Quality of Life of Recently Treated Patients with Breast Cancer

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Abstract. Aim: To investigate whether the negative quality of life result of a large randomized exercise intervention study (BREX) was due to considerable spontaneous recovery after adjuvant treatments. Patients and Methods: The change in QoL was studied in the control patients of the BREX study (Group 1) and a group of similar follow-up patients that did not participate in any intervention study (Group 2). QoL was measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 with the breast cancer module supplement 6 and 12 months after surgery. Results: QoL improved in both groups between 6 and 12 months after surgery. The improvement was similar in both groups for global QoL and for most of the QoL sub-scales. Conclusion: No evidence was found to support the hypothesis that participation in an exercise intervention per se significantly improves QoL. Spontaneous improvement in QoL began during the first six months after the primary treatments, which might have confounded the results of the intervention of the BREX study.

The quality of life (QoL) of patients with breast cancer is often impaired during the rehabilitation period, i.e. soon after the adjuvant treatment has been completed. The impairment is associated with side-effects of treatment such as fatigue, depression, hair loss, menopausal symptoms, lymphedema and reduced libido (1, 2). Physical activity has positive effects on physical functions, psychological outcomes, and QoL in patients after breast cancer treatment (3-7). Although cancer survivors are motivated to make positive changes in their health behavior, exercise promotion may be needed to facilitate those changes (8, 9). Before exercise rehabilitation programs are to become an integral component of multi-disciplinary management of cancer survivors, large-scale randomized controlled trials are required (10).

Exercise interventions being timed with the rehabilitation period have been considered advisable (14) and denote the possibly challenging transition from the medical and social support of the treatment to the normal life (11-13). To date, the only study with QoL as an end-point, where exercise intervention was started immediately after completing adjuvant treatment, is our recently conducted prospective randomized controlled BREast cancer and Exercise (BREX) trial. In that study 500 breast cancer survivors were randomized into either a 12-month physical exercise intervention or a control group (15). Interestingly, we were unable to confirm the positive effect of the exercise intervention on the QoL of the patients. This could be related to the significant spontaneous recovery of QoL, which has been demonstrated not only in the BREX study, but also in other studies during the rehabilitation period (16-18). Another possibility is the bias of the control group as the control patients of the BREX study increased their physical activity which correlated positively with their QoL (19). In addition, participation in the study itself provided extra social support.
for the participants of the control group, which may also have contributed to improvement in their QoL.

The aim of the current study was to assess the role of participation in an exercise intervention study per se on QoL by comparing the recovery of QoL of the control patients of the BREX study with another similar breast cancer population that did not participate in an exercise study or any other intervention. This information is valuable for designing future studies, especially in timing of physical activity intervention and in patient selection.

Patients and Methods

Control group of the original BREX study (Group 1). A group of 237 women aged 35 to 68 years with histologically-proven, newly-diagnosed invasive breast cancer from the Departments of Oncology at the Helsinki, Tampere or Turku University Central Hospitals were enrolled into the control group of the one-year supervised aerobic exercise intervention study (BREX) between September 2005 and September 2007 (2, 19, 20). Inclusion and exclusion criteria are presented in Table I. The adjuvant treatment was carried out according to clinical guidelines. The BREX trial was registered in the Helsinki and Uusimaa Hospital District Clinical Trials Register (www.hus.fi) (trial number 210590) and at http://www.clinicaltrials.gov/ (identifier number NCT00639210).

Participants of the follow-up study (Group 2). Patients in Group 2 were selected from an ongoing large prospective follow-up study of the effects of surgical techniques on QoL of patients with breast cancer in the Helsinki University Central Hospital, Department of Plastic Surgery. The group included 228 patients whose data collection started in September 2008. For this study, all patients with newly-diagnosed breast cancer and with some type of surgical treatment were followed up. Patients were recruited when visiting the hospital prior to surgical treatment. Written consent for participation was required, but otherwise the participants received standard-care without any intervention. After surgery, adjuvant treatment was carried out according to clinical guidelines, which had remained the same for a few years and were similar for both groups of this study. Based on the analysis of patient records, only patients who would have fulfilled the inclusion criteria of the BREX study were included in the analyses (Table 1). Thus, the final follow-up study population (group 2) consisted of 108 patients.

Methods. Group 1: The medical history of the patients was surveyed during the baseline visit for the BREX study after adjuvant treatments, and included a medical examination and laboratory tests. Physical fitness was tested by a 2-km walking test and a figure-8 running test (21, 22). In addition the patients filled-out a questionnaire covering QoL, basic demographics and lifestyle issues. After the baseline visit and completion of the questionnaires, patients were randomized either into one-year supervised exercise training or to a control group. The measurements were repeated annually for up to three years, then again five years from baseline, and will be repeated at the 10-year follow-up visit. Group 2: The patient’s medical history was reviewed from the patient records. Patients filled out QoL questionnaires prior to surgery, and again at three, six (T1) and 12 (T2) months after surgery. All patients received routine care and additional physician visits were not arranged.
QLQ-C30) (version 3) (23), which was used together with the breast cancer module supplement (BR-23) (24). QoL for each group was measured at two time points: patients of group 1 were evaluated after adjuvant treatments (T1) (median 7–8 months from breast surgery) and six months later (median 13–14 months post surgery) (T2); and patients of group 2 were evaluated at six (T1) and 12 (T2) months after surgery. We compared the change in QoL between groups at T1 and T2.

**Statistical analysis.** The data are presented as means with standard deviations (SD) or as counts with percentages. The most important outcomes are given with 95% confidence intervals (95% CI), which were obtained with bias-corrected bootstrapping (5,000 replications). The comparison between groups was carried out with a $t$-test, bootstrapped type $t$-test, chi-square test or the Fisher Freeman Halton test, when appropriate. When adjusting for age and the first measurement value a bootstrapped type analysis of covariance was used.

**Results**

**Patients’ characteristics.** The patients’ characteristics are presented in Table II. Group 1 patients were slightly younger ($p=0.005$), had more lymph node-positive disease ($p=0.002$) and were more often treated with chemotherapy ($p<0.001$) and radiotherapy ($p=0.005$). The response rate to both questionnaires at T1 and T2 were 94% for group 1 and 89% for group 2.

**EORTC QLQ-C30 and BR-23.** At six months post-surgery (T1), the groups were well-balanced except for role and cognitive function in EORTC QLQ-C30 (Figures 1 and 2). The role function was significantly better for group 1 with a mean (SD) of 86.5 (19.3) vs. 80.7 (20.5) for group 2 ($p=0.015$). Corresponding figures for cognitive function were 83.5 (20.6) for group 1 and 91.4 (14.1) for group 2 ($p<0.001$).

During the six-month follow-up, the only statistically significant difference between the groups in change of QoL (EORTC QLQ-C30) was found in physical functioning, which improved somewhat more in group 2 ($p=0.009$ adjusted for the first measurement point value and age) (Figure 1). Future perspective and body image measured by EORTC QLQ-BR-23 improved statistically significantly more in Group 1 during the six-month follow-up period after adjuvant treatment, as compared to group 2 ($p=0.020$ and 0.040, respectively), adjusted for the first measurement and age (Figure 2).

**Discussion**

The change in global QoL and most QoL subscales of the control patients of group 1 did not differ from that of the patients not taking part in a behavioral intervention study (group 2). Thus, just participation in an exercise intervention study *per se* does not improve the QoL of breast cancer survivors and, furthermore, does not explain the lack of intervention effect in the BREX study. The negative QoL result in the BREX study seems to be related to the significant spontaneous recovery of all patients during this period.

In general, the months after the end of adjuvant treatment seem to be a time of transition with poor adjustment and decreased QoL in breast cancer survivors (13, 17, 25, 26). Similarly in the BREX study, the QoL of the patients was impaired shortly after adjuvant treatment. Impaired QoL was especially associated with fatigue and depression (2). During the one-year follow-up period, most scores of EORTC QLQ-C30 improved significantly for both the exercise and control groups, with no significant differences between groups (19). In previous non-exercise studies, QoL improved spontaneously during a five-year follow-up in the majority of cancer survivors; considerable improvements have been seen during the first year after breast cancer treatment, particularly with respect to physical and psychosocial functioning (18, 26-28). Likewise in the present study, social, physical, and role functioning of the patients improved significantly. In addition, treatment-related adverse effects diminished significantly. Goodwin et al. have argued that QoL measured during the initial phases of adjuvant treatment may largely mirror toxicity (29) and that might be also true shortly after adjuvant treatment. Based on the present study, the essential issue during the rehabilitation period seems to be spontaneous recovery of QoL and this could have played a significant role in the original BREX study.

The amount of physical activity increased significantly during the 12-month follow-up in both groups in the original BREX study, which could be interpreted being due to bias of the control group. Even in randomized trials, there is always a possibility that participating in a study itself encourages the
Figure 1. The baseline scores (T1) for functional scales of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) (A) and the change in scores between T1 and T2 for the two study populations (B) (means with 95% confidence intervals). QL ‘Global health score’, PF ‘Physical Function’, RF ‘Role Function’, EF ‘Emotional Function’, CF ‘Cognitive Function’, SF ‘Social Function’.

Figure 2. The scores for BR-23 scales (A) and the change in scores between T1 (six months post surgery) and T2 (12 months post surgery) (B) in the two study populations (means with 95% confidence intervals). BI ‘Body image’, SEF ‘Sexual functioning’, SEE ‘Sexual enjoyment’, FU ‘Future perspective’, CT ‘Systemic therapy toxicity’, RT ‘Breast symptoms’, SY ‘Arm symptoms’.
patients of the control group to increase their physical activity. Interestingly, in the present analysis, physical functioning score improved even more significantly in the follow-up study population (group 2) than in the BREX controls (group 1), which might reflect spontaneous physical activation of all patients with breast cancer after the treatment. Generally, after breast cancer diagnosis, patients are motivated to improve their lifestyle and increase the amount of physical exercise they undertake (14). Unfortunately, there is no activity data available for the follow-up population so that the role of spontaneous physical activity cannot be determined in this study. On the other hand, improvement in physical functioning in group 1 might be prolonged simply due to the fact that patients in group 1 received chemotherapy more often than patients in group 2.

As the BREX study was an open randomized study, it could not exclude the possibility that participation in an exercise study as such was sufficient to induce QoL improvement. We performed this additional non-randomized comparison of the BREX control group to another group of breast cancer survivors with similar breast cancer treatment participating in a prospective follow-up study of routine care without any additional interventions. The patients from that study were selected so that they would have fulfilled the inclusion criteria of the BREX study. The measurement of QoL occurred at approximately similar time points in both studies. We believe that this is the best way of evaluating the effect of participation in a lifestyle intervention per se on QoL. Even though participation in the BREX study could also have physically motivated the participants in the control group, based on the present study we did not find any evidence of participation having an effect on global QoL per se. However, the participants of the BREX study experienced more significant improvement in future perspective and body image in comparison to the follow-up study participants.

Many patients with cancer find the period immediately after adjuvant treatment challenging due to the sudden decline in both medical and social support. Offering exercise interventions during the rehabilitation period might provide social support to cancer survivors and could help them in the transition from the intense levels of support they receive during treatment to lower levels of support (15). Despite the negative result of the BREX study, exercise intervention timed to the rehabilitation period is still justified, at least by the following considerations: Firstly, levels of physical activity decline significantly after a cancer diagnosis (30-32), secondly, cancer diagnosis is a life-changing event and completion of treatment is identified as a motivator for initiating the lifestyle changes promoted in the intervention. Patients themselves feel fit enough to make behavioral changes at three to five months post-treatment, while not yet having lost their motivation to change (33). They prefer to begin an exercise program immediately or soon after treatment, rather than during treatment (32, 34). It seems, however, that interventions with unselected populations might not be optimal for improving QoL, as many patients experience significant spontaneous recovery and for the others, motivating by encouraging them could be sufficient. If aimed at improving QoL by exercise intervention, a more careful selection of patients with individually-tailored interventions could be more reasonable. It should be noted that the results of this study cover only the field of QoL. Although spontaneous improvement in QoL is good news for patients, exercise interventions timed to the rehabilitation period of merit, e.g., in improving bone mineral density and strengthening muscle; both of these are very beneficial for women after breast cancer treatment.

In conclusion, while the observed motivation effect and spontaneous recovery is indeed positive news for breast cancer survivors, our results emphasize that the role of such phenomena must be rigorously addressed in future exercise intervention trials during the rehabilitation period. It now seems likely that unselected exercise interventions may not bring additional QoL benefits to all patients. This conclusion suggests that future exercise intervention studies targeting on improvement of QoL should identify groups of patients that could benefit the most from an intervention and tailor the interventions to their specific needs.

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