4)
Thyroid disorder	3 (4)
Fibromyalgia/multiple sclerosis	2 (3)
Cancer diagnosis and treatment	
Tumor stage	
I	17 (23)
II	47 (64)
III	9 (12)
Chemotherapy protocol	
ACT	32 (44)
ACTT	15 (21)
DC	13 (18)
TDC	8 (11)
Experimental protocol[b]	5 (7)
Primary surgery	
Breast-conserving	53 (73)
Mastectomy	20 (27)
Radiation therapy	67 (92)
Hormonal therapy	
Aromatase inhibitor	16 (22)
Selective estrogen receptor modulator	44 (60)
None	13 (18)

[a]Missing $n = 4$ responses from participants who withdrew prior to completing demographics questionnaire.
[b]Experimental protocol on clinical trial consisting of four cycles of doxorubicin and cyclophosphamide 2 or 3 weeks apart, followed by 14 cycles of either trastuzumab and pertuzumab, or trastuzumab-emtansine and pertuzumab.
Abbreviations: ACT, adriamycin, cyclophosphamide, and paclitaxel; ACTT, adriamycin, cyclophosphamide, paclitaxel, and trastuzumab; DC, docetaxel and cyclophosphamide; SD, standard deviation; TDC, docetaxel, cyclophosphamide, and trastuzumab.

consultation during the study recruitment dates, of whom 772 (82%) were ineligible and 154 were eligible (16%) for the study. Reasons for ineligibility included the following: not receiving adjuvant chemotherapy ($n = 620$), living outside of Vancouver lower mainland ($n = 45$), non-English speaking ($n = 37$), noninvasive breast cancer ($n = 34$), having stage IV or metastatic breast cancer ($n = 17$), not having decided on adjuvant treatment plan prior to study closure ($n = 8$), disability/mobility issues ($n = 6$), multiple comorbidities and safety concern for group-based exercise ($n = 3$), or male gender ($n = 2$). Medical oncologists referred 82 eligible patients and 12 noneligible patients who were part of this master list. An additional 15 patients were referred who were not part of this list ($n = 109$ referrals total) due to having their consultation prior to the start of program recruitment ($n = 5$) and unknown reasons ($n = 10$).

Uptake of the program was 78% (73 of 93). Sixteen of the 109 patients referred were ineligible, and 20 declined participation (Fig. 2). Of the 93 who were referred and eligible, 73 enrolled in the program (Table 2). Nine participants requested withdrawal from the study between enrollment and completion of chemotherapy due to living too far from the gym ($n = 4$), illness prior to starting chemotherapy ($n = 1$), migraines ($n = 1$), work schedule ($n = 1$), family obligations ($n = 1$), and personal reasons ($n = 1$); therefore, retention was 88% for the treatment phase. Five of these participants withdrew prior to starting the program (or completing any exercise sessions). Following treatment completion, an additional seven participants did not attend any further sessions due to moving away ($n = 2$), returning to work ($n = 2$), treatment symptoms ($n = 1$), mental health ($n = 1$), and unknown reasons ($n = 1$). Therefore, retention for the entire program duration was 78%. The program length was 45.0 ± 8.3 (27.3–64.9) weeks. Regarding representativeness, participants in the program were significantly younger (50.8 ± 10.6 years) than eligible women who were not referred (55.6 ± 10.6 years, $p < .01$).

Effectiveness

Regarding physical activity levels over the previous 6 months, MVPA significantly increased from baseline to end of program ($p = .008$), was maintained (i.e., did not change) between end of program and 1-year follow-up ($p = .465$), and remained significantly higher than baseline at 1-year follow-up ($p = .009$; Table 3). The pattern for proportion of participants meeting or

Table 3. Effectiveness and maintenance of physical activity behavior and health-related quality of life

Measure	Baseline	End of treatment	End of program	1-year follow-up	*p* value
Self-reported average weekly physical activity over previous 6 months	($n = 73$)		($n = 57$)	($n = 47$)	
MVPA (minutes per wk)[a]	115 ± 14	N/A	156 ± 14[b]	172 ± 23[b]	**.007**
Resistance training (minutes per wk)	11 ± 4	N/A	39 ± 4[b]	19 ± 5[c]	**<.001**
Physical activity correlates	($n = 51$)	($n = 60$)	($n = 62$)	($n = 52$)	
Exercise self-efficacy (5–55)	30 ± 2	27 ± 2	29 ± 2	30 ± 2	.292
Number of perceived barriers (0–21)	4.5 ± 0.3	3.5 ± 0.2[d]	3.5 ± 0.2[d]	4.7 ± 0.4[e,f]	**<.001**
Exercise enjoyment (1–5)	4.1 ± 0.2	4.2 ± 0.1	4.2 ± 0.2	4.1 ± 0.2	.730
Health-related quality of life	($n = 63$)	($n = 61$)	($n = 62$)	($n = 53$)	
Physical component summary	44 ± 1	42 ± 1	47 ± 1[e]	49 ± 1[d,e]	**<.001**

Data are estimated marginal mean $\pm$ standard error. Significant main effects are bolded.
[a]Required removal of one case to enable model fit.
[b]Significantly greater than baseline $p_{Bonferroni} < .017$.
[c]Significantly less than end of program for $p_{Bonferroni} < .017$.
[d]Significantly different from baseline for $p_{Bonferroni} < .010$.
[e]Significantly greater than end of treatment for $p_{Bonferroni} < .010$.
[f]Significantly greater than end of program for $p_{Bonferroni} < .010$.
Abbreviations: MVPA, moderate-to-vigorous physical activity; N/A, not available.

Table 4. Estimated startup and minimal annual operating costs (U.S. dollars) for the Nutrition and Exercise during Adjuvant Treatment program

Items	Estimated annual cost
Startup costs	**Subtotal $3,055**
Computer	$530
Printer (standard laser black and white)	$150
Heart rate monitors (35 participants)	$2,200
Basic automatic blood pressure monitor	$115
Stop watches	$60
Personnel	**Subtotal $40,906**
Lead exercise trainer and program coordinator ($23.00 per hour + 5% benefits for 20 hours per wk)	$25,116
Graduate student exercise trainer ($20.00 per hour for 10 hours per wk)	$10,400
Undergraduate student program assistant ($14.50 per hour for 5 hours per wk)	$3,770
Volunteer kinesiology undergraduate students (no pay for 15 hours per wk)	$0
Registered dietitian ($45 per hour for 3 hours to deliver each monthly session)	$1,620
Program operations	**Subtotal $860**
Annual exercise equipment maintenance	$300
Therabands for home resistance program	$60
Cleaning supplies (disinfectant wipes, tissues)	$200
Office supplies (printer paper and toner, post-its, pens, staples, folders)	$300
Total costs for first year	**$44,821**
Total costs for subsequent years	**$41,766**

exceeding the guidelines of 150 minutes of MVPA per week was similar, with an increase from 44% to 65% at end of program ($p = .034$). This increase was maintained at 1-year follow-up (55%, $p = .302$ relative to end of study).

From baseline to end of program, average minutes of resistance training increased (for all models, $p < .017$), and decreased between end of study and 1-year follow-up (for all models, $p < .017$). At 1-year follow-up, resistance training was not significantly higher than baseline (for all models, $p > .017$; Table 3).

Exercise self-efficacy and exercise enjoyment did not change over time ($p = .292$, $p = .730$, respectively; Table 3). The number of perceived barriers was reduced from baseline to end of treatment ($p = .001$), and did not change further from end of treatment at end of program ($p = .810$). However, from end of program to 1-year follow-up, perceived barriers increased ($p = .002$), and it was no longer different from baseline ($p = .769$; Table 3).

Health-related quality of life did not change between baseline and end of treatment ($p = .214$) nor end of study

Table 5. Participant satisfaction survey responses

Question	*n*	Response		
		Easy/very easy (%)	Neutral (%)	Difficult/very difficult (%)
Ease of attending supervised exercise sessions	59	36 (61)	14 (24)	9 (15)
Ease of performing home-based exercise sessions	57	26 (46)	23 (40)	8 (14)
		Very/quite (%)	Neutral (%)	Somewhat/not at all (%)
Clear program expectations	59	52 (88)	4 (7)	3 (5)
Clear information from exercise trainers	59	53 (90)	3 (5)	3 (5)
Clear information from dietitian	58	41 (71)	12 (21)	5 (9)
Helpful topics covered in nutrition session	56	37 (66)	13 (23)	6 (11)
Ability to continue with lifestyle changes now	59	49 (83)	4 (7)	6 (10)
Supportive dietitian	55	31 (56)	17 (31)	7 (13)
Supportive exercise trainers	60	58 (97)	0	2 (3)
Interesting study overall	60	54 (90)	3 (5)	3 (5)
Recommend program	60	58 (97)	1 (2)	1 (2)

($p = .106$), although the latter mean change exceeded the MCID. Health-related quality of life significantly increased between end of treatment and end of study ($p < .001$). At 1-year follow-up, HRQoL was not different from end of study ($p = .113$), but was significantly higher than baseline ($p < .001$; Table 3).

Implementation

The average exercise adherence across participants was 60% ± 26%, 52% ± 33%, and 50% ± 38% for the treatment, post-treatment, and maintenance phases, respectively. Eighty-four percent (57 of 68) of participants attended the group healthy eating session.

The estimated cost of the NExT program for the first year and for subsequent years is $44,821 and $41,766 USD (Table 4). The estimated average cost per participant starting the program is $1,273, and per exercise session delivered is $22 USD. Participant satisfaction outcomes were available for 87% of participants (Table 5). The majority felt it was easy to attend sessions, thought the study was interesting and the program expectations were clear, and felt supported. Most of the respondents felt that they could continue with their lifestyle changes and would recommend the program to a friend.

Regarding safety, no major adverse events occurred. In the 12 months prior to baseline, injuries preventing the completion of normal daily activities were reported by 32% of participants, and this prevalence was not different during the program (40%, $p = .310$). Regarding injuries potentially related to the exercise program, new repetitive strain injury of the foot/leg attributed to walking/running or resistance training were reported by 5% during the treatment phase, and 16% during the post-treatment or maintenance phases. Reported causes for other new injuries occurring during the program included home-based physical activities ($n = 7$), falls during daily activities ($n = 3$), late chemotherapy side effects ($n = 2$), and other causes ($n = 3$). There were no diagnosed cases of lymphedema during the program.

Discussion

Clinical experience suggests a high demand and interest among breast cancer survivors for lifestyle-based programs, and this population consistently reports health goals related to increasing physical activity, eating a healthier diet, and managing body weight [29]. Furthermore, there are calls to action from health care professionals for institutions, policy makers, and other leaders to include exercise and healthy eating in the supportive care services provided for cancer survivors [9, 13, 30]. The NExT study was designed to translate efficacy trials into a clinical care setting and address the reported barriers to delivery of this programming as supportive care for cancer survivors [13].

The NExT program was successful in receiving referrals from a dedicated team of medical oncologists and enrolling patients undergoing adjuvant chemotherapy, and met the benchmarks chosen a priori for program reach. Participants referred to the program were on average younger than those who were not referred. This may suggest a bias of the referring oncologists, and a future opportunity to increase reach by addressing potential barriers to the referral of older age groups. Regardless, program uptake was high, and retention rate exceeded those reported by other community-based cancer rehabilitation programs [31–33], suggesting a large demand for programming when available. This is particularly noteworthy considering that the NExT program was substantially longer than previous community programs and randomized trials (45 vs. 12–24 weeks). Opportunities for continued access to dedicated exercise facilities and professionals may be an important consideration following completion of cancer treatment. By design, the study targeted women receiving adjuvant treatment, for whom need for supervised programming may be greatest. However, two-thirds of patients who had a breast medical oncology consultation during the 15 months of study recruitment did not receive adjuvant chemotherapy, which suggests the need to consider expanding programming eligibility to increase the availability of services for the majority of breast cancer survivors seen by medical oncologists.

The NExT exercise program was effective in increasing MVPA and resistance training levels, and maintaining MVPA but not resistance training levels above baseline for an additional year without study contact. In total, the 1-year follow-up time point was approximately 2 years after diagnosis. Physical inactivity is a modifiable risk factor for a number of chronic diseases (e.g., cardiovascular disease, diabetes mellitus, obesity, hypertension, arthritis, depression) and all-cause mortality [34]. Among breast cancer survivors, a reduction in physical activity levels following diagnosis and treatment is common [35, 36]. Importantly, physical activity following a cancer diagnosis is associated with a 38% reduction in breast cancer-specific mortality [37] and an incremental reduction of cardiovascular events in breast cancer survivors [38]. Therefore, the success of NExT in increasing physical activity levels and maintaining this increase for a period of 2 years after initiating adjuvant treatment has the potential to influence important clinical outcomes. The number of perceived barriers to exercise were reduced from baseline to end of treatment, and were maintained at end of program. Some of the barriers assessed in the questionnaire included access to knowledgeable exercise staff, experience of fatigue, nausea, or pain, costs related to engaging in exercise, and fear of injury [23]. Although neither exercise self-efficacy nor enjoyment changed at any point, 83% of participants indicated that they were confident in their ability to continue with lifestyle changes on their own at program completion, suggesting that NExT did enhance skills relevant to lifestyle management. However, this could be partially attributed to a relatively high level of exercise self-efficacy and enjoyment at baseline.

The NExT program was also successful in mitigating the reduction in the physical component of HRQoL that is commonly observed to occur with adjuvant treatment, which is consistent with the effect of exercise during treatment established by randomized controlled trials (RCTs) [39]. At end of program, HRQoL was significantly increased relative to end of treatment, and although not statistically significant relative to baseline, there was a clinically meaningful change. It should be noted that our outcome assessment rates at 1-year follow-up for participants who did not withdraw were 73%–83%. It is likely that those who were less healthy and active at follow-up were less inclined to return, which would positively bias our results.

A key element of effectiveness is intervention adherence in a real-world setting. Previous efficacy studies utilizing a similar supervised exercise prescription (2–3 moderate-intensity weekly sessions) in similar populations have reported higher exercise adherence rates (70%–72% during chemotherapy only [15–17]) relative to NExT (60% throughout chemotherapy and radiation). Because there were less-stringent enrollment criteria with regard to expectations around adherence [18] and a longer duration relative to previous efficacy trials (i.e., 16–24 weeks), lower adherence was not unexpected for NExT, and provides insight into the adherence pattern that is more reflective of what can be expected in a supportive care program.

Overall, the majority of participants were satisfied with the program. The exercise component included multiple sessions per week, as opposed to the singular nutrition session. This was an improvement upon past trials with no nutrition component, but the addition of more nutrition sessions to support continued healthy eating habits during treatment as well as weight-reduction strategies following completion of treatment may be warranted.

An important finding regarding safety was the lack of adverse events. A key element of recruitment when assessing effectiveness was expanding eligibility beyond the stringent eligibility criteria that are typically used in efficacy trials. The intention was to offer the program to all newly diagnosed women receiving adjuvant chemotherapy, including those with stable comorbid conditions. The rate of injuries from any cause also did not increase during adjuvant treatment concurrent with the exercise program relative to the year prior to adjuvant treatment. Of note, there were 10 injuries to the lower extremity of a nonacute origin (i.e., repetitive strain) reported by participants that could be attributed to the exercise training performed in the program. This is consistent with injury types and rates commonly observed with initiation of aerobic exercise in a previously sedentary population [28]. Additional strategies for injury prevention, monitoring, and referral for treatment, including for potential cases of lymphedema, are important to consider for future exercise programming for women with breast cancer.

Although comprehensive cost-effectiveness analyses were not part of the primary trial, the cost for running the NExT program is reported to provide some insights for future program development. The main annual cost is for personnel ($40,906). Personnel are the most critical component of a successful program because they are the primary conduits for delivering a safe, effective, enjoyable, and engaging program. Oncology-specific training programs or certifications have significantly increased capacity for exercise and nutrition professionals to support the implementation of lifestyle programming for cancer survivors [40–42]. A smaller but important cost to consider is cleaning supplies, because a strict cleaning protocol is required for individuals with compromised immune systems.

Strengths and Limitations

The NExT study has a number of strengths. The program addressed key knowledge translation gaps identified for including exercise and healthy eating programming as part of supportive care: namely, engagement of the medical oncologist to prescribe the program, and utilization of professionally educated staff for the exercise (bachelor's/master's degree in kinesiology) and healthy eating (registered dietitian) components. Furthermore, NExT took place in a dedicated facility near the cancer treatment center, and utilized exercise and healthy eating content that is evidence-based and specific to breast cancer. The programming was also delivered to a wider range of women with breast cancer (e.g., one-third nonwhite ethnicity, wide range of comorbid conditions and age) than is typical in many trials, in a format resembling how a clinical program might operate, thereby producing generalizable results. Another strength was the examination of eligibility of all new patients during study recruitment, which provided helpful information for planning clinical programs and identified reasons for noneligibility that may be able to be addressed in future programs to increase reach.

A limitation of the program was that exercise programming was only offered on three mornings/afternoons, with no opportunities to make up for missed sessions. Although this was

purposeful to mirror the format of a potential clinical program offered in an institutional/clinical setting, a balance between personnel costs and allowing more flexible access to improve adherence should be considered. Further, the NExT gym location in a metropolitan center with a large clinical catchment area could have impacted referral rate and uptake. The extra travel required to engage in supervised exercise training on top of medical visits may be difficult for some patients due to time, transportation, and financial constraints. As a lifestyle intervention, there was an imbalance between the amount of time allocated to exercise programming relative to the healthy eating component. In future trials, increased opportunities to meet with dietitians and receive individualized support should be considered, especially if weight management is a key outcome.

Conclusion

The NExT study assessed effectiveness of an exercise and healthy eating program prescribed as a part of supportive care for early breast cancer patients receiving adjuvant chemotherapy. The NExT program reached a broader population of women on chemotherapy than typical efficacy trials and resulted in increased self-reported physical activity levels and a maintenance of HRQoL during and following adjuvant chemotherapy. Given the significance of physical activity levels for prevention of comorbid conditions and mortality, the maintenance of MVPA levels above baseline 1 year after NExT program completion represents an important outcome for women receiving adjuvant chemotherapy for early breast cancer. The NExT program is a model of an effective, safe, and low-cost approach that provides a strong rationale for the provision of funded lifestyle programming as a standard part of supportive care within a clinical oncology setting.

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Disclosures

The authors indicated no financial relationships.

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For Further Reading:

Jessica M. Scott, Susan Lakoski, John R. Mackey et al. The Potential Role of Aerobic Exercise to Modulate Cardiotoxicity of Molecularly Targeted Cancer Therapeutics. ***The Oncologist*** 2013;18:221–231.

Implications for Practice:

Cardiotoxicity, a frequent and devastating adverse complication of some molecularly targeted therapies (MTTs), can lead to potentially life-threatening cardiovascular complications, therapy discontinuation, and poor quality of life. In non-cancer patients with left ventricular dysfunction and heart failure, aerobic exercise is one of the mainstay clinical interventions for the prevention and treatment of cardiovascular disease. However, few studies have investigated the efficacy of aerobic exercise in the prevention and/or treatment of MTT-induced cardiac injury. This topic is of particular importance because cardiac function is a strong predictor of cardiovascular and all-cause mortality, quality of life, and fatigue, and maybe even cancer-specific mortality. Here, we provide a comprehensive overview of cardiac molecular and cell-signaling pathways specific to MTT-induced cardiac toxicity. This review also outlines many pertinent aerobic exercise-induced molecular signaling pathways that may uniquely prevent and/or treat MTT cardiac injury. Overall, information presented in this review provides critical information for basic scientists, clinicians, and exercise oncology researchers who are investigating the application of exercise in cancer control.