The Egyptian Journal of Hospital Medicine (July 2024) Vol. 96, Page 3346-3351

The Effect of Cardiac Rehabilitation on Quality of Life and 6-Minute Walk Test in Breast Cancer Patients During Ongoing Anthracycline Based Therapy

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ABSTRACT

Background: Breast cancer (BC) accounts for 38.8% of all cancers in Egyptian women, making it the most frequent cancer in this community. BC mortality is thought to be around 11%, and it is the second cause of cancer-related death after liver cancer. Chemotherapy for BC sometimes exacerbates symptoms of depression and exhaustion. Many women have a large reduction in physical activity following a BC diagnosis, and this reduction persists even after treatment is finished. Putting in place a customized cardiac rehabilitation program might be a useful tactic to stop the reduction in physical activity and enhance the quality of life (QOL) for individuals with BC. There is a lack of information on the early use of combined cardiac rehabilitation while receiving anthracycline treatment.

Objective: To investigate the effect of tailored combined cardiac rehabilitation program on QOL and 6-minute walk test in BC patients after starting anthracyclines.

Patients and Methods: Sixty BC patients scheduled for anthracyclines cycles were divided into two groups; Study group (n=30) participated in combined home based and hospital based cardiac rehabilitation and Control group (n=30) received the usual cancer care. Functional capacity was assessed after study period by 6-Minute Walk Test (6-MWT). All patients were personally interviewed for assessment of QOL after study period using (FACT-B) questionnaire.

Results: The Study group showed significant increase in 6-minute walk distance (p=0.037), percentage of expected of 6-MWT (p=0.01), and QOL score (p=0.005). Among the Study group, there was significant increase in METS (p<0.001), ET (p<0.001), maximal HR (p<0.001), HRR (p<0.001) along with significant decrease in basal HR (p<0.001).

Conclusion: The implementation of a cardiac rehabilitation program during anthracycline treatment can enhance functional ability and QOL in BC patients.

Keywords: Anthracyclines, Breast cancer, Cardiotoxicity, Cardio-oncology, FACT-B, 6-MWT.

INTRODUCTION

BC is the most common cancer in the world to be diagnosed and the primary cause of cancer-related deaths in women. BC accounts for 38.8% of all malignancies in Egyptian women, making it the most frequent cancer in this group [(1,2)]. BC is the second cause of cancer-related death after liver cancer, with an estimated 11% mortality rate. Chemotherapy for BC frequently causes worsening symptoms of sadness and tiredness, which have a detrimental impact on QOL and frequently last long beyond the course of treatment [(3)].

After receiving a diagnosis of BC, many women have a considerable reduction in physical activity, which persists even after therapy is finished [(4)]. When exposed to different chemotherapeutic regimens, cardiorespiratory fitness (CRF) decreases and may not increase again after treatment ends [(5)].

The cornerstone of modern cardiac rehabilitation (CR) is exercise training, which has been shown to improve CRF and lower cardiovascular morbidity and related symptoms in people with pre-existing cardiovascular disease (CVD). A rising corpus of research, however less well established, assesses the impact of organized exercise treatment on cardiovascular outcomes in cancer patients [(6)].

The prognosis may suffer if anthracyclines are not used because of worries about cardiac adverse effects, as they have a high effectiveness in treating solid tumors [(7)]. However, anthracyclines have the potential to harm the heart irreversibly, which would negatively impact prognosis [(8)].

Assessing cardiovascular reserve capacity by incremental exercise tolerance testing, which measures CRF, offers a comprehensive and reliable evaluation. It has been shown that in women undergoing chemotherapy with adjuvant therapy, CRF can decrease by 5% to 20%. This fall continues for years after treatment is stopped. Therefore, intervention techniques that have the potential to both avoid myocardial harm associated with cancer therapy and to reduce damage across the circulatory system may be of great therapeutic significance. In women in the general population, both intentional physical activity, or exercise, and general physical activity are very significant independent predictors of cardiovascular events, CVD, and all-cause mortality. Life expectancy increases by three years as a result of this risk decrease [(9)].

Objective: We investigated the effect of an early tailored combined cardiac rehabilitation program on QOL (using FACT-B questionnaire) and 6-MWT in BC patients scheduled for treatment with anthracyclines.

PATIENTS AND METHODS

This was a 2-arm parallel prospective, randomized, controlled study conducted at Ain Shams University

Received: 22/04/2024
Accepted: 20/06/2024

Hospitals over a period of 6 months on breast cancer patients scheduled for anthracyclines containing regimes.

Inclusion criteria:

(1) Anthracycline therapy at large dosages (such as; doxorubicin ≥250 mg/m^2, epirubicin ≥600 mg/m^2).

(2) Therapy with reduced dosage of anthracycline alone in addition to having at least two risk factors (dyslipidemia, obesity, diabetes mellitus, hypertension, smoking), being older (60 years or older) at the time of cancer treatment, or having impaired heart function (myocardial infarction history, borderline or low LVEF, moderate valvular disease)**.**

Exclusion Criteria:

(1) LVEF<50%, recent acute coronary syndrome or myocardial infarction (within 1 month), recent hospitalization for decompensated heart failure.

(2) Conditions affecting the musculoskeletal system or the health prohibiting light-to-moderate aerobic activity.

(3) Reversible reasons of tiredness that go untreated including the following: Hemoglobin below 10 g/dL; thyroid dysfunction (thyroid-stimulating hormone beyond normal ranges); untreated adrenal insufficiency; chronic renal failure with creatinine clearance estimated at less than 30 mL/min; active infection or neutropenic fever; decompensated congestive heart failure; uncontrolled pulmonary disease (inhaler β-agonists prior to exercise does not prevent exercise-induced asthma; COPD with forced expiratory volume in 1 second less than 1.5 L; resting hypoxia necessitating oxygen to maintain >92%).

(4) Previous participation in a CR program.

The BC patients scheduled for anthracyclines were divided by simple computer-generated randomization into 2 groups: **Control group:** did not participate in cardiac rehabilitation program but still received the usual care. **Study group:** participated in modified cardiac rehabilitation program at Ain Shams University hospitals.

Study Tools: All patients were subjected to:

A- Before Cardiac Rehabilitation Program:

1. **Thorough history taking:** Regarding smoking status, HTN, DM, family history of ischemic heart disease, functional capability according to the NYHA categorization, other comorbidities, and medical treatment including beta blockers (BBs) or other heart rate control medications.
2. **Physical examination:** Overall health condition, BMI, WC, evidence of heart failure, cardiac and carotid murmurs, pulse, blood pressure, extremities for orthopedic pathology and the presence of arterial pulses, and neurological problems.
3. **12-lead surface electrocardiography (ECG):** Standard ECG was obtained from all patients.
4. **Echocardiography (to exclude patients with EF<50% or any valvular heart disease, which may hinder exercise):** For each patient, EF was assessed using 2D modified biplane Simpson's technique, left ventricular dimensions were determined, and segmental wall motion anomalies, diastolic function, and degree of mitral regurgitation (if present) were analyzed [(10)].

B- Cardiac Rehabilitation Protocol for Study Group:

The cardiac rehabilitation program included supervised exercise training, risk factor management, and health education. Patient received 4 cycles of chemotherapy each dose every 21 days. The program's length was 12 weeks of combined home based Tele cardiac rehabilitation in the first 10 days following the chemotherapy dose then another 10 days of hospital based cardiac rehabilitation.

First 10 days: Tele Rehabilitation (Home based CR)

Patient was followed up daily by telephone and was asked to walk for 30 minutes daily all over this period and record the diary sheet..

The 1st 10 days following chemotherapy session were associated with higher rate of side effects as fatigue, nausea and vomiting, which explains that patients were referred to Hospital based CR in the next 10 days following the dose.

Second 10 days: combined hospital based (3 sessions) and Tele CR (daily in the other days):

Study group had 3 sessions in between each cycle, so that total of 9 sessions were conducted in addition to home-based CR.

Initial treadmill exercise test was done by using Modified Bruce Protocol to determine:

a) Baseline heart rate reserve (HRR), exercise time and achieved METs.

b) Exercise intensity determined by the clinical status of the patient in order to reach 40–80% of HRR using the **Karvonen formula[(11)]:** Target training HR = ((HRmax - HRrest) x % intensity desired) + HRrest. Each treadmill exercise session lasted for 40 minutes (warm-up period 10 min, aerobic training at predetermined heart rate rang 20 min and cool-down period 10 min), for 3 times during the 10 days preceding the next chemotherapy dose .

Reassessment of HRR, exercise time and achieved METs was done after cardiac rehabilitation program to the Study Group.

Every patient in the research group received personalized consultation and education regarding the risk factors for heart disease and the effects of lifestyle changes on heart conditions. In addition to psychological counseling and information regarding the nature of heart disorders, participants got consultations regarding food and lifestyle changes, as well as advice on quitting smoking.

C – Quality of life and functional capacity assessment for both groups {Study and Control} (2 weeks after last dose of anthracyclines):

1- QOL assessment:

Via "Functional Assessment of Cancer Therapy – Breast Cancer " (FACT-B+4) questionnaire.

The BC-specific questionnaire (FACT-B+4) consists of 36 items, 27 of which pertain to general QOL and 9 to particular concerns of patients with BC (using a validated Arabic translation) [(12)].

It is broken down into six independent scales: questions GP1 through GP7 on the physical well-being scale, questions GS1 through GS7 on the social/family well-being scale, questions GE1 through GE6 on the emotional well-being scale, questions GF1 through GF7 on the functional well-being scale, questions B1 through B9 on the BC subscale, and questions B3 and B10 to B13 on the arm subscale, all of which range from 0 to 28. A Likert scale with five points is used to show the replies. The points for each question are added up to determine the score for each scale individually. When determining the final score, the values for a few questions (GP1 through GP7, GE1, GE3 to GE6, B1 through B3, B5 to B8, B10 to B13) are reversed. The mean of the completed questions was taken into account for that scale in cases where there were any unanswered questions. The ultimate total score, which ranges from 0 to 164, is calculated by adding the outcomes. The patient's QOL is greater the higher the score [(12)].

2- Functional capacity assessment: Via "6-minute walk test" (6-MWT)

As per the thorough criteria of the American Thoracic Society [(13)], the 6-MWT involves measuring the distance covered in a 30-meter straight hospital hallway over a period of 6 minutes. Prior to the test, baseline dyspnea and general exhaustion were evaluated using the Modified Borg scale, and blood pressure and pulse were taken. At the end of the test, the patient was asked to grade both again. We also calculated the percentage of the age-predicted distance for each patient compared to similar healthy adults using the following gender-specific equations created by **Enright and Sherrill [(14)].**

Men: 6-MWD = (7.57 X height) – (5.02 X age) – (1.76 X weight) – 309

Women: 6-MWD = (2.11 X height) – (2.29 X weight) – (5.78 X age) + 667

Whereas the following are expressed: age in years, weight in kg, height in cm, and 6MWD, or 6 minute walk distance, represented in meters.

Ethical approval:

This study has been approved by the Ain Shams Faculty of Medicine's Ethics Committee. Following receipt of all information, signed consent was provided by each participant. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

Software called SPSS 20.0 was used to code and input the data. Appropriate statistical analyses were applied. Frequencies and relative percentages were used to display the qualitative data. The mean ± standard deviation (SD) and range were used to express quantitative data. Two independent groups of regularly distributed variables (parametric data) were compared using the t-test. Paired T-test was used to compare pre- and after rehabilitation in the Study group. To compare qualitative variables, the X^2-test was employed. P less than 0.05 was regarded as statistically significant.

RESULTS

Sixty breast cancer patients were enrolled in this study and randomly assigned to either case group who participated in CR program or Control group who received the usual care for breast cancer. There wasn't significant difference between the two groups as regards age, medical history, BMI and Anthracycline drug used (Table 1).

Table (1): Comparison between both groups as regards age, BMI, medical history and anthracycline drug used

		Control group	Study group	Test value	P-value	Sig.
		No. = 30	No. = 30			
Age	Mean ± SD Range	44.40 ± 7.09 32 – 58	44.63 ± 6.44 31 – 57	-0.133•	0.894	NS
HTN	Negative Positive	12 (40.0%) 18 (60.0%)	14 (46.7%) 16 (53.3%)	0.271*	0.602	NS
DM	Negative Type I Type II	12 (40.0%) 4 (13.3%) 14 (46.7%)	16 (53.3%) 2 (6.7%) 12 (40.0%)	1.392*	0.499	NS
BMI	Mean ± SD Range	33.37 ± 6.97 21.64 – 49.53	32.94 ± 3.82 25.39 – 41.5	0.293•	0.771	NS
Anthracycline drug	Doxorubicin Epirubicin	14(46.7%) 16(53.3%)	19(63.3%) 11 (36.7%)	1.684•	0.194	NS

*: Chi-square test; •: Independent t-test, Sig. Significance, NS: Non-significant.

6-MWT Data

when comparing both groups, the 6 MWD and percentage of expected was significantly higher in Study group than Control group (Table 2).

Table (2): Comparison between two groups as regards 6 MWD and percentage of expected of 6-MWT

		Control group	Study group After CR.	Test value	P-value	Sig.
		No. = 30	No. = 30			
6MWD (meter)	Mean ± SD Range	334.20 ± 67.48 200 – 456	368.52 ± 56.29 250 – 480	-2.139•	0.037	S
% of expected	Mean ± SD Range	59.73 ± 8.54 40.24 – 75.22	65.30 ± 7.72 47.55 – 83.08	-2.653•	0.010	S

When comparing both groups, there was significant decrease in both Borg Dyspnea and Borg fatigue scales post 6-MWT in the Study group while there was no significant difference between them in pre 6-MWT (Table 3).

Table (3): Comparison between both groups as regards Borg Dyspnea and Borg Fatigue scales pre and post 6-MWT

		Control group	Study group	Test value	P-value	Sig.
		No. = 30	No. = 30			
Borg Dyspnea (pre)	Mean±SD Range	0.40 ± 0.77 0 – 3	0.13 ± 0.35 0 – 1	-1.402‡	0.161	NS
Borg Dyspnea (post)	Mean±SD Range	2.53 ± 1.96 0 – 6	0.83 ± 0.99 0 – 3	-3.439‡	0.001	HS
Borg Fatigue (pre)	Mean±SD Range	0.53 ± 1.17 0 – 5	0.30 ± 0.65 0 – 2	-0.462‡	0.644	NS
Borg Fatigue (post)	Mean±SD Range	2.60 ± 2.16 0 – 6	1.00 ± 1.31 0 – 4	-2.977‡	0.003	HS

‡: Mann Whitney test

Quality of life data (FACT-B)

When comparing both groups, there was significant increase in total score (FACT-B) as well as in physical, functional, and breast cancer subscales in Study group after CR than Control Group. However, there wasn't significant difference between both groups as regards Social and emotional subscales (Table 4).

Table (4): Comparison between both groups as regards QOL scores

		Control group	Study group After CR.	Test value	P-value	Sig.
		No. = 30	No. = 30			
FACT-B	Mean±SD Range	8.00 ± 20.80 -43 – 42	25.77 ± 16.35 -11 – 57	-2.832	0.005	HS
Physical	Mean±SD Range	-9.50 ± 5.31 -23 – 0	-6.37 ± 3.72 -13 – 0	-2.337	0.019	S
Emotional	Mean±SD Range	-4.53 ±5.02 -15 – 3	-2.50 ±3.76 -10 – 4	-1.455	0.146	NS
Functional	Mean ± SD Range	17.00 ± 4.53 4 – 25	22.27 ± 3.11 16 – 28	-5.255	0.000	HS
Social	Mean ± SD Range	21.40 ± 4.83 12 – 28	22.30 ± 5.14 6 – 28	-0.699	0.487	NS
BC	Mean±SD Range	-15.03 ± 8.65 -28 – 17	-9.67 ± 5.47 -20 – 0	-3.321	0.001	HS

There was significant increase in max achieved training HR, METS, ET, HRR while there was significant decrease in basal HR in the Study group (Table 5).

Table (5): Effect of rehabilitation program on Study Group (comparison between different measures before and after rehabilitation program)

Study group		Pre rehabilitation	Post rehabilitation	Test value	P-value	Sig.
		No. = 30	No. = 30			
Basal HR	Mean ± SD Range	87.60 ± 4.51 80 – 95	77.20 ± 4.83 70 – 90	11.360•	<0.001	HS
Max. HR	Mean ± SD Range	163.93 ± 11.24 140 – 181	169.7 ± 9.35 152 – 184	7.079•	<0.001	HS
HRR	Mean ± SD Range	76.33 ± 14.44 50 – 100	92.5 ± 11.75 72 – 114	12.531•	<0.001	HS
METs	Mean ± SD Range	8.43 ± 1.81 5 – 13	11.53 ± 1.74 7 – 13.4	12.364•	<0.001	HS
ET (min)	Mean ± SD Range	12.15 ± 1.62 9 – 16	15.41 ± 1.53 13 – 18	11.496•	<0.001	HS

•: Paired t-test.

DISCUSSION

Breast cancer represent a local major health problem in women with many deleterious social, economic and functional impact on Egyptian women. For early-stage BC, adjuvant combination chemotherapy increases survival, but it may also have unfavorable effects on QOL, tiredness, and physical functioning. Many exercise studies included cancer survivors but few studies included patients during ongoing treatment [(1,2)].

We tried to implement a tailored exercise based comprehensive cardiac rehabilitation in the process of care of our breast cancer patients in Ain Shams University Hospital during ongoing anthracycline based therapy. The home based part was carried out in the 1st 10 days following chemotherapy session and then a hospital based CR in the next 10 days.

The indirect assessment of CRF in different cancer groups is done using the 6-MWT. More 6-MWT distance was linked, in a moderate to strong way, to both subjective physical function and maximal exercise capacity [(15,16)].

In our study, there was significant improvement in 6 MWD and percentage of expected 6 MWD for age in the Study group. Also, **Bellissimo *et al.*** [(17)] discovered that engaging in physical activity was linked to lessened decreases in heart function and exercise capacity, which are frequently seen in this group.

In 2017, **Leclerc and her colleagues** [(18)] studied the advantages for women receiving BC treatment of a 3-months interdisciplinary rehabilitation program. This study was a controlled non-randomized trial. They used 6-MWT as a measure of functional capacity as well as maximal oxygen consumption (VO2 peak). The study showed significant improvement in both 6MWD and VO2 max in experimental group than Control group.

When assessing QOL, we used the (FACT-B) questionnaire, which has well-established validity and reliability. Our study showed significant improvement in QOL in Study group, with improvement being significantly higher in physical, functional and breast cancer subscales in Study group than Control group, without significant difference regarding emotional and social subscales [(19)].

In 2017, **De Jesus *et al.*** [(20)] studied the viability of an exercise intervention in a community-based cardiac rehabilitation program for tired BC patients. The study had only one arm. The FACT B subscales measuring overall well-being and physical and functional aspects showed statistically significant improvements.

Cancer patients' tiredness continues to have a complex and unclear explanation. Patients describe tiredness as a condition of loss of function and bodily disruption, with weariness serving as the primary cause of decreased physical activity. In addition to being brought on by the illness and its treatment, severe weariness is also a side effect of leading an inactive lifestyle [(21)].

Our study showed that there were significantly lower levels of fatigue reported as Borg Fatigue Scale in post intervention 6-MWT in Study group than Control group, thus proposing the idea that cardiac rehabilitation had ameliorated cancer related fatigue, which had an influence on both functional capacity and QOL, which supported by statistically non-significant difference between both groups as reported by Borg Fatigue Scale pre intervention 6-MWT. Also, same results are applied as regards Borg dyspnea scale pre and post 6-MWT, which showed non-significant difference between both groups in pre 6-MWT while showing significantly lower scores for post 6- MWT in Study group than Control group [(22)].

In the Study group regarding exercise data (using modified Bruce protocol) pre and post intervention (METS, ET, basal HR, HRR, Max HR), we found significant increase in METS, ET, Max HR and HRR while there was significant decrease in basal HR denoting improved level of cardiorespiratory fitness as evidenced by increased METS and ET, also decrease basal HR with increased Max HR and HRR implying more gradual increase in heart rate, which leads to a healthier and more physically active outcome.

Numerous exercise modalities and intensities have been employed in prior research. It has been suggested that low-intensity home-based exercise regimens could be simpler for chemotherapy patients to adhere to, while supervised higher-intensity exercise regimens that include aerobic and resistance training might work best. This supports the implementation of a modified tailored cardiac rehabilitation program, which is not just dependent on hospital based exercise sessions but also encouraging the patients to start home based exercise sessions during treatment with chemotherapy sessions to overcome the decline in functional capacity and QOL, which is multidimensional as cancer related symptoms added to the cytotoxic chemotherapeutic regimen effects would affect the patients mental and physical health and as a result would have detrimental effects on the patient's CRF [(23)].

LIMITATIONS

1. Small number of cases.
2. The study was conducted in one centre.

CONCLUSION

The study's findings showed that a customized cardiac rehabilitation program initiated early in the course of continuous anthracycline therapy enhances functional capacity and QOL in patients with BC who have had anthracycline treatment.

RECOMMENDATIONS

To enhance CRF and QOL, we propose that a multicomponent supervised cardiac rehabilitation program be introduced into the normal treatment of BC patients and begin prior to the initiation of anthracycline-based medications.

- **No funding.**
- **No conflict of interest.**

REFERENCES

1. **Parkin D, Fernandez L (2006):** Use of statistics to assess the global burden of breast cancer. Breast J., 12(1):70-80.
2. **DeSantis C, Bray F, Ferlay J *et al.* (2015):** International variation in female breast cancer incidence and mortality rates. Cancer Epidemiol Biomark Prev., 24: 1495-506.
3. **Ancoli-Israel S, Moore P, Jones V (2001):** The relationship between fatigue and sleep in cancer patients: a review. European Journal of Cancer Care, 10(4):245-55.
4. **Irwin M, Crumley D, McTiernan A *et al.* (2003):** Physical activity levels before and after a diagnosis of breast carcinoma. Cancer, 97:1746-57.
5. **Jones L, Courneya K, Mackey J *et al.* (2012):** Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. J Clin Oncol., 30: 2530–2537.
6. **Scott J, Nilsen T, Gupta D *et al.* (2018):** Exercise therapy and cardiovascular toxicity in cancer. Circulation, 137: 1176–1191.
7. **Early Breast Cancer Trialists' Collaborative Group (2005):** Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet, 365:1687–1717.
8. **Felker G, Thompson R, Hare J *et al.* (2000):** Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med., 342:1077–1084.
9. **Lee D, Pate R, Lavie C *et al.* (2014):** Leisure-time running reduces all-cause and cardiovascular mortality risk. J Am Coll Cardiol., 64:472–81.
10. **Harkness A, Ring L, Augustine D *et al.* (2020):** Normal reference intervals for cardiac dimensions and function for use in echocardiographic practice: a guideline from the British Society of Echocardiography. Echo Research and Practice, 7(1): 1-8.
11. **Thompson P, Arena R, Riebe D *et al.* (2013):** American College of Sports, M. ACSM's new preparticipation health screening recommendations from ACSM's guidelines for exercise testing and prescription, ninth edition. Curr Sports Med Rep., 12: 215–217.
12. **Basen-Engquist K, Bodurka-Bevers D, Fitzgerald M *et al.* (2001):** Reliability and validity of the functional assessment of cancer therapy–ovarian. Journal of Clinical Oncology, 19(6):1809-17.
13. **Directors A (2002):** ATS Statement: Guidelines for the six-minute walk test this official statement of the American Thoracic Society. Am J Respir Crit Care Med., 166: 111-17.
14. **Enright P, Sherrill D (1998):** Reference equations for the six-minute walk in healthy adults. American Journal of Respiratory and Critical Care Medicine, 158(5):1384-87.
15. **Sikandari M, Siddiqui A, Ahmad M *et al.* (2024):** Effect of exercise on fatigue and depression in breastcancer women undergoing chemotherapy: a systematic review and meta-analysis. Support Care Cancer, 32: 515. https://doi.org/10.1007/s00520-024-08703-z
16. **But-Hadzic J, Dervisevic M, Karpljuk D *et al.* (2021):** Six-minute walk distance in breast cancer survivors-A systematic review with meta-analysis. Int J Environ Res Public Health, 18(5):2591. doi: 10.3390/ijerph18052591.
17. **Bellissimo M, Canada J, Jordan J *et al.* (2023):** Physical activity during breast cancer therapy associates with preserved exercise capacity and cardiac function (WF97415). JACC Cardio Oncol., 5(5):641-652.
18. **Leclerc A, Foidart-Dessalle M, Tomasella M *et al.* (2017):** Multidisciplinary rehabilitation program after breast cancer: benefits on physical function, anthropometry and quality of life. Eur J Phys Rehabil Med., 53(5):633-42.
19. **Brady M, Cella D, Mo F *et al.* (1997):** Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. Journal of Clinical Oncology, 15(3): 974-86
20. **De Jesus S, Fitzgeorge L, Unsworth K *et al.* (2017):** Feasibility of an exercise intervention for fatigued breast cancer patients at a community-based cardiac rehabilitation program. Cancer Management and Research, 9:29-39.
21. **Lucía A, Earnest C, Pérez M *et al.* (2003):** Cancer-related fatigue: can exercise physiology assist oncologists? Lancet Oncol., 4: 616-25.
22. **ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories (2002):** ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med., 166: 111–117.
23. **Baumann F, Bloch W, Weissen A *et al.* (2013):** Physical activity in breast cancer patients during medical treatment and in the aftercare: A review. Breast Care, 8:330-334.