O impacto de dois diferentes programas de exercício físico na performance física e na fadiga relacionada ao câncer

Impact of two different exercise programs on persistent cancer-related fatigue and physical fitness

Fabiana Reis[1], Rebeca Boltes Cecatto[2], Christina May Moran de Brito[3], Paulo Marcelo Gehm Hoff[4], Linamara Rizzo Battistella[5]

RESUMO

A fadiga relacionada ao câncer é um dos sintomas mais comuns entre pacientes com câncer, relatada em 70% a 100% desses pacientes resultando em uma redução significativa da qualidade de vida, funcionalidade e independência. O exercício físico tem sido identificado como um elemento central de reabilitação de muitas doenças crônicas como câncer, e cada vez mais evidências apoiam a tese de que a atividade física é uma intervenção útil, que pode ser utilizada em conjunto com terapias convencionais durante o tratamento da fadiga relacionada ao câncer. **Objetivo:** O objetivo deste estudo é avaliar o impacto de dois programas de exercício físico sobre os níveis de fadiga e desempenho físico de pacientes com câncer. **Método:** Relato de uma série consecutiva de 44 doentes adultos com doença neoplásica (sólido ou hematológicas), e diagnóstico médico de fadiga, submetidos a dois diferentes programas de exercício físico. Todos os doentes foram avaliados quanto a desempenho físico com o uso do teste de caminhada de 6 minutos e avaliados quanto aos níveis de fadiga com o teste de Piper, antes e depois de 4 meses de atividade física supervisionada (exercícios aeróbicos isolados e treino de resistência combinado ao exercícios aeróbicos). **Resultados:** Após 16 semanas, os doentes que participaram do programa de exercícios aeróbicos ou que participaram do protocolo de exercício aeróbico combinado com anaeróbio, relataram níveis significativamente mais elevados do desempenho físico (6 minutos teste de caminhada, p = 0,0009 e p = 0,001, respectivamente) e níveis de fadiga significativamente menor (PFS- R, p = 0,003 e p = 0,002, respectivamente) do que no início do programa de exercícios. **Conclusão:** Estes resultados demonstram que tanto um protocolo de exercício aeróbico quanto de exercício aeróbico combinado com exercício anaeróbio apresentam melhora significativa do desempenho físico e dos níveis de fadiga de doentes oncológicos. Os dados deste estudo corroboram a literatura mostrando que a atividade física é uma estratégia eficaz para o tratamento da fadiga. Os resultados deste estudo confirmam que o exercício físico pode ser útil na reabilitação de sobreviventes de câncer, especialmente para pacientes com fadiga oncológica.

Palavras-chave: aptidão física, exercício, fadiga, neoplasias, reabilitação

ABSTRACT

Cancer-related fatigue is a common symptom in patients with cancer, which is experienced by 70% to 100% of these patients and brings some impairment of physical and mental performance, hinders their working or carrying out regular daily activities, and hence results in a substantial reduction of the quality of life. Physical exercise has consistently been identified as a central element of rehabilitation for many chronic diseases like cancer, and increasing evidence supports the contention that physical activity is a valuable intervention that can be utilized in conjunction with conventional therapies during CRF treatment. **Objective:** The aim of this study was to assess the impact of a program of physical exercise on fatigue levels and physical performance of cancer patients. **Method:** A consecutive series of 44 adult patients with neoplastic disease (solid or hematological), with a medical diagnosis of fatigue, who were enrolled in an oncological treatment, with the ability to walk and willing to enter a rehabilitation program of exercise for at least 4 consecutive months. The exercise program was performed two times per week, each session lasting one hour and consisting of aerobic, resistance, and flexibility exercises. The protocol was divided into aerobic exercise and resistance training combined with aerobic exercise. The patients were evaluated with two assessments: one prior to their beginning the exercise program and other at the end of the four-month program. In both assessments the patients completed the Revised Piper Fatigue Scale and the six-minute walk test. The primary outcome of change over baseline and after 16 weeks in PFS-R score and six-minute walk test were compared using a two sample two-sided t-test for both groups. Alpha level was set at $p < 0.05$. **Results:** After 16 weeks, the patients who participated in the aerobic or the combined exercise program reported significantly higher levels of physical functioning (6-minute walking test, p = 0.0009 and p = 0.001, respectively) and significantly lower fatigue (PFS-R, p = 0.003 and p = 0.002, respectively) than at the beginning the exercise program. **Conclusion:** The results of patients who underwent aerobic or aerobic + anaerobic exercise showed statistically significant improvement of physical performance and of fatigue. Data from this study corroborates with the literature showing that exercise programs with aerobic or resistance exercises are an effective strategy for the treatment of fatigue. The results of this study confirm that physical exercise could be useful in rehabilitation of cancer survivors, especially for fatigued patients.

Keywords: exercise, fatigue, neoplasms, physical fitness, rehabilitation

1 Fitness Trainer of the *Instituto do Câncer do Estado de São Paulo* - ICESP (Rehabilitation Center of the São Paulo State Cancer Institute).
2 Physiatrist, Rehabilitation Service of the São Paulo State Cancer Institute.
3 Physiatrist, Medical Coordinator of the Rehabilitation Service of the São Paulo State Cancer Institute and of the *Hospital Sírio Libanês* (Syrian-Lebanese Hospital).
4 Lecturer, Full Professor at the University of São Paulo School of Medicine, Director of the Oncology Clinic at the University Hospital of the University of São Paulo School of Medicine, and Director General of the São Paulo State Cancer Institute.
5 Lecturer, Associate Professor at the University of São Paulo School of Medicine, President of the Board of Directors of the Institute of Physical Medicine and Rehabilitation at the São Paulo University Hospital (FMUSP).

Mailing Address:
Physical Fitness sector of the Rehabilitation Service
São Paulo State Cancer Institute - ICESP
Fabiana Reis
Av. Doutor Arnaldo, 251
CEP 01246-000
São Paulo - SP
E-mail: fbr.reis@ig.com.br

Submitted on January 6, 2013.
Accepted on January 10, 2013.

DOI: 10.5935/0104-7795.20120031

INTRODUCTION

In Brazil, the estimates for the year 2012 indicate the occurrence of approximately 518,510 new cases of cancer, including cases of non-melanoma skin cancer.[1]

Cancer treatment is associated with substantial psychosocial and physical side effects, including muscular atrophy, weight changes, fatigue, pain, depression, and an overall decrease in quality of life. Furthermore, cancer survivors are at increased risk for cancer recurrence and for additional side effects, such as cardiovascular toxicity, bone loss, and a decline in function and participation.[2,3]

Cancer-related fatigue (CRF) is a very common symptom in patients with cancer and is nearly universal in those undergoing cytotoxic chemotherapy, radiation therapy, bone marrow transplantation, or treatment with biological response. The symptom is experienced by upwards of 70% of those patients with cancer[4] who undergo multi-modal treatments and dose-dense, dose-intense protocols. It is a distressingly persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with normal functioning.[4]

Although the reported prevalence of CRF varies between studies, the consensus is that it is high both during and after cancer treatment. In addition, numerous studies have suggested that increased levels of fatigue are positively associated with sleep disturbance, depression, and pain, and that these symptoms have a negative impact on functional status and quality of life.[3]

The pathogenesis of CRF has not been thoroughly described and several mechanisms can contribute to its development. Among the described mechanisms are the effects of cancer and its treatment on the central nervous system, muscle energy metabolism, sleep, circadian rhythm, inflammation and stress mediators, immune system activation, hormonal alterations related to the effects on hypothalamus-pituitary axis, early menopause, or androgen deprivation in men.[5]

The impairment of physical and mental performance impedes working or carrying out regular daily activities and thereby results in a substantial reduction of the quality of life. In response to fatigue, patients are usually advised to rest and down-regulate their level of daily activities. But since inactivity induces muscular catabolism, extended rest can actually help to perpetuate fatigue.[6] On the other hand, exercise has consistently been identified as a central element of rehabilitation for many chronic diseases like cancer, and increasing evidence supports the contention that physical activity is a valuable intervention that can be utilized in conjunction with conventional therapies for CRF treatment.[7]

The evidence suggests that physical activity enhancement, and specifically exercise helps manage CRF, both during and after cancer treatment. Current evidence does not clarify which elements of exercise are most effective, including type (aerobic and/or resistance), mode, and dose, (frequency, intensity, length of sessions).[8]

OBJECTIVE

On the basis of these considerations, the purpose of this case series was to examine the impact of an exercise program on persistent CRF and physical fitness.

METHOD

A consecutive series of 44 patients with CRF were enrolled in an Exercise Program at the Rehabilitation Center of the Instituto do Cancer da Faculdade de Medicina da Universidade de São Paulo (Cancer Institute of the School of Medicine of the University of São Paulo), between December 2009 and December 2011.

Inclusion criteria

Inclusion criteria were that they be adult cancer patients with neoplastic disease (solid or hematological), with a medical diagnosis of CRF, were enrolled in oncological treatment, and had the ability to walk and the willingness to participate in a rehabilitation program with exercises for at least four consecutive months.

Exclusion criteria

Exclusion criteria were a hemoglobin concentration < 8 g/dl, a platelet count < 50/nl, a terminal disease, a chronic infection, the presence of neutropenia, hyponatremia, hypernatremia, or hypercalcemia, chronic diseases which could be exacerbated or complicated by exercise (i.e. coronary artery disease, chronic cardiac disease, chronic obstructive pulmonary disease, diabetes mellitus), acute thromboembolic disorders, or skeletal metastases resulting in bone instability. In addition to this, we avoided or discontinued physical training if the subject showed:

- Resting diastolic blood pressure > 100 mmHg or resting systolic blood pressure > 180 mmHg;
- Diastolic pressure that rose > 20 mmHg above resting value;
- Heart rate to increase with increasing exertion;
- Signs of poor perfusion (light-headedness, confusion, pallor, cyanosis, or cold and clammy skin);
- Angina or angina-like symptoms;
- Body temperature > 38°C;
- Ongoing bleeding, fresh petechiae, or new bruises.

Exercise program

The exercise program was performed two times per week, lasted one hour per session, and consisted of aerobic, resistance, and flexibility exercises. The aerobic exercises were performed on a treadmill, stationary bike, and/or step machine. Resistance exercises included exercises for major muscle groups (chest, back, arm, and leg), which varied according to the patient's limitations and condition, consisting of a maximum of five muscle groups per session, using weights, dumbbells, and pulleys. The flexibility exercises were performed at the end of each session and each position was maintained for 30 seconds and repeated three times.

The patients were included in one of the two exercise programs

- Aerobic exercise: Patients began with 15 to 20 minutes of aerobic activity, which ramped up to 40 minutes per session, performed on two different aerobic machines per session, not exceeding 70% of maximum heart rate established by age and/or a rating of around 7 on the Borg Scale of Perceived Exertion. At the end of the session, the patient performed stretching exercises for major muscle groups.

- Resistance training combined with aerobic exercise (mixed exercise): the patient underwent 10-15 minutes of aerobic exercise, proceeded to the series of resistance exercises, doing first 2 sets of 8 to 12 repetitions, progressing to 3 sets of 8 to 12 repetitions for each exercise, and then rested for 1 minute between series. The exercises were increased according to the ability of the individual patient, who was monitored for possible signs and symptoms of exercise intolerance. At the end of the session the patient performed stretching exercises for the major muscle groups.

During all exercises, the patients were monitored for heart rate, blood pressure, scale of perceived exertion (Borg), and oxygen saturation.

Assessment

The patients participated in two assessments: one prior to beginning the exercise program and the other at the end of the four-month program. In both assessments the patients completed the Revised Piper Fatigue Scale (PFS-R). The PFS-R has 22 items, each rated on a 0 to 10 numeric rating scale. The PFS-R has four subscales that assess four dimensions of fatigue: sensory, affective, cognitive-emotional, and behavioral-intensity. The PFS-R total score and its subscale scores range from 0 to 10. It was originally developed to measure fatigue in persons with cancer and has excellent reliability and estimative validity. Fatigue scores are categorized by mild (1-3), moderate (4-6), and severe (7-10).[9]

The six-minute walk test was also performed. It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. The self-paced six-minute walk test assesses the submaximal level of functional capacity. Is a simple tool for the evaluation of functional exercise capacity, which reflects the capacity of the individual to perform activities of daily living.[10,11]

Statistical analysis

Descriptive statistics were calculated for the total study sample and subgroups. Data were analyzed using SPSS for Windows (Version 9). Baseline subject characteristics in the two exercise groups were compared using independent *t* - tests for continuous variables. The primary outcome of change over baseline and after 16 weeks in PFS-R score and six-minute walk test were compared using a two-sample two-tailed *t* - test on both groups. Alpha level was set at $p < 0.05$.

RESULTS

The average age of the participants was 53 years, 88.6% of participants were women. There were 11 different types of cancers, breast cancer were 66% and 9% of melanoma cases. Only 5 patients were receiving chemotherapy and 3 patients had received pharmacological measures to control their fatigue at the time of the exercise program.

At baseline, there were no statistically significant differences between the aerobic exercise and the mix group regarding the PFS-R. The average baseline level of the PFS-R was 5.38 in the aerobic exercise group and 5.78 in the mix group ($p = 0.56$). But, there were differences between the baseline average of six-minute walk test (428.62 in the aerobic exercise group and 356 in the mix group with $p = 0.01$). The sample's demographic characteristics are listed in Table 1.

The fatigue ratings and the six-walk minute test values are listed in Table 2.

Figures 1 and 2 show the differences in the measurements pre and post-intervention between the aerobic exercise group and the mix exercise group. After 16 weeks, the patients who participated in the aerobic or mix exercise program reported significantly higher levels of physical functioning (6-minute walking test, $p = 0{,}0009$ and $p = 0{,}001$, respectively) and significantly lower fatigue (PFS-R, $p = 0{,}003$ and $p = 0{,}002$, respectively) than at the beginning the exercise program.

DISCUSSION

This study evaluated the impact of two different exercise programs on persistent CRF and physical fitness of cancer patients and showed a statistically significant benefit in patients undergoing either the aerobic or aerobic + anaerobic exercise protocol.

Over the last 10 years, oncological rehabilitation programs have been developed with the aim of improving quality of life of cancer survivors who continue to experience physical and emotional problems. The effectiveness of such oncological rehabilitation programs has been reported on and seems to vary depending on the content of the program and the target outcome measurement.[12] The literature suggests that although there are specific risks that need to be considered in patients with cancer, there seems to be consistent evidence that exercise is safe during and after cancer treatment.[13]

Improvements induced by exercise training can be expected concerning aerobic fitness, muscular strength, and quality of life in cancer survivors. Physical activity has positive effects on physiology, body composition, physical functions, psychological outcomes, and quality of life in patients after treatment for breast cancer. When patients with cancer other than breast cancer were also included, physical activity was associated with the reduction of body mass index and body weight, an increase of peak oxygen consumption and peak power output, and an improvement in quality of life.[14]

In this study, the results of patients who underwent aerobic or aerobic + anaerobic exercise showed a statistically-significant improvement in physical performance and fatigue. In both training programs the average time to perform the exercises was approximately 40 minutes, the aerobic exercise program generally used the entire 40 minutes, but the time of exercise program of resistance training combined with aerobic was divided into 20 minutes for resistance training and 20 minutes for aerobic exercise training.

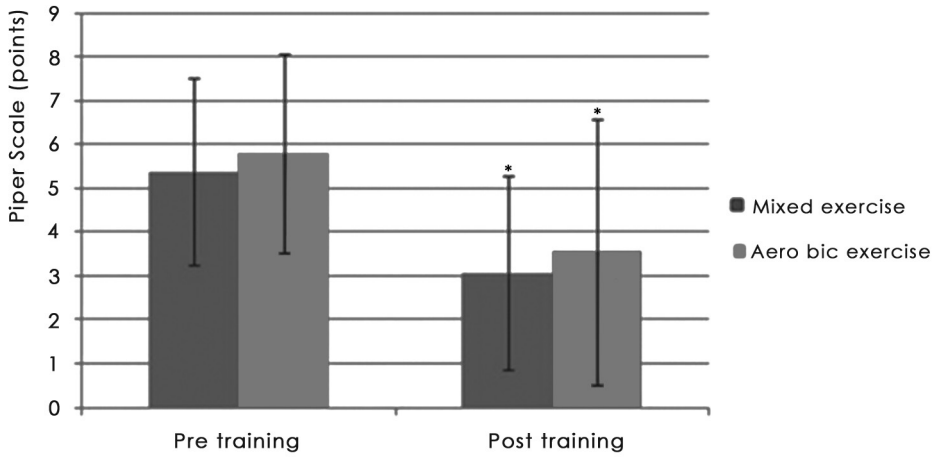
But the literature still reports divergent findings,[8] and the evidence for the efficacy of resistance training is only beginning to emerge, either in the resistance exercise alone or in combination with aerobic exercise.

Table 1. Medical and demographical data

Patients	N = 103
Mean age (years)	53
Gender	
Male	5
Female	39
Diagnosis	
Breast	29
Melanoma	4
Other tumors	11
At chemotherapy	5

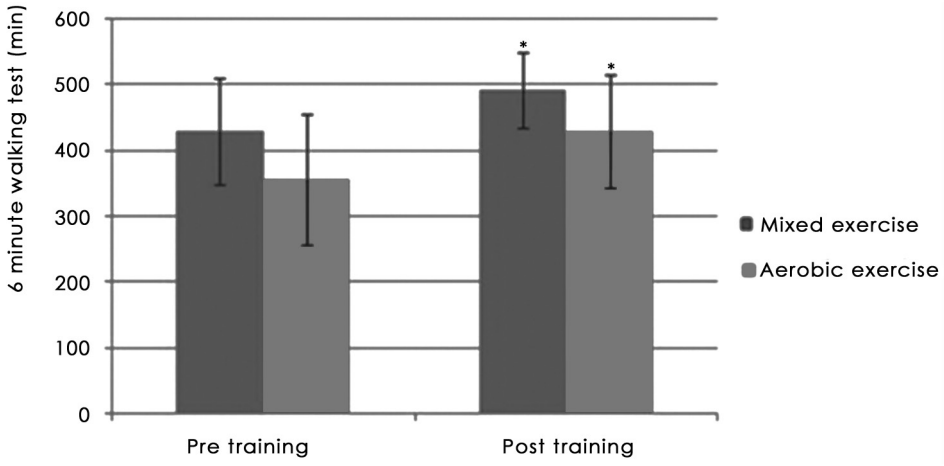
Table 2. Ratings and the six-walk minute test values

	Mixed Exercise			Aerobic Exercise		
	Pre	Post	*p*	Pre	Post *p*	*p*
Piper Scale (mean ± SD)	5,38 ± 2,12	3,06 ± 2,21	0,0002	5,7 ± 2,27	3,5 ± 3,03	0,003
6 MWT (mean ± SD)	428,62 ± 80,5	491,77 ± 57,72	0,001	356,00 ± 99,18	429,05 ± 86,51	0,0008



** p < 0.05 between pre and post training*

Figure 1. Piper scale evaluation



** p < 0.05 between pre and post training*

Figure 2. Six minute walking test (6MWT) evaluation

On the other hand, a round table organized by the American College of Sports and Medicine, came to the consensus that both aerobic and resistance exercise should be prescribed for cancer patients.[13] There is increasing evidence that a program of aerobic and resistance exercise can improve physical performance and reduce levels of fatigue in cancer patients after treatment.[6,15]

Exercise is a promising and effective therapeutic approach to persistent CRF. However, it does not affect all components of the fatigue syndrome, which are the cause of substantial impairment in cancer patients. Moreover, the role of attention, motivation, and social interaction in connection with the positive effects of exercise on CRF needs to be further evaluated.[6]

Data from this study concurs with the literature,[16] showing that exercise programs, with aerobic and resistance exercises, are an effective strategy for the treatment of CRF, and will improve physical performance during and following cancer treatment.[17]

CONCLUSION

In conclusion, four months of a supervised program of aerobic exercise and/or resistance training leads to a substantial improvement of physical performance and reduced levels of fatigue in cancer patients.

The results of this study confirm that the physical exercise could be useful in the rehabilitation of cancer survivors, especially for fatigued patients. This study suggests that exercise is a promising and effective therapeutic approach to persistent CRF, with improvements in physical performance and contributions to the quality of life of cancer patients.

REFERENCES

1. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2012: incidência de câncer no Brasil. Rio de Janeiro: INCA; 2011.
2. De Backer IC, Vreugdenhil G, Nijziel MR, Kester AD, van Breda E, Schep G. Long-term follow-up after cancer rehabilitation using high-intensity resistance training: persistent improvement of physical performance and quality of life. Br J Cancer. 2008;99(1):30-6. http://dx.doi.org/10.1038/sj.bjc.6604433
3. Dodd MJ, Cho MH, Miaskowski C, Painter PL, Paul SM, Cooper BA, et al. A randomized controlled trial of home-based exercise for cancer-related fatigue in women during and after chemotherapy with or without radiation therapy. Cancer Nurs. 2010;33(4):245-57. http://dx.doi.org/10.1097/NCC.0b013e3181ddc58c
4. Berger AM, Abernethy AP, Atkinson A, Barsevick AM, Breitbart WS, Cella D, et al. Cancer-related fatigue. J Natl Compr Canc Netw. 2010;8(8):904-31.
5. Campos MP, Hassan BJ, Riechelmann R, Del Giglio A. Cancer-related fatigue: a review. Rev Assoc Med Bras. 2011;57(2):211-9. http://dx.doi.org/10.1590/S0104-42302011000200021
6. Dimeo F, Schwartz S, Wesel N, Voigt A, Thiel E. Effects of an endurance and resistance exercise program on persistent cancer-related fatigue after treatment. Ann Oncol. 2008;19(8):1495-9. http://dx.doi.org/10.1093/annonc/mdn06
7. Noble M, Russell C, Kraemer L, Sharratt M. UW WELL-FIT: the impact of supervised exercise programs on physical capacity and quality of life in individuals receiving treatment for cancer. Support Care Cancer. 2012;20(4):865-73. http://dx.doi.org/10.1007/s00520-011-1175-z
8. Berger AM, Gerber LH, Mayer DK. Cancer-related fatigue: implications for breast cancer survivors. Cancer. 2012;118(8 Suppl):2261-9. http://dx.doi.org/10.1002/cncr.27475
9. Mota DD, Pimenta CA, Piper BF. Fatigue in Brazilian cancer patients, caregivers, and nursing students: a psychometric validation study of the Piper Fatigue Scale-Revised. Support Care Cancer. 2009;17(6):645-52. http://dx.doi.org/10.1007/s00520-008-0518-x
10. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. Am J Respir Crit Care Med. 2002;166(1):111-7. http://dx.doi.org/10.1164/ajrccm.166.1.at1102
11. Iwama AM, Andrade GN, Shima P, Tanni SE, Godoy I, Dourado VZ. The six-minute walk test and body weight-walk distance product in healthy Brazilian subjects. Braz J Med Biol Res. 2009;42(11):1080-5. http://dx.doi.org/10.1590/S0100-879X2009005000032
12. Van Weert E, May AM, Korstjens I, Post WJ, van der Schans CP, van den Borne B, et al. Cancer-related fatigue and rehabilitation: a randomized controlled multicenter trial comparing physical training combined with cognitive-behavioral therapy with physical training only and with no intervention. Phys Ther. 2010;90(10):1413-25. http://dx.doi.org/10.2522/ptj.20090212

13. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvão DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42(7):1409-26. http://dx.doi.org/10.1249/MSS.0b013e3181e0c112
14. Fong DY, Ho JW, Hui BP, Lee AM, Macfarlane DJ, Leung SS, et al. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. BMJ. 2012;344:e70. http://dx.doi.org/10.1136/bmj.e70
15. Mutrie N, Campbell AM, Whyte F, McConnachie A, Emslie C, Lee L, et al. Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial. BMJ. 2007;334(7592):517. http://dx.doi.org/10.1136/bmj.39094.648553.AE
16. Mock V, Frangakis C, Davidson NE, Ropka ME, Pickett M, Poniatowski B, et al. Exercise manages fatigue during breast cancer treatment: a randomized controlled trial. Psychooncology. 2005;14(6):464-77. http://dx.doi.org/10.1002/pon.863
17. Harris SR, Schmitz KH, Campbell KL, McNeely ML. Clinical practice guidelines for breast cancer rehabilitation: syntheses of guideline recommendations and qualitative appraisals. Cancer. 2012;118(8 Suppl):2312-24. http://dx.doi.org/10.1002/cncr.27461