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Support Group Intervention in Primary Breast Cancer

Health-Related Quality of Life, with Special Reference to Anxiety, Depression and Fatigue

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Abstract
Granstam Björneklett, H. 2012. Support Group Intervention in Primary Breast Cancer: Health-Related Quality of Life, with Special Reference to Anxiety, Depression and Fatigue. Acta Universitatis Upsaliensis. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 819. 77 pp. Uppsala. ISBN 978-91-554-8485-9.

The aim of this thesis was to investigate in a (RCT) the effect of support group intervention in women with primary breast cancer in the short term, and with a long-term follow-up. Women with primary breast cancer were randomized between April 2002 and November 2007 and stratified according to adjuvant treatment with chemotherapy. Of 382 eligible patients, 191+191 patients were randomized to intervention and control groups respectively. Control patients were subjected to standard follow-up procedures. Patients in the intervention group received support intervention at the Foundation of Lustgården Mälardalen during one week followed by four days of follow-up two months later. Patients in intervention and control groups filled in questionnaires at baseline, after 2, 6 and 12 months and in the long-term follow-up after a mean of 6.5 years. In paper I, we studied the effect of the intervention on anxiety and depression measured by the HAD scale and we could show that a significantly lower proportion of women in the intervention group had high anxiety scores compared with women in the control group after 12 months; however, the proportion of women with high depression scores were unaffected. In paper II, we studied the effect of the intervention on fatigue and health-related quality of life (HRQoL) measured by the Norwegian version of the fatigue questionnaire (FQ) and EORTC-QLQ 30 and BR 23.We could not demonstrate any significant effect of the intervention. In paper III, we studied the effect of the intervention on sick-leave, healthcare utilization and the effect of the intervention in economic terms. We used a specially formulated questionnaire. There was a trend towards longer sick leave and more health-care utilization in the intervention group. The difference in total costs was statistically significantly higher in the intervention group after 12 months ($p= 0.0036$). In paper IV, we studied the long-term effects of the support intervention on anxiety, depression, fatigue and HRQoL. We could show a significant effect of the intervention on cognitive function, body image, future perspective and fatigue, the largest effect was seen among women who received chemotherapy; however, no effects on anxiety and depression were demonstrated.

Keywords: Support group intervention, breast cancer, anxiety, depression, fatigue, health-related quality of life, sick-leave, health-care utilization

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The secret of health for both mind and body is not to mourn for the past, worry about the future, or anticipate troubles, but to live in the present moment wisely and earnestly.

Buddha 563 f Kr-483 f Kr

To Are, Oscar, Anton and Agnes

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Björneklett HG, Lindemalm C, Rosenblad A, Ojutkangas ML, Letocha H, Strang P, Bergkvist L. A randomized controlled trial of support group intervention after breast cancer treatment: results on anxiety and depression. *Acta Oncol*. 2012 Feb;51(2):198-207. Epub 2011 Sep 19.

II. Björneklett HG, Lindemalm C, Ojutkangas ML, Berglund A, Letocha H, Strang P, Bergkvist L. A randomized controlled trial of a support group intervention on the quality of life and fatigue in women after primary treatment for early breast cancer.
Support Care Cancer. 2012 May 11. [Epub ahead of print]

III. Björneklett HG, Rosenblad A, Lindemalm C, Ojutkangas ML, Letocha H, Strang P, Bergkvist L. A randomized controlled trial of a support group intervention: Results on sick leave, healthcare utilisation and health economy. Accepted for publication in *Acta Oncol*.

IV. Björneklett HG, Rosenblad A, Lindemalm C, Ojutkangas ML, Letocha H, Strang P, Bergkvist L. Long-term follow-up of a randomized study of support group intervention in women with primary breast cancer. (Submitted).

Contents

Abbreviations

HRLQoL	Health related quality of life
QOL	Quality of life
RCT	Randomized controlled trial
OS	Overall survival
PFS	Progression free survival
CBTH	Cognitive behavioral therapy
NCCN	National Comprehensive Cancer Network
WHO	World Health Organization
GEE	Generalized estimating equations
EORTC	European Organisation for Research and Treatment of Cancer
HAD	Hospital Anxiety and Depression scale
FQ	Fatigue Questionnaire
QLQ BR	Quality of Life Questionnaire-Breast Cancer Module
EBCTCG	European Cancer Triatlists Collaborating Group
SPSS	The Statistical Package for Social Sciences
OR	Odds ratio
M-W	Mann-Whitney

Introduction

Breast cancer is the most common malignant disease among women world-wide. The risk of women developing some form of invasive breast cancer is about one in eight. Nearly 8000 women in Sweden are annually diagnosed. In Europe, breast cancer corresponds to 28.2 % of all cancer in women and was responsible for 17 % of all cancer deaths in 2008, the leading cause of cancer death in women (1). In Sweden breast cancer is the second cause of cancer death in women after lung cancer (2).

The treatment of breast cancer is individual. In the primary setting, most women are treated with surgery, sector resection or mastectomy, sentinel node and/or axillary clearance. Thereafter, depending on tumour-related factors, risk factors, comorbidity and age, they receive adjuvant therapy with chemotherapy, radiotherapy, antibody treatment, antihormonal therapy, alone or in combination.

Breast cancer is a disease, which during recent years has been characterized by improvements in treatment and diagnostics. Early diagnosis by means of regular mammography screening (3) has been shown to lower the death rate. Improvements in surgery, with less mutilating operations including sector resection and sentinel node have led to less sequelae (4) There have also occurred improvements in chemotherapy treatments (5). Bergh et al found an absolute mortality reduction in women with node-positive disease of polychemotherapy in 12 % of women younger than 50 years and 6 % in women age 50-69.

New treatment modalities in the form of antibody treatment with trastuzumab (6) have shown significant overall survival benefit in women with Her2 positive disease. There have also been improvements in radio-therapy and according to a European Cancer Triatlists' Collaborating Group (EBCTCG) study, Darby et al (7) showed an absolute reduction of 3.8 % in the 15 year risk of breast cancer death. Anti-hormonal therapies with tamoxifen for 5 years reduce the annual breast cancer death rate by 31% (8) and treatment with aromatase inhibitors has further improved disease-free survival as Howell et al (9) have shown in the ATAC trial. In the Ma 17-trial (10), letrozole administration led to a statistically significant prolongation in disease-free survival (DFS), however, improved overall survival has been demonstrated in the long-term follow-up of the BIG-98 trial (11). Five years of treatment with letrozole compared with 5 years of

tamoxifen gave an absolute improvement in survival of 11.5 %. All these improvements have contributed to a positive trend in prognosis during the last 10-15 years. The 5-year survival in Sweden, today, is almost 90 % and the 10 years almost 80% (2).

Treatments with chemotherapy, radiotherapy, antihormonal therapy and antibody therapy are often intense, and give many patients side-effects, both physically and psychosocially, and those affect the patients' quality of life. Due to improved survival, more women live with the side-effects of diagnosis and treatment, both physically and mentally. In the United States, breast cancer survivors represent 22% of estimated cancer survivors and 40% of all female survivors. The prevalence of women with breast cancer in Sweden today is approximately 89 000 and the average age at the time of diagnosis is 60 years (2).

Reactions to cancer

Many women initially react at diagnosis, with symptoms such as anxiety, depression, aggression, helplessness and hopelessness and also problems regarding self-esteem and identity (12). This is often summarized in the term distress. The National Comprehensive Cancer Network (NCCN) Distress Management Guidelines Panel defines distress as (13) " a multifactorial unpleasant emotional experience of psychological (cognitive, behavioral, emotional), social, and/ or spiritual nature that may interfere with the ability to cope with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears, to problems that can become disabling such as depression, anxiety, panic, social isolation and spiritual crisis".

Women also show normative mood changes, an increased sense of vulnerability, uncertainty, feelings of loss, concerns about body image, self-concept, sexuality, emotional distress related to role adjustments and family response and also concerns about finances and employment as showed in a review by Knobf (14). Earlier studies have shown that between 20-30% of breast cancer patients show measurable signs of anxiety and depression in the year after diagnosis (14). The corresponding prevalence of anxiety and depression in the general population was 8% and 6 %, respectively, in a healthy Swedish population (15) (measured by HAD). The depressive symptoms are most pronounced during the first year after diagnosis, whereas most women recover within one year (16) but symptoms of anxiety may persists for several years (17). Risk factors for depression in the first 5 years after diagnosis are more related to the patient than to the disease or its treatment. Breast cancer patients have been shown to have higher levels of depressive symptoms than other cancer patients, despite

their better survival rate (18).The reason is unknown, but the anti-hormonal treatment may contribute to perceived symptoms.

Symptoms of depression have a negative influence on patients' quality of life (19) and may affect compliance to medical treatment (20), as well as recurrence, recovery and survival (21). Low levels of distress and fatigue have been associated with longer recurrence free survival (22). Fatigue, past history, or recent episodes of depression after the onset of cancer, cognitive attitudes of helplessness/hopelessness and resignation are risk factors for depression or part of the depressive mood and might impair quality of life (12). In addition to psychological symptoms, women also change their perspectives and appreciation of life. Furthermore, sources of suffering symptoms that often affect breast cancer patients, but are often neglected, are those of an existential character (23).
Women's adjustment to breast cancer has been extensively studied during the last decades.

The most common outcome measures in studies of symptoms after breast cancer and treatment have been anxiety, depression and other aspects of HRQoL. Other symptoms that may affect HRQoL are distress, fatigue, reduced energy and loss of stamina.

The first study on HRQoL in breast cancer patients was published in 1974 (24), according to a review by Montazeri and pursuant to his review, it was not until the late 1980s and early 1990s that the literature was gradually supplemented with papers using relatively standard and established instruments to measure quality of life in breast cancer patients, During the last 15-20 years, the literature has expanded enormously (25).

Health-related quality of life (HRQoL)

Health-related quality of life (HRQoL) has been defined as a "global concept, conceived to reflect the totality of human well-being, including, but not limited to physical, psychological, social, economic and spiritual domains (26). The notion of health-related quality of life (HRQoL) addresses QOL as it is affected by disease and treatment.

HRQoL in cancer patients has gained great interest since studies, especially in the 1980s but also in recent years (22), have shown that quality of life measures might be independent predictors (27) and a prognostic (28) indicator of survival but this has been questioned by others (29-31). Goodwin et al (29) investigated 140 prognostic associations in their study on 397 women with stage I and II breast cancer disease, and they could not find any association with medical outcome of HRQoL and psychosocial status. Likewise, Coates et al (30) found no prognostic significance of HRQoL scores in the adjuvant setting in breast cancer treated women; however, they

found a strong prognostic significance of HRQoL scores after disease relapse. In a large international multicenter study, Efficace et al. (31) could not find any prognostic value of HRQoL variables for overall survival (OS) or disease free survival in women with non-metastatic breast cancer. However, two other studies suggest a relationship between HRQoL and progression free survival and overall survival in advanced breast cancer (30, 32).

There are few studies with a longitudinal follow-up, both in terms of HRQoL and interventions made to improve HRQoL. Ganz found that long-term disease-free survivors with no adjuvant therapy reported good health-related quality of life, but those who received adjuvant therapy had poorer functioning in several dimensions of HRQoL (33). Since many women have symptoms of their breast cancer and treatment that persists for years after treatment, there is a need for studies with long-term follow-up.

Fatigue

Cancer-related fatigue has been defined by the National Comprehensive Cancer Network (NCCN) as "a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning" (34). Many cancer survivors identify fatigue as the most frequent and distressing cancer-related symptom (34, 35) and, in many studies, fatigue seems to be the predominant cause of reduced HRQoL. Arndt et al (36) found that fatigue was the strongest predictor of impaired HRQoL at 1 year after diagnosis and Meeske (37) found that 41% of breast cancer survivors experienced fatigue 2-5 years post diagnosis and that the fatigue was associated with a poorer HRQoL.

Patients' needs

Health care is often good at dealing with side-effects of treatment such as nausea, vomiting, neutropenia and mucositis, but often not prepared to deal with the side-effects both physical and emotional that come after treatment is completed. This means that women treated for breast cancer often have unmet needs that are not taken into consideration by the health-care system. Studies have been performed to investigate women's needs (38-41). Ernstmann et al (38) found that 19% of cancer survivors reported unmet needs for this kind of service 22 months (mean) after the time of diagnosis, but only 10% were actually using psychosocial services and Thorsen (41) found that 63 % reported a need for at least one rehabilitation service, where physical therapy (43%) and physical training were in greatest demand and 24% required supportive group sessions (41). Women treated for breast

cancer were more likely to report the need of physical therapy and supportive group sessions than patients with other diagnoses (41). However, Vilstrup Holm (40) found in a population-based cohort study of 3,439 patients with any cancer diagnosis, that one third of the cancer patients reported needs for physical rehabilitation and one third for psychological rehabilitation and that breast cancer patients participated more often in physical rehabilitation than other cancer patients.

In the literature, discussions about how to identify the needs of women have been performed, and different screening instruments have been put forward. In the last decade, screening for distress has been positioned as the sixth vital sign in cancer care by NCCN (42), in addition to the first five, which are measurements of pulse, respiration, blood pressure, temperature and pain.

Interventions

The improved treatment possibilities available to breast cancer patients, leading to more cancer survivors, raise new questions. Interventions to improve women's symptoms after breast cancer treatment have been developed for many years. The World Health Organization (WHO) has defined rehabilitation as: "a process intended to enable people with disabilities to reach and maintain optimal physical, sensory, intellectual, psychological and/or social function"(43).

To improve women's symptoms and improve their quality of life, many different types of studies on interventions have been performed. To obtain a structure and be able to distinguish the different types of intervention Cunningham in 1995 (44) made a classification of psychosocial interventions which has been used in review articles and meta-analyses (45) to compare the contents in various interventions. The classification was arranged according to a hierarchy of increasingly active participation by the recipient, and noting the status of evidence for their efficacy. However, spiritual / existential therapies have seldom been used in practice.

Providing information (*patient education*)
Emotional support (*social support, support groups*)
Behavioral training in coping skills *(cognitive, cognitive behavioral, behavioral methods supposed to modify cognitions or behaviors by active acquisition of specific coping skills*)
Psychotherapy (*psychodynamic, existential, supportive or eclectic therapeutic approaches and crisis intervention*)
Spiritual/existential therapy *Not used by Rehse and Pukrop*

Cunninghams classification.(44)
Text in Italics is as used in the meta- analysis by Rehse and Pukrop(45)

The most common interventions today are psychoeducation, cognitive behavioral therapy and social and emotional support. All types of intervention have somehow shown positive results on quality of life;however, the methodological quality has differed as noted by the reviews (45-49).

Rehse and Pukrop (45) found in a meta-analysis that educational programme were more effective than the other three (emotional support, behavioral training in coping skills, psychotherapy) ranked higher with regard to active patient involvement, but they had no explanation for this. They could not show any statistically significant difference between the effects of social support, coping skills and psychotherapy on HRQoL. In a review by Moyer (46) of all studies between January 1980 and December 2005 with any kind of HRQoL outcome, 673 reports with 46.665 patients were included. They studied different cancer diagnoses, but the predominant one was breast cancer (70.5 %). One fifth of the interventions were primarily educational, more than a half included therapeutic ingredients, such as stress and symptom management (i.e. relaxation training, guided imagery). Approximately one fifth included a multimodal intervention and close to one fifth involved complementary and alternative medicine and products not considered part of conventional medicine. Even if 62.9% were randomized studies, there were some methodological problems such as low statistical power, and high levels of drop-out. They found a significant improvement in the use of randomized design when they compared studies performed between 1980 and 1998 and compared with projects reported between 1999 and 2005. There was also a significant increase over time in the proportion of projects that reported the initial number of patients in the sample and also a significant increase in the proportion of studies that examined group equivalence at baseline and used intention-to-treat analyses.

Raingruber et al (47) reviewed 19 randomized controlled trials between 2006 and 2011 of which 11 showed positive outcomes from psychological interventions. Although the studies were randomized, the overall study quality was limited, not all studies were adequately described, not all contained hypothesis and several did not randomize appropriately. There was also a lack of recruitment dates, eligibility criteria, power analysis and they concluded that studies should have comparable outcomes. Newell (48) reviewed all identifiable publications about psychological therapies used by for cancer patients published before December 1998. They showed that no intervention could be recommended for reducing patients' fatigue or increasing patients' survival and relatively few tentative recommendations about the effectiveness of psychological intervention strategies at improving cancer patients' outcome. Fors et al (49) supported those results in 2011, they observed limited and indifferent documentation on the effect of psycho

education and social and emotional support, but documented some benefit of cognitive behavioral therapy (CBT), such as short- term effects on depression, anxiety and HRQoL.

There have also been studies on telephone-assisted interventions, brief art therapy, yoga and mindfulness but these are outside the scope of this thesis.

When we planned our study, individual therapy was commonly used (50), there were some data supporting that structured short-term educational programme were of benefit (51, 52) and the discussion within the profession argued that relaxation, health education, neuropsychological training, behavioral training, art therapy and psycho education could be included in a support group programme, which was also shown in a study published the year after we started our study (53). Few results from randomized studies were presented (54) and often entailed patients with mixed tumour groups (50) and the results were diverging, perhaps due to incomplete methodology and lack of comparable outcomes (48, 55) and some studies were performed on women with metastatic breast cancer (56).

Return to work and health care utilization

More than half of all women are diagnosed before the age of 65, and thus on full-time work. In Sweden, more than 80 % of women are employed. Returning to work after initial treatment is, therefore, of interest for both the individual and society. For the individual woman returning to work is a measure of normalization and recovery (57). For society, sick leave means loss of production and costs for health insurance. The majority of breast cancer survivors return to work. Bouknight (58) found that more than 80% returned to work within 18 months but Johnsson found that 41% were sick-listed part-time or full-time 10 months after surgery (59). Several factors have been found to be associated with returning to work, such as chemo-therapy (60, 61), age (62), education (61, 63, 64) and income (58), but very few randomized controlled studies have been carried out into interventions aimed at reducing the proportion of patients not returning to work.

The improved treatment possibilities of breast cancer, which have led to more patients being cured and that allow those not cured to live longer with their disease, have placed emphasis on the psychological support of survivors. Many questions remain also on how to best design a programme, and, from the literature, it is obvious that the effect of different approaches is still uncertain. This level of uncertainty was even greater when we planned our study. The overall intention of this thesis was to test a pre-existing programme and to evaluate the effect of this on HRQoL, fatigue, anxiety and depression on a short and long-term basis, and also to evaluate the economic consequences of the programme and the return to work.

Specific aims

To study the effect of an educational support group intervention in a homogenous group of women with primary breast cancer on

Paper I

- Anxiety and depression measured by the HAD scale.

Paper II

- Fatigue and health- related quality of life measured by the Norwegian version of the fatigue scale and EORTC QLQ 30 and BR 23.

Paper III

- Sick leave, health-care utilization and societal costs (health economy).

Paper IV

- The long-term effect of support group intervention on anxiety, depression, fatigue and health-related quality of life.

Materials and methods

Subjects

All newly diagnosed breast cancer patients between April 2002 and November 2007 presenting at the Department of Oncology at the Central Hospital in Västerås, Sweden, for postoperative radiotherapy were scrutinized for participation.

During this period, 770 patients were referred for radiotherapy and 709 were assessed for eligibility. The decision to select patients who were scheduled for radiotherapy was made for logistical reasons. However, most patients treated at the hospital were referred for radiotherapy; only a few elderly women who had undergone a mastectomy for stage I disease were excluded, see flow chart (Figure 1).

The inclusion criteria were a newly diagnosed primary breast cancer, the physical and mental capability to participate in group interventions, ability to fill in questionnaires and an expected survival of more than 12 months. Individuals with dementia, patients with severe visual and auditive impairments serious mental illness, active alcohol abuse and physical impairment because of the conference centres' premises were excluded. Patients who had participated in group rehabilitations previously or had a former history of any malignant disease were excluded, in total 54 patients.

All meeting the inclusion criteria were informed about the study and, after acceptance to participate, all patients gave their written informed consent. The Ethics Committee at the University of Uppsala approved the study.

Patients were stratified into those who received adjuvant chemotherapy and those who did not, and randomized in blocks of four by the use of closed envelopes. Based on a power calculation, 382 women were included in the study, 191 in the intervention group and 191 in the control group.

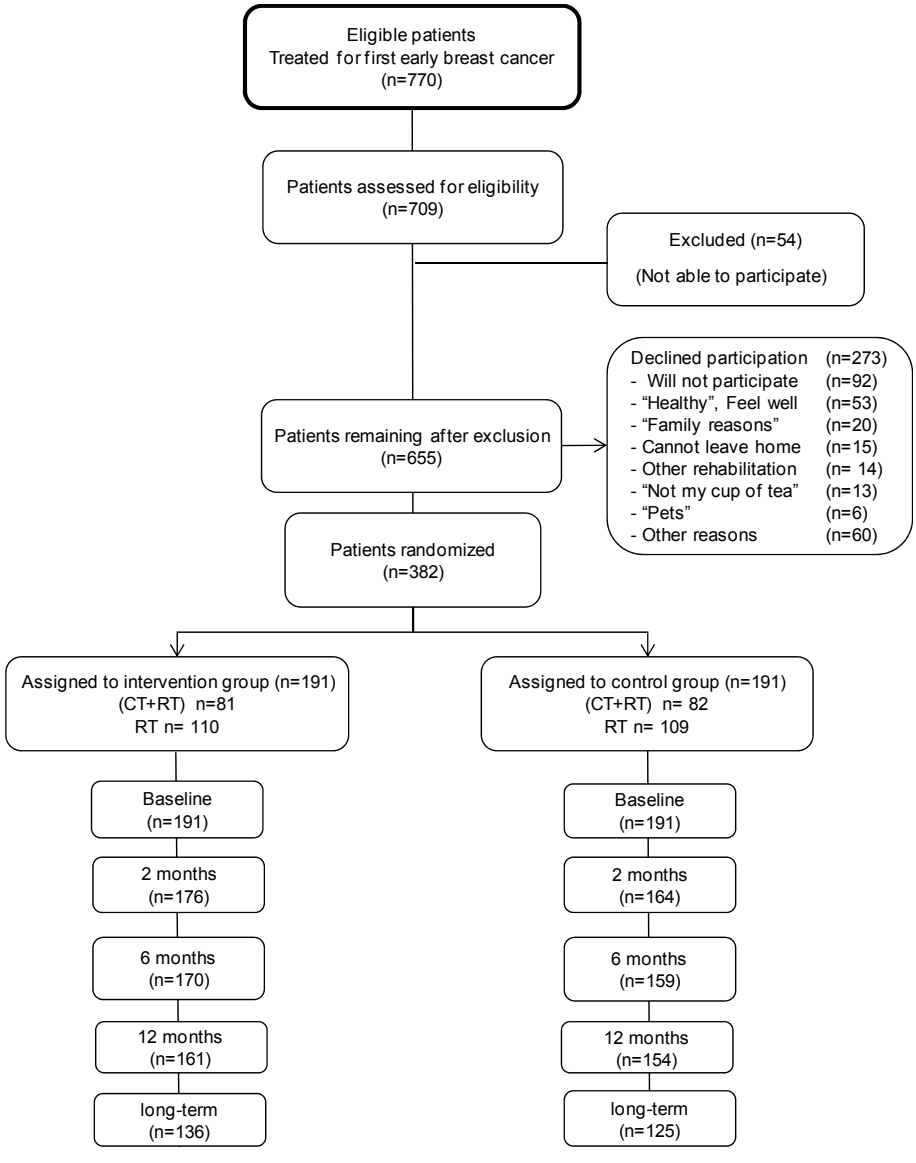


Figure 1. Flow chart of participants' progress through the randomized trial.
CT=Chemotherapy RT=Radiotherapy

The distribution of women in the intervention and control groups were comparable according to tumour size, receptor status, lymph node status, menopausal status, hormone replacement treatment (HRT) before diagnosis, civil status and education level (Table 1).

Treatment

Surgery

Eighty-nine patients in the study were treated with mastectomy and 293 with breast conserving surgery. One hundred and sixty five underwent sentinel node biopsy only, 198 underwent a level I-II axillary dissection and 21 patients had no axillary surgery.

Chemotherapy

A total of 161 patients were administered chemotherapy. Standard chemotherapy was given in the form of 5-fluorouracil (600 mg/m2), Epirubicin (60-75mg/m2) and Cyclophosphamide (600 mg/m2) (FEC in 6-7 cycles) (n=68). Sixteen patients had large, inflammatory or inoperable tumours and were given neoadjuvant chemotherapy with 4 cycles of FEC before and 3 cycles of FEC after surgery (n=4) or 3 cycles of Epirubicin and Docetaxel and 3 cycles of Docetaxel (n= 12).

In addition, some patients were included in 3 different randomized studies of adjuvant or neoadjuvant treatment and were treated according to the respective study protocols.

Radiotherapy

Radiation with (6 MV photons) was delivered to the breast in fractions of 2 Gy doses to a total of 50-52 Gy in all patients with breast conserving operations (n=293).Young patients (age below 45 years) were given a 10 Gy boost during the last years of the study. Patients with lymph node involvement had additional radiation delivered to adjacent lymph node stations in the axilla and supraclavicular fossa. Patients who had undergone mastectomy due to large tumours (> 3 cm) or multifocal tumours received radiotherapy towards the chest wall in fractions of 2 Gy to 50-52 Gy and young patients were given a 10 Gy boost in more recent years.

Antibody treatment

Patients with HER2 positive tumours were initially included in the HERA study (6) and, after August 2005, all patients with HER2 positive tumours were given adjuvant trastuzumab. A total of 15 patients received 17 cycles of adjuvant trastuzumab.

Endocrine therapy

Tamoxifen was offered to all pre-menopausal women with endocrine responsive tumours and postmenopausal women with stage I tumours. A total of 249 patients received tamoxifen treatment. Postmenopausal women with stage II tumours or more received sequential treatment with 2-3 years of tamoxifen and 2-3 years of aromatase inhibitors. A few patients changed treatments after a few weeks due to side-effects either from tamoxifen to aromatase inhibitor or vice versa. Altogether, 94 patients received aromatase inhibitors. The endocrine treatment usually started after radiation therapy (Table 1).

Table 1. Distribution of patients according to surgical intervention, node status, tumour characteristics, menopausal status, post-operative endocrine treatment and civil status at baseline, with values given separately for all patients and those remaining in the long-term follow-up

	All patients			Long-term follow-up patients		
	Intervention *(n=191)*	**Control** *(n=191)*	**P-value**	**Intervention** *(n=136)*	**Control** *(n=125)*	**P-value**
Age, mean (range)	57.8 (30-84)	58.7 (38-83)	0.360	58.0 (40-79)	59.2 (38-83)	0.276
≤50 år	46	42	0.784	29	26	0.393
51-65 år	106	105		82	69	
≥ 65 år	39	44		24	31	
Surgery						
Mastectomy	42	47	0.545	27	32	0.298
Breast conservation	149	144		108	94	
Sentinel node biopsy	85	80	0.606	67	51	0.138
Axillary clearance	95	103	0.413	61	70	0.094
Neither axillary dissection, nor sentinel node	11	10	0.822	7	6	0.875
Cancer in situ	12	14	0.685	8	8	0.887
Lymph nodes						
Negative	104	107	0.370	83	63	0.274
≤3	53	62		35	48	
4-8	16	8		9	7	
≥9	7	4		1	2	
Lgll not done	11	10		7	6	
Receptors						
ER+	158	158	0.730	113	110	0.676
ER-	21	24		14	11	
ER not known	12	9		8	5	
PR+	109	115	0.800	77	80	0.567
PR-	69	65		49	39	
PR not known	13	11		9	7	
Her2+	15	10	0.585	9	6	0.662
Her2-	82	84		58	60	
Her2 not known	94	97		68	60	
Tumour size						
≤2 cm	109	122	0.174	81	82	0.397
>2 cm	82	69		54	44	
Menopause						
Pre-menopausal	53	42	0.158	34	26	0.143
Post-menopausal	127	143		92	97	
Not known	11	6		9	3	
Chemotherapy†	81	80	0.918	55	59	0.322
Radiotherapy	188	187	1.000‡	133	123	0.675‡
Tamoxifen	123	126	0.747	87	87	0.431
Aromatase inhibitor	52	42	0.235	33	35	0.540
Hormone before cancer diagnosis	24	32	0.247	19	19	0.818
Civil status						
Married, cohabiting	136	151	0.076	98	97	0.415
Single, divorced, widow	55	40		37	29	
Have children living at home	47	43	0.629	31	25	0.540
Education level						
Elementary school	60	59	0.815	48	41	0.699
High school	42	46		33	30	
College/University	77	71		46	50	

† Randomization stratified on this variable. ‡P-value from Fisher's exact test.

The educational support-intervention programme at the Foundation Lustgården Mälardalen started in 1992 partly inspired by a discussion in the scientific society concerning the connections between emotions, immunity and malignant diseases. It was also influenced by communications with different professionals and patients concerning what they thought would improve quality of life, or rather, would meet the needs of the patients not by that time met by ordinary clinical procedures. The procedure indicates a reasonable degree of face validity. This led to our knowledge-information based support programme supplemented with relaxation, Qi-gong and liberating dance. The intervention took place within four months after the patients had finished their primary treatment, except for trastuzumab and long-term endocrine treatment, which could be on going.

The rehabilitation programme consisted of one week on a residential basis from Sunday to Saturday and four days of follow-up two months after the initial visit. The team leader was the director of the Foundation responsible for the time-schedules, all practical arrangements as well as taking care of the group outside the actual supportive rehabilitation programme. The members of the support team were oncologists (n=3), social workers (n=2), physical therapists (n=1), dietician (n=1), art and dance therapists (n=2) and a person trained in qigong and mental visualization. All personnel had several years of occupational experience. The guests received information from the oncologist about breast cancer, etiology, risk factors, treatments, physical and psychological effects of diagnosis and treatments. Questions from the guests were discussed.

Psychological effects and coping strategies were the responsibility of the psychologist and, to some extent the social worker, who, in addition, informed about practical-social details, such as being on the sick-list, insurance and economic consequences.

The dietician had information discussions about the importance of food and nutrition.

The informative-educational parts were mixed with mild physical exercise, relaxation training, qi-gong, mental visualisation and non-verbal communication (art and liberating dance therapy).

Social activities, such as concerts, visits to museums and restaurants were provided as were the opportunities for the guests to be together with individuals with similar experiences in a beautiful and restful milieu not burdened by troubles of daily living, such as taking care of family members or keeping a household and a job going. The re-assembly was an opportunity to review the support-period, discuss problems after returning home, meet the team leader, dietician, the massage therapists and the companions met during the intervention. The programme has previously been described in a pilot study of unselected patients with different tumour diagnoses (65).

The guests gave their opinions about the rehabilitation and their answers were continuously evaluated.

The consultants had regular guidance from a psychologist not taking part in the intervention and organised meetings were held once every six months to discuss the procedures, observations made and experience gained.
All patients who participated in the first week of intervention completed this and the four days of follow-up.

Control patients were subjected to standard follow-up procedures.

Questionnaires

Paper I-III

Study patients and control patients answered questionnaires before rehabilitation and after 2, 6 and 12 months.

Paper IV

Study patients and control patients answered questionnaires average 6.5 years after randomization.

Paper I

The Swedish version of the HAD scale was used to measure symptoms of anxiety and depression. It is a validated scale, commonly used worldwide to discriminate between anxiety and depression (66-68). The responses to the HAD scale were analysed as originally described (69). The scale consists of seven items reflecting anxiety and seven reflecting depression. Each item is rated on a four point scale; 0- less than before; 1- not so much; 2- quite a lot and 3- very much, giving a maximum of 21 for depression and anxiety, respectively. Scores >10 on either subscale indicate probable cases of depression or anxiety and subscale scores in the range of 8-10 represent possible cases (66, 69). In the statistical analysis, we considered only those with a high anxiety score (probable anxiety or depression).This scale was originally designed to detect emotional disturbances in non-psychiatric patients treated in hospital clinics (69). It has been used in many breast cancer studies (70) and has been shown to have a stable factor structure and high reliability (66).

Paper II

Health-related quality of life (HRQoL)

Health-related quality of life (HRQoL) was measured using the Swedish version of the European Organization for Research and Treatment of Cancer (EORTC) QLQ 30 (quality of life questionnaire) and BR 23 (breast cancer-module) (71). This is a 30-item standardized measure, composed of multi-item scales and single items that reflect the multidimensionality of the quality of life construct. It includes a global health and quality of life scale (two items), five functioning scales (physical, role, emotional, cognitive, and social) of combined items, three multi-item symptom scales (fatigue, pain and emesis) and the remaining single items assess additional symptoms commonly reported by cancer patients (dyspnoea, sleep disturbance, appetite, diarrhoea, constipation) and finally, the financial impacts of the disease and treatment.

The breast cancer module BR 23 includes 23 breast cancer specific questions grouped into the functioning scale (i.e., body image, sexuality, and future perspective) and the symptom scales and single item assess systemic side-effects, arm symptoms, breast symptoms, and hair loss. The scoring of the QLQ-C30 and QLQ-BR 23 items were performed in accordance with the EORTC scoring manual. All scores were linearly transformed to a 0-100-points scale. In both instruments, high functioning scores represent better functioning and HRQoL; whereas high symptomatic scores indicate more severe symptoms.

Fatigue

Fatigue was measured by a Swedish translation of the Norwegian version of the fatigue questionnaire (FQ) (72, 73). The FQ is a self-report instrument for assessment of fatigue, including symptoms experienced during the last month compared with how the subject felt when last feeling well. Additionally, two items ask about the duration and the extent of fatigue. FQ measures physical fatigue (PF) and encompasses seven items, while mental fatigue (MF), encompasses four items. All 11 items are designated total fatigue (TF). Each item has four response choices. Likert-scoring (0, 1, 2, 3) is used for the construction of PF, MF and TF. Higher scores imply more fatigue. The FQ has originally been validated in primary care and has shown good face and discriminative validity (74) but has also been used on cancer patients (73).

Paper III

We used a questionnaire with questions about family situation, occupation, sick leave and health care utilization with a questionnaire that we formulated. No registry data were used.

Paper IV

In paper IV intervention and control patients received the same questionnaire as that used in the previous two first studies.

Statistical analyses

Before the study started, a power calculation was performed based on the assumption that 50% of women treated for breast cancer show some sign of psychological distress, which was reported in the literature at that time. To be able to detect a difference of 15 percentage points between the intervention and control group in the proportion of patients with psychological distress after one year with a power of 80% and a significance level of 5%, we would need a total number of 340 patients. In order to allow for at least a 10% dropout rate, we aimed at 400 patients. The statistical analyses in paper I, III and IV were performed in IBM SPSS Statistics (IBM Corp., Armonk, New York, USA) version 15-20. Additionally, R (R Foundation for Statistical Computing, Vienna, Austria) was used for some analyses in papers III and IV). In paper II the linear mixed effect models were performed using SAS.

Paper I

The anxiety and depression scores were treated as ordinal data and were tested with Pearson's χ^2-test. Correlations between anxiety and depression scores were calculated using Spearman`s correlation coefficient r. Changes in anxiety and depression over time were analyzed using a multivariate generalized estimating equations (GEE) ordinal logistic regression model.

Paper II

Linear mixed effect models were used to evaluate longitudinal changes. In order to test whether outcomes for the two groups varied in time, an interaction term was included between time and intervention.

Paper III

Differences between intervention and control group where tested univariately with Pearson's χ^2-test for categorical variables, except for a couple of cases where the assumptions underlying Pearson's χ^2-test were not fulfilled, in which case Fisher's exact test was used instead. The Mann-Whitney (M-W) test was used when testing for differences between intervention and control groups for discrete and continuous variables.

Paper IV

Differences between intervention and control group were tested univariately with Pearson's χ^2-test for categorical data and Mann-Whitney`s U test for continuous data. When the assumptions underlying Pearson's χ^2-test were not fulfilled, Fisher's exact test was used instead. Univariate tests of difference between baseline and the 12 months follow-up within the intervention and control group, respectively, were performed using McNemar`s test for categorical data and Wilcoxon`s signed rank test for continuous data. For multivariate analyses, linear regression analysis was used when the outcome variable was continuous and logistic regression analysis when the outcome variable was categorical.

Results

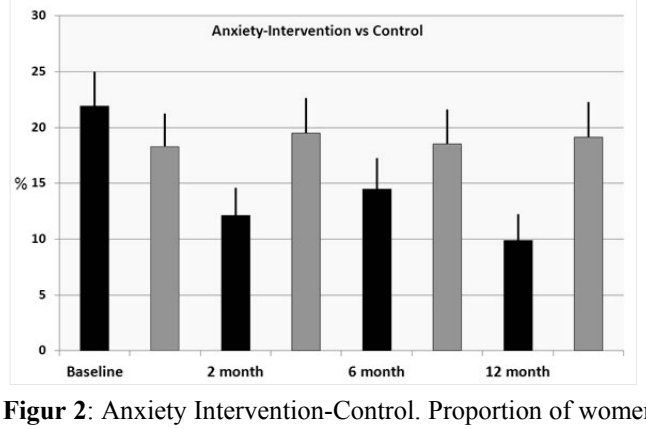
Paper I

Anxiety

At baseline, there were no statistically significant differences in anxiety scores between women who were allocated to the intervention and control groups, respectively. Twenty-two per cent in the intervention group had a high anxiety score, compared with 18 % in the control group (p=0.518). After 12 months, 10 % in the intervention group and 19% in the control group had a high anxiety score (p=0.055), see Figure 2.

In a multivariate generalized estimating equations (GEE) ordinal logistic regression model, (Table 2) there was an interaction between time and intervention. However, the interaction between time and intervention variables showed that the anxiety level in the intervention group decreased significantly ($p<0.001$) more than in the non-intervention group. The interpretation was, thus, that only intervention patients showed a statistically significant decreasing level of anxiety over time.

When we stratified the patients into those who had received chemotherapy and those who had not, there were no significant overall effects on decreasing anxiety over time in either of the groups, but, in both groups, there was a significant effect on decreasing anxiety levels more in the intervention group than in the non-intervention group.



Figur 2: Anxiety Intervention-Control. Proportion of women with anxiety level over 10 on the HAD scale at baseline, 2, 6 and 12 months after randomisation for patients in intervention (dark grey bars) and control groups (light grey bars)

Depression

At baseline, 7 % of the patients in the intervention group and 9 % in the control group had a high depression score (p=0.818). Compared with their baseline values, the proportion of women with high scores diminished slightly over time in the intervention group, whereas there was an increase in the proportion with high scores in the control group at 2 and 6 months, and thereafter a drop between 6 and 12 months. At 12 months, 5 % in the intervention group and 4 % in the control group had a high depression score (p=0.433), Figure 3.

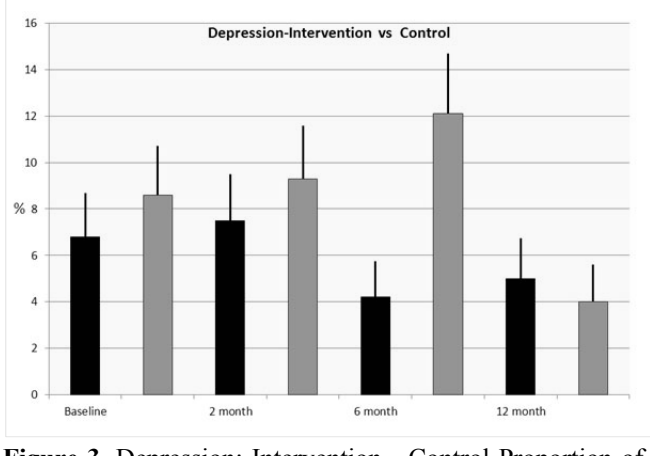


Figure 3. Depression: Intervention - Control Proportion of women with depression level over 10 points on the HAD scale at baseline, 2, 6 and 12 months after randomisation for patients in intervention (dark grey bars) and control groups (light grey bars).

From the multivariate generalized estimating equations ordinal logistic regression model, it was found that neither time, nor interaction between time and intervention or between time and chemotherapy had a significant impact on lowering the depression level over time (Table 2). Thus, the conclusion is that intervention had no statistically significant effect on decreasing the level of depression over time.

Table 2. Changes in anxiety and depression over time. Results from multivariate generalized estimating equations ordinal logistic regression model with three-level anxiety and depression response variables, adjusted for differences in baseline levels between intervention and chemotherapy groups. Odds ratios for being at a higher level.

		Full model		Final model	
Outcome	Predictor	OR (95% CI)	P value	OR (95% CI)	P value
Anxiety	Time	0.999 (0.975-1.024)	0.923	0.992 (0.972-1.013)	0.407
	Time × Intervention	0.944 (0.914-0.974)	<0.001	0.945 (0.914-0.975)	<0.001
	Time × Chemotherapy	0.984 (0.954-1.016)	0.307	Not in model	
Depression	Time	0.994 (0.966-1.023)	0.682	0.979 (0.960-0.999)	0.036
	Time × Intervention	0.990 (0.951-1.030)	0.610	Not in model	
	Time × Chemotherapy	0.976 (0.938-1.016)	0.235	Not in model	

Paper II

Quality of life

At baseline, there were no significant differences between intervention and control group, but the levels on the functional scales were lower and levels on symptomatic scales were higher (Table 3 and 4) when compared with data from healthy Swedish women (75).

In a mixed linear multivariable regression model, there was a statistically significant effect over time on the global health score ($p<0.05$), role functioning ($p<0.05$), emotional functioning ($p<0.05$) and social functioning ($p<0.05$) in both the intervention and control groups. There was also an effect over time on the symptom scales; fatigue ($p<0.05$), nausea and vomiting ($p<0.05$), insomnia ($p<0.05$) and financial difficulties ($p<0.05$). Similar time-dependent effects were seen on the breast scale (BR 23) on body image ($p<0.05$), sexual functioning, future perspective ($p<0.05$), systemic side effects and breast symptoms ($p<0.05$), but none of these differences were affected by intervention, only by time.

There were no significant effects of intervention (compared with controls) on health-related quality of life as measured by the EORTC QLQ 30 and BR 23, neither for the whole intervention group nor for the patients who had received chemotherapy and those who had not (Tables 3 and 4).

Table 3. EORTC QLQ-C30 mean scores from time of baseline in the intervention and control groups using a linear mixed model adjusted for marital status, number of children and level of education.

EORTC QLQ-C30		Time				
Outcome	Group	Baseline	2 months	6 months	12 months	P-value
QLQ2	Intervention	62.6	66.3	67.5	69.7	
	Control	60.2	65.0	63.0	64.6	0.6442
PF	Intervention	76.5	79.1	80.2	76.5	
	Control	76.5	78.3	77.8	77.9	0.7580
RF	Intervention	70.5	77.3	79.6	80.1	
	Control	68.7	80.4	76.8	76.2	0.4949
EF	Intervention	66.8	71.8	74.4	77.3	
	Control	68.0	73.9	71.5	74.4	0.3538
CF	Intervention	72.7	73.6	75.1	75.6	
	Control	75.2	77.0	78.1	76.1	0.8727
SF	Intervention	74.3	81.4	81.4	83.2	
	Control	73.3	83.5	82.2	83.4	0.8654
FA	Intervention	42.1	33.4	31.9	30.2	
	Control	42.7	34.3	34.7	32.9	0.9066
NV	Intervention	7.9	5.7	3.9	4.0	
	Control	6.7	4.1	5.8	4.1	0.2018
PA	Intervention	30.1	24.9	25.8	22.3	
	Control	30.5	22.8	26.4	27.2	0.4541
DY	Intervention	28.0	25.8	28.0	24.5	
	Control	30.4	26.3	26.9	26.4	0.8196
SL	Intervention	40.8	38.0	33.8	29.7	
	Control	41.4	37.6	39.1	35.2	0.5454
AP	Intervention	10.3	7.7	7.6	6.0	
	Control	11.1	7.1	9.6	7.1	0.8282
CO	Intervention	9.8	10.2	8.0	6.6	
	Control	11.1	7.6	9.5	8.4	0.4450
DI	Intervention	10.9	7.2	9.0	9.1	
	Control	9.9	7.5	9.7	10.1	0.8997
FI	Intervention	19.5	18.8	18.9	14.7	
	Control	22.7	14.5	17.1	13.7	0.1631

QLQ2=Global health status, PF=Physical functioning, RF=Role functioning, EF=Emotional functioning, CF=Cognitive functioning, SF=Social functioning, FA=Fatigue, NV=Nausea and vomiting, PA=Pain, DY=Dyspnoea, SL=Insomnia, AP=Loss of appetite, CO=Constipation, DI=Diarrhoea, FI=Financial impact

Table 4. EORTC BR23 mean scores from baseline in the intervention and control groups, using a linear mixed- model adjusted for marital status, number of children and level of education.

EORTC QLQ-BR23		Time				
Outcome	Group	Baseline	2 month	6 months	12 months	P-value
BRBI	Intervention	70.1	79.4	80.3	81.2	
	Control	69.1	77.5	77.3	78.1	0.9467
BRSEF	Intervention	21.1	24.0	26.1	27.7	
	Control	18.1	18.5	21.8	23.2	0.9226
BRSEE	Intervention	60.3	61.0	60.5	57.7	
	Control	58.6	58.7	61.7	59.5	0.8746
BRFU	Intervention	50.9	55.5	61.9	64.7	
	Control	49.6	56.9	55.6	60.2	0.3183
BRST	Intervention	23.1	20.1	17.8	18.4	
	Control	23.9	21.5	22.2	20.7	0.4744
BRBS	Intervention	34.9	26.4	22.8	16.6	
	Control	34.4	23.4	23.1	19.1	0.4087
BRAS	Intervention	19.0	25.4	23.3	20.5	
	Control	23.4	22.1	24.6	23.6	0.1245
BRHL	Intervention	44.0	32.3	27.6	35.3	
	Control	51.2	14.7	45.1	36.7	0.1176

BRBI=Body image, BREF=Sexual functioning, BREE=Sexual enjoyment, BRFU=Future perspective, BRST=Systemic therapy side-effects, BRBS=Breast symptoms, BRAS= Arm symptoms, BRHL=Upset by hair loss

Fatigue

At baseline, there were no statistically significant differences between the intervention and control groups, either with regard to mental or physical fatigue. In the intervention group, the medium level of mental fatigue was 5.6 and 5.4 in the control group. The median level of physical fatigue was 11.1 in the intervention group and 11.0 in the control group. This is a much higher value than in a healthy population (72). There was a decrease in fatigue between baseline and 2 months both in the intervention and control groups and the fatigue score continued to improve over time up to 12 months in both groups but the differences between the groups were not statistically significant (Figure 4).

Patients who had received chemotherapy scored higher on both mental and physical fatigue both in the intervention and control groups, but there were no statistically significant differences between the intervention and control groups at any point in time.

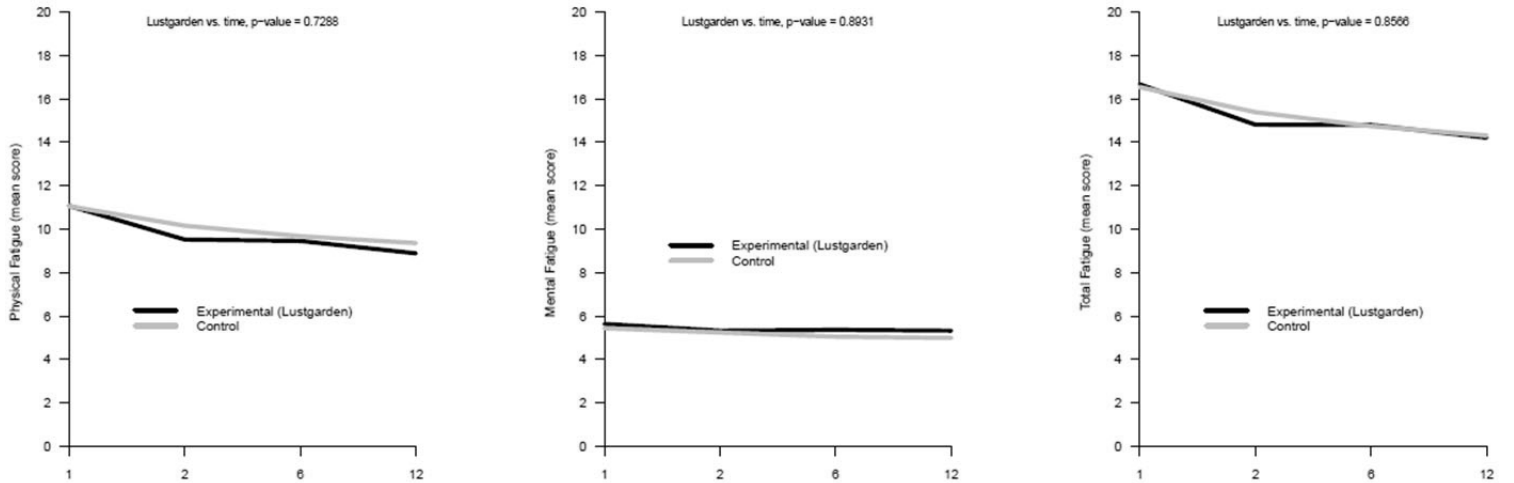


Figure 4 Fatigue measured by the Norwegian version of the fatigue scale.
Intervention/controls vs. time
Intervention =dark grey, Control= light grey
First figure: Physical fatigue, Second figure: Mental fatigue, Third figure: Total fatigue

Paper III

Response rate was 92% at baseline, 88% at 2 months, 84% at 6 months and 81% at 12 months se flow chart (Figure 1).

Sick leave

At baseline, 63.4% in the intervention and 60.2% in the control group were of working age, if early disability was excluded (p=0.528).

At baseline (time of randomization), 64.5 % in the intervention group and 63.7% in the control group were on sick leave (p=0.901). After 2, 6 and 12 months, 44.3 and 45.7 (p=0.853), 36.2 and 32.6 (p=0.599), 27.1 and 25.3 (p=0.783) per cent were on sick leave in the intervention and the control groups, respectively. The differences between the groups were not statistically significant (Figure 5).

At baseline, women treated with chemotherapy in the intervention group had, on average, been on sick leave for 241 days during the previous 12 months compared with 234 in the control group. The accumulated sick leave for the previous 12-month period increased slightly in both the intervention and control group until the 2 month cut-off, but, thereafter, the proportion of women on sick leave decreased up to the 12-month follow-up in both groups. The differences between the groups were not statistically significant (Table 5).

Women not treated with chemotherapy in the intervention group, had on average only been on sick leave for 84 days compared with 86 days during the previous 12 months in the control group. This increased slightly in the intervention group up to the 6- month follow-up. In the control group, there was a decrease at 2 months and an increase at 6 months but a significant decrease in both groups up to 12 months. There was no significant difference between the groups at any point in time (Table 5).

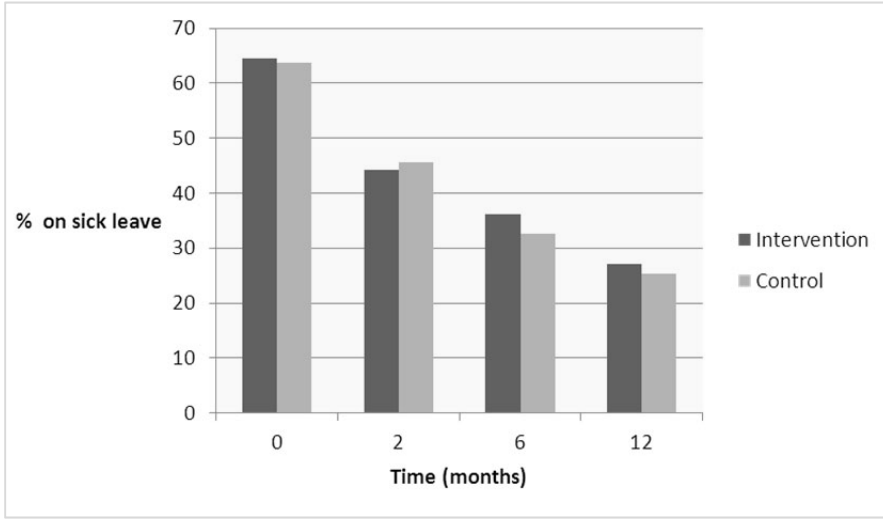


Figure 5. Proportion of women of working-age on sick leave, at baseline, 2, 6 and 12 months post intervention. Women with retirement pension, disability pension and women with temporary disability are excluded.

Table 5. Sick leave: Mean days on sick leave during the last 12 months following randomization in women of working age. Retirees, early retirees or women with unpaid work are excluded. Comparison between intervention and control groups, Patients are stratified according to treatment with chemotherapy.

		Sick leave						
		Intervention			Control			M-W
	Time	n=	Mean(days)	sd	n=	Mean(days)	sd	p value
Chemo-therapy	0 Month	57	241.4	±88.1	56	233.8	±82.3	0.401
	2 Months	58	246.6	±97.7	50	252.8	±98.7	0.646
	6 Months	56	240.5	±125.6	46	208.7	±119.3	0.164
	12 Months	48	154.8	±153,4	45	123.3	±148.8	0.319
Not Chemo-therapy	0 Month	51	84.5	±91.4	44	85.8	±75.5	0.539
	2 Months	48	86.2	±85.4	40	79.1	±81.2	0.949
	6 Months	49	93.4	±108.4	38	89.9	±99.7	0.959
	12 Months	45	49.0	100.8	40	40.0	±87.7	0.399

Health care utilization

There was no statistically significant difference between the groups regarding the number of visits to medical specialists, general practitioners or physiotherapists at any time after the intervention period. There was no significant difference between the groups regarding contacts with other health care providers (e.g. chiropractors, naprapaths and masseurs) at baseline or at 2 months. Of those treated with chemotherapy, women in the intervention group consulted other health care providers more often than women in the control group after six and 12 months ($p=0.006$ and $p=0.015$, respectively) (Table 6).

Health economics

The total costs for sick leave and consumption of health services at each follow-up during the study period decreased in both the intervention and control group from baseline to the 12- month follow-up. The total costs for the intervention group were higher at all points in time and the differences between the groups reached statistical significance after 12 months (Mann-Whitney $p=0.036$) (Table 7) (Figure 6)

Table 6. Health care utilization: Average number of visits to general practitioners, hospital specialist physiotherapists and other health care providers for the 12 months following randomization. Intervention group vs. control group at baseline, 2, 6 and 12 months after randomization. Patients are stratified according to treatment.

			Healthcare utilization						
			Intervention			Control			M-W
			n=	Mean	sd	n=	Mean	sd	p value
Chemotherapy	0 Month	Gen.prac	71	0,9859	±1,57201	70	1,2857	±2,27872	0,904
		Specialist	66	4,8333	±4,8185	66	4,8636	±4,84811	0,94
		Physiother.	74	1,027	±2,4605	64	1,0938	±2,64106	0,862
		Other	63	1,9524	±2,52362	59	1,4746	±2,47996	0,331
	2 Months	Gen.prac	72	1,1806	±1,99525	62	1,1613	±2,36916	0,497
		Specialist	66	4,576	±4,671	64	3,531	±4,125	0,173
		Physiother.	70	1,3571	±2,67048	60	2,1333	±4,05248	0,738
		Other	70	0,6286	±2,11394	62	0,5	±1,81749	0,459
	6 Months	Gen.prac	69	1,5797	±2,71383	64	1,1719	±1,93181	0,799
		Specialist	71	2,916	±3,652	61	2,279	±3,204	0,233
		Physiother.	68	2,3235	±3,94908	65	2,1538	±3,70064	0,71
		Other	71	1,2254	±2,88938	61	0,1639	±0,82017	**0,006**
	12 Months	Gen.prac	66	1,4394	±2,30136	61	1,1311	±1,727	0,603
		Specialist	63	1,952	±2,524	59	1,475	±2,48	0,079
		Physiother.	65	2,6154	±4,09532	60	2,0333	±3,77308	0,402
		Other	64	1,2969	±3,09982	56	0,25	±1,49241	**0,015**
Not Chemotherapy	0 Month	Gen.prac	98	1,051	±2,13644	89	1,0112	±1,99713	0,986
		Specialist	90	2,4778	±3,20543	87	1,7586	±2,91733	0,051
		Physiother.	96	0,6771	±2,36863	93	1,0645	±2,72989	0,128
		Other	89	0,7978	±1,31581	81	0,8148	±1,60555	0,828
	2 Months	Gen.prac	94	0,8191	±1,30312	84	1,0238	±1,94488	0,672
		Specialist	92	2,0543	±2,694	80	1,725	±2,882	0,125
		Physiother.	96	0,5521	±1,86305	88	0,8182	±2,41901	0,987
		Other	92	0,1957	±1,18821	86	0,2674	±1,39262	0,633
	6 Months	Gen.prac	91	1	±1,63299	85	1,4706	±2,50518	0,559
		Specialist	93	1,882	±2,734	81	1,617	±2,634	0,506
		Physiother.	92	1,1522	±3,0162	81	1,0988	±2,80002	0,893
		Other	89	0,4045	±1,62172	77	0,1818	±1,02247	0,28
	12 Months	Gen.prac.	89	0,8764	±1,67074	82	1,122	±2,28463	0,883
		Specialist.	89	0,798	±1,316	81	0,815	±1,605	0,542
		Physiother.	93	1,086	±2,90672	84	0,9524	±2,55496	0,902
		Other	93	0,3011	±1,63378	80	0,25	±1,2376	0,701

Table 7. Total cost of sick leave and health care utilization (SEK) for the 12 months following randomization. Intervention group compared with control group.

	Intervention		**Control**		
Time	n	Mean±SD	n	Mean±SD	P-value†
0 month	143	86511.1±83014.0	141	78071.5±82415.9	0.172
2 months	146	85748.5±86165.8	130	80861.1±89899.4	0.407
6 months	148	78075.2±90088.7	128	67639.0±80454.3	0.240
12 months	141	49450.7±83196.7	132	38074.0.±72259.0	**0.036**
Difference 0-12 months	112	33098.8±74681.1	114	41231.1±64549.2	0.222

† P-values from Mann-Whitney test

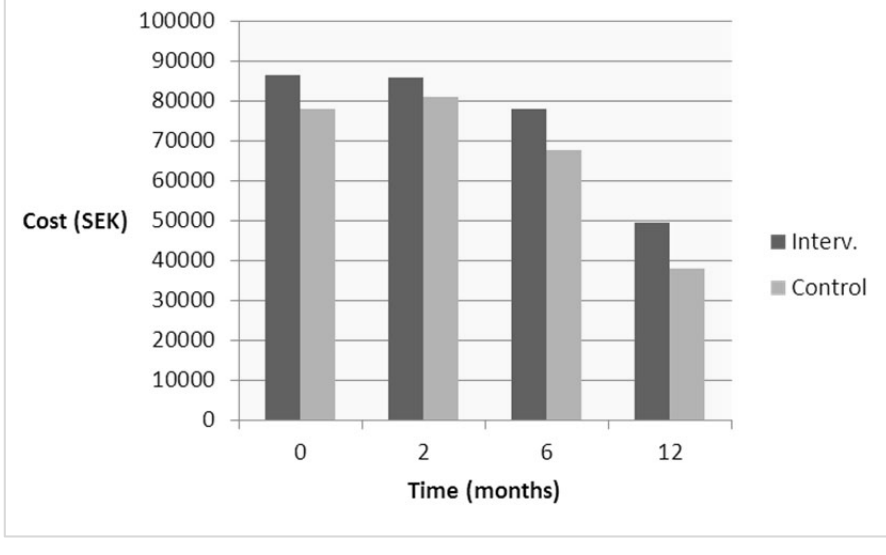


Figure 6. Total cost of sick leave and health care utilization (SEK) for the 12 months following randomization for the whole study population. Cost of intervention not included.

When the cost of the intervention was included in the calculation, there was a statistically significantly higher total cost for the intervention group compared with the control ($p<0.001$) after 12 months for both patients treated with chemotherapy and the group who did not receive chemotherapy

Paper IV

Long-term results

Of the 382 women included in the study at baseline, 39 (10.2%) had died, 22 (11.5%) in the intervention group and 17 (8.9%) in the control group ($p=0.398$). Furthermore, 12 (3.5%) of those women still being alive, 7 (4.1%) in the intervention group and 5 (2.9%) in the control group ($p=0.523$), were assessed to be in too poor health to be able to fill in the questionnaires. The questionnaires were thus sent to 331 (86.6%) of the 382 participants included at baseline; 261 (78.9%) of these responded. The response rate was significantly higher ($p=0.026$) in the intervention group (n=136, 84.0%) than in the control group (n=125, 74.0%) (Figure1).
The mean (SD) time of follow-up was 6.54 (1.58) years for the intervention group and 6.52 (1.68) years for the control group ($p=0.970$).

Anxiety

In the intervention group, 11.9 % of women had high HAD-anxiety scores compared with 14.4% in the control group (p=0.558). After adjusting for baseline anxiety level, chemotherapy treatment, age, marriage status, education level and having children at home in a multivariate binary logistic regression model, the difference between the groups was still not statistically significant (p=0.385). There was an improvement in both groups from baseline and also an improvement in the control group from the 12-month follow-up. However, there was impairment in the intervention group since the 12-month follow-up (Figure 7). Neither of these changes was statistically significant. In the stratified groups, there was no statistically significant effect of the intervention in any of the groups.

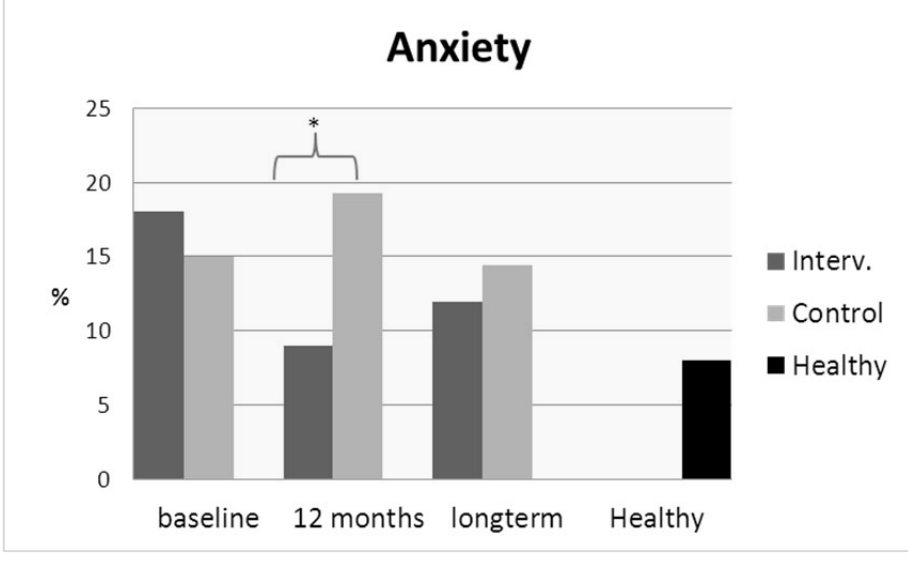


Figure 7. Proportion of women with high anxiety scores at baseline, 12 months and long-term follow-up. Intervention group (dark grey bars) and control group (light grey bars) compared with a healthy Swedish population (black bar)

Depression

In the intervention group, 5.2 % had high depression scores compared with 5.7 % in the control group (p=0.857). After adjusting for baseline depression level, chemotherapy treatment, age, marriage status, education level and having children at home, in a multivariate binary logistic regression model, the difference between the groups was not statistically significant (p=0.700). There was an improvement in the control group from baseline, but somewhat poorer since the 12 month follow-up. In the intervention group there had been impairment from both baseline and the 12 month follow-up. Neither of these changes were statistically significant. In the stratified groups, there was no statistically significant effect of the intervention in any of the groups.

Fatigue

The level of fatigue in the intervention and control groups decreased significantly over time. Women in the intervention group had a mean score of 7.7 for physical fatigue, 4.6 for mental fatigue and 12.2 for total fatigue, at the long-term follow-up and these were statistically significant improvements when compared with baseline values. In the control group, mean scores for physical fatigue at the long- term follow-up was 8.9, mental fatigue 5.2 and total fatigue 14. 0. These were also improvements compared with the baseline values. Even if the improvement in fatigue was larger in the intervention group, the difference in improvement did not attain statistical significance in the univariate analysis (p=0.081 for physical, p=0.119 for mental fatigue and 0.067 for total fatigue) (Table 9). After adjustment for baseline levels of fatigue, chemotherapy treatment, age, marriage status, education level and having children at home in a multivariate regression model there was a significant effect of the intervention on physical fatigue (p=0.017), mental fatigue (p=0.019) and total fatigue (p=0.009). The largest effect was seen in women treated with chemotherapy. (Table 8)

Table 8. Mean value of fatigue measured by the Norwegian version of the fatigue scale at baseline and long-term follow-up and change from baseline to long-term follow-up within the groups and comparison between intervention and control groups. P-values are from Wilcoxon's signed rank test for comparison between baseline and long- term follow-up within the intervention and control groups, respectively, and from Mann-Whitney's *U*-test for comparisons between the intervention and control groups.

	Intervention				**Control**				
	Baseline	Follow-up	Change	P-value[a]	Baseline	Follow-up	Change	P-value[a]	P-value[b]
	Mean (SD)	Mean (SD)	Mean (SD)	Within group	Mean (SD)	Mean (SD)	Mean (SD)	Within group	Between groups
Fatigue									
Physical	10.6 (4.2)	7.7 (3.2)	-3.0 (4.2)	**<0.001**	10.8 (4.0)	8.9 (4.2)	-2.0 (4.6)	**<0.001**	0.081
Mental	5.4 (2.4)	4.6 (1.8)	-0.9 (2.2)	**<0.001**	5.5 (2.1)	5.2 (2.2)	-0.4 (2.3)	**0.053**	0.119
Total	16.1 (6.1)	12.2 (4.3)	3.9 (5.8)	**<0.001**	16.4 (5.6)	14.0 (5. 9)	2.4 (6.0)	**<0.001**	0.067

[a]P-value for test of difference between baseline and follow-up within intervention and control groups, respectively.
[b]P-value for test of difference in change from baseline to follow-up between intervention and control groups.

Health-related quality of life

For the EORTC QLQ-C30 instrument, there was a statistically significant improvement from baseline within both the intervention and the control groups, mostly as regards function and the symptom scales. There was also a statistically significant improvement within both the intervention and control groups on the EORTC QLQ-BR23 scales body image, future perspective, systemic therapy and breast symptoms. However, cognitive function (p=0.002) and pain (p=0.049) improved significantly only in the intervention group while hair-loss reached statistical significance only in the control group (p=0.034). Comparing the values at baseline with the long-term follow-up, there was a statistically significantly greater improvement in the intervention group as regards emotional function (p=0.042), cognitive function (p=0.049) fatigue (p= 0.023), body image (p=0.025), future perspective (p=0.019) and breast symptoms (p= 0.029) (Table 9).

After adjustment for baseline QLQ levels, chemotherapy treatment, age, marriage status, education level and having children at home in a multivariate linear regression model a statistically significant effect of the intervention on cognitive function (p=0.042), body image (p=0.019) and future perspective (p=0.003) (Table 10) was demonstrated, but not on emotional function, fatigue and breast symptoms, as measured by EORTC QLQ 30. In the stratified groups, there was also a statistically significant effect of the intervention on global health status (p=0.044), fatigue (p=0.003), and upset by hair loss (p=0.021) in women treated with chemotherapy.

Table 9. Health- related quality of life measured by EORTC QLQ 30 and BR 23: Mean scores at baseline and follow-up and mean changes within the groups from baseline to follow-up.and comparison between the intervention and control groups

		Intervention				Control				
		Mean value			p value change within the group	Mean value			p value change within the group	p value change between the groups
		Baseline (SD)	follow-up (SD)	mean (SD) change		Baseline (SD)	follow-up(SD)	Mean (SD) change		
EORTC-QLQ30	Global health status†	68.4(18.7)	75.0(21.7)	6.6(21.3)	**<0.001**	66.4(22.8)	70.4(24.2)	4.0(25.3)	**0.032**	0.459
	Physical function†	79.0(18.6)	78.8(22.1)	-0.2(17.6)	0.684	80.6(19.3)	78.5(21.8)	-2.1(19.6)	0.407	0.463
	Role function†	74.2(30.9)	84.1(26.5)	9.9(31.7)	**0.001**	72.4(33.6)	80.6(27.8)	8.2(36.0)	**0.020**	0.656
	Emotional function†	71.4(21.5)	81.2(21.2)	9.8(19.1)	**<0.001**	72.9(25.0)	77.5(22.7)	4.7(22.4)	**0.031**	**0.042**
	Cognitive function†	78.5(22.0)	84.4(18.5)	5.9(20.0)	**0.002**	81.4(21.6)	81.4(22.0)	0.0(22.2)	0.976	**0.049**
	Social function†	77.3(24.4)	88.3(20.7)	11.0(23.0)	**<0.001**	77.2(26.8)	84.3(25.5)	7.1(27.1)	**0.002**	0.242
	Fatigue‡	37.8(25.1)	24.7(23.8)	-13.0(24.6)	**<0.001**	36.2(24.5)	29.7(25.7)	-6.5(24.5)	**0.003**	**0.023**
	Nausea/Vomiting‡	6.4(15.2)	5.2(14.0)	-1.2(18.5)	0.433	4.5(11.8)	4.2(10.9)	-0.3(15.0)	0.785	0.459
	Pain‡	27.9(28.9)	24.1(28.7)	-3.8(25.7)	**0.049**	25.8(27.8)	26.5(29.3)	0.7(32.4).	0.795	0.410
	Dyspnoea‡	23.0(25.4)	19.1(24.6)	-3.9(28.9)	0.127	25.5(26.6)	23.5(27.6)	-2.0(30.0)	0.490	0.525
	Insomnia‡	39.8(34.0)	33.8(30.2)	-6.0(30.0)	**0.026**	37.2(33.7)	30.0(30.2)	-7.3(34.2)	**0.027**	0.970
	Appetite loss‡	7.8(18.0)	6.2(18.6)	-1.6(20.0)	0.423	8.5(17.0)	8.8(19.7)	0.3(22.4)	0.939	0.788
	Constipation‡	8.6(19.7)	9.9(21.5)	1.3(20.7)	0.429	10.6(23.7)	8.4(19.5)	-2.2(25.2)	0.273	0.202
	Diarrhoea‡	7.6(16.9)	6.2(15.6)	-1.3(21.2)	0.492	7.0(18.4)	8.2(18.4)	1.1(16.3)	0.448	0.315
	Financial problems‡	12.8(21.5)	8.0(20.5)	-4.8(23.8)	**0.031**	15.7(26.8)	7.4(20.6)	-8.3(29.0)	**0.003**	0.745
BR-23	Body image†	71.4(29.7)	86.0(23.9)	14.6(23.8)	**<0.001**	72..0(27.8)	80.3(26.2)	8.3(25.7)	**<0.001**	**0.025**
	Sexual functioning†	24.2(23.9)	22.0(22.4)	-2.2(22.7)	0.201	19.9(23.0)	18.7(22.1)	-1.0(22.0)	0.716	0.745
	Sexual enjoyment†	64.4(25.3)	65.2(28.7)	0.8(33.3)	0.933	67.7(26.5)	66.6(24.3)	-1.1 (25.1)	0.808	0.607
	Future perspective†	52.6(28.7)	70.4(26.4)	17.7(25.9)	**<0.001**	54.0(31.7)	62.4(27.8)	8.5(31.5)	**0.003**	**0.019**
	Systemic therapy‡	21.0(15.5)	15.6(13.1)	-5.4(12.5)	**<0.001**	21.5(17.8)	18.8(16.0)	-2.7(17.0)	**0.027**	0.146
	Breast symptoms‡	33.0(22.9)	10.3(13.6)	-22.6(23.0)	**<0.001**	29.6(23.3)	12.8(16.5)	-16.8(21.8)	**<0.001**	**0.029**
	Arm symptoms‡	15.4(18.4)	14.7(21.3)	-1.0(19.1)	0.581	19.0(23.0)	17.1(23.1)	-2.0(21.7)	0.260	0.573
	Hair loss‡	7.7(23.2)	6.7(20..3)	-1.1(29.6)	0.676	5.2(19.5)	11.0(26.3)	5.7(28.2)	**0.034**	0.236

† Higher is better; ‡ Lower is better.

Table 10. Health- related quality of life measured by EORTC QLQ 30 and BR 23 in a linear regression model; Effect of intervention adjusted for treatment with chemotherapy age, marriage, education and children at home.

	Domain	Slope (95%CI)		p value	R^2
EORTC-QLQ30	Global health status†	2.842	(-2.163-7.847)	0.264	0.489
	Physical function†	0.550	(-3.516-4.615)	0.790	0.206
	Role function†	1.835	(-4.463-8.133)	0.567	0.373
	Emotional function†	3.894	(-0.631-8.420)	0.091	0.272
	Cognitive function†	4.698	(-0.182-9.214)	**0.042**	0.271
	Social function†	3.315	(-1.847-8.477)	0.207	0.330
	Fatigue‡	-5.220	(-10.471-0.031)	0.051	0.059
	Nausea‡/Vomiting	0.961	(-2.216-4.137)	0.552	0.270
	Pain‡	-2.181	(-8.572-4.209	0.502	0.181
	Dyspnoea‡	-2.926	(-9.108-3.256)	0.352	0.310
	Insomnia‡	2.551	(-3.947-9.049)	0.440	0.174
	Appetite loss‡	-2.121	(-6.643-2.401)	0.356	0.203
	Constipation‡	2.438	(-2.320-7.197)	0.314	0.181
	Diarrhoea‡	-1.711	(-5.727-2.304)	0.402	0.112
	Financial problems‡	1.829	(-3.263-6.921)	0.480	0.373
BR-23	Body image†	6.6.233	(1.016-11.430)	**0.019**	0.329
	Sexual functioning†	0.672	(-4.165-5.509)	0.784	0.201
	Sexual enjoyment†	1.472	(-10.331-13.276)	0.804	0.296
	Future perspective†	9.080	(3.089-15.071)	**0.003**	0.372
	Systemic therapy‡	-2.828	(-5.820-0.164)	0.064	0.147
	Breast symptoms‡	-3.207	(-6.861-0.448)	0.085	0.327
	Arm symptoms‡	0.132	(-4.648-4.913)	0.957	0.045
	Hair loss‡	-4.562	(-10.623-1.499)	0.139	0.045

† Higher is better; ‡ Lower is better.

Discussion

The scientific interest in, and the idea that intervention would improve quality of life and prolong survival was, for many, probably created by the study in 1989 when Spiegel et al (56) published what would be a landmark in studies on supportive care. They found an effect of support group intervention in women with metastatic breast cancer on survival. This study formed the basis for many studies conducted to prove the usefulness of different types of interventions. However, when they tried to replicate their own study in 2007 (76), they could not find any significant effect of support group intervention on survival. This has turned out to be a problem with other studies. Therefore, there is a need for further controlled randomized studies on different aspects of intervention programmes.

In this thesis, four papers are presented, aimed at describing the effect of a support group intervention in several dimensions. We have in a randomized controlled trial of women treated for a primary breast cancer studied the effect of a support group intervention on anxiety, depression, fatigue, HRQoL, sick leave, health-care consumption and the economic gain of it, with a long-term follow-up. We studied the effect of a pre-existing comprehensive concept for rehabilitation containing different methods of intervention developed by the initiators and professionals in collaboration with the patients according to patient wishes and needs.

In paper I, we could show an effect in the short-term follow-up of the intervention on anxiety but not on depression. However, this effect did not remain in the long-term follow-up (paper IV). Even if the reductions in anxiety levels were small, they might be of importance for the individual patient. The low initial level of depression, which was comparable to healthy women, may have contributed to the lack of any association between social support and intervention. Our results in paper I, were in line with a meta-analysis by Sheard and Maguire (77), in which they separately analyzed the effect of psychosocial interventions on anxiety and depression among cancer patients. They included 19 studies measuring anxiety and 20 measuring depression and found a clinically significant effect on anxiety but not on depression. This has also been confirmed in later studies (78, 79) . However, in a later review by Fors (49) et al only limited documentation was found on the efficacy of psychosocial rehabilitation which was supported by

Boesen (80), who could not find any statistically significant effect of the intervention on any of the psychosocial parameters. However, Fors found promising results after CBT. Decreased levels of depression and anxiety were found and an improved HRQoL. However, they emphasized the importance of extended treatment length, weekly admissions for 6-12 weeks.

In paper II, we found no statistically significant effect of the intervention on fatigue or health-related quality of life in the short perspective. However, in paper IV with the extended follow-up, we could show a significant effect after long-term follow-up on physical, mental and total fatigue. In paper IV we could also, when comparing the baseline values with the long-term values and after adjustment for chemotherapy age, marriage, education and children at home, demonstrate a statistically significant greater improvement in the intervention group as regards cognitive function, body image and future perspective. Since a significant part of the effects on fatigue was achieved in the chemotherapy treated group, a possible explanation might be that the treatment-related fatigue dominated during the first 12 months and therefore possible benefits from the intervention were not detectable. Coping and relaxation strategies might have had a more discernible effect when the treatment-related fatigue faded out.

The effect on body image and future perspective may also be a late effect of the intervention and of late recovery but we cannot exclude the possibility that chance may have played a role. However, studies have shown that symptoms may persist even if HRQoL improves (81), indicating that HRQoL is influenced by more than symptoms alone (82).
Our intervention was, with few exceptions, only psycho-educational with little or no physical activity, which means that you could not expect any effect on the physical parameters. In contrast Fillion (83) et al showed in an RTC that intervention that combines stress management, psycho-education, and physical activity resulted in an improvement in fatigue, energy levels, emotional distress at the 3-month follow-up, and physical HRQoL at post-intervention.

The treatment of breast cancer patients in Sweden today can be considered good, with a lot of emphasis put into psychosocial support in the primary handling of the patients. Therefore, the addition of a brief extra support intervention might not be expected to provide any great effect. Mandelblatt (84) et al found that the process of care and not the therapy itself, seems to be the most important determinant of long term HRQoL in a study which, however, only included women aged more than 65 years.
In paper III we studied the effect of the intervention on sick leave, health care utilization and the effect of the intervention in economic terms. Here we could show a trend towards longer sick leave and more health care

utilization in the intervention group. However, the differences between the groups were not statistically significant except for other care providers. The finding that women treated for breast cancer have more health care utilization has also been shown in two previous studies (85, 86).

Women in the intervention group had significantly more contacts with other care providers after 6 and 12 months. This is contrary to the results of Simpson et al (87) who found a 23.5 % cost reduction after psycho-social intervention, but they only studied the effect of the intervention on the cost of health-care consumption, whereas we also included contacts with therapists outside the formal health-care sphere.

The content of the intervention might have been suboptimal to demonstrate any direct impact on sick leave and health care consumption. There exist only a few previous studies for comparison, since psychosocial intervention studies rarely measured sick leave or had RTW as an outcome (88). A recently published Cochrane review demonstrated low quality evidence for psychological interventions on return to work rates and a moderate quality evidence for multidisciplinary interventions involving physical, psychological and vocational components (89). Another important aspect may be that the intervention actually influenced the patients' thoughts and feelings and created a need for sick leave to handle and cope with their anxiety. This was also discussed in an article by Damjaer (90) et al where they studied early retirement after breast cancer. During the intervention, many women had the opportunity to focus on themselves for the first time in their life and not take care of family and relatives. This may have led to a change of priorities in favour of a longer sick leave (91). The study participants had, during the intervention, received an opportunity to try different methods of alleviating symptoms, such as massage, relaxation and qigong. This may have contributed to that, women in the intervention group searched for other health care providers such as massage therapists.

Bouknight (58) showed that work-place adjustments played an important role in breast cancer patients' return to work, which has also been shown by Pryce (92) in a study of patients with different cancer diagnoses. Perhaps this is a better way forward, having a multimodal approach and working closely with employers, when planning for patients' return to work. Previous studies have put forward the idea that interventions to help patients return to work should be individually tailored and conducted in close co-operation with occupational health experts and employers (93, 94). Studies on this are on-going and the results are awaited.

General Discussion

Cancer patients and especially women affected by breast cancer, their reactions, both physical and mental after the diagnosis and treatment have been described in a variety of papers. There is also a large amount of work published on different types of interventions made to improve various symptoms such as distress, anxiety, depression and fatigue, and to improve quality of life.

Proposed effects

In previous studies, educational programme appeared to be sufficient (53) but, in recent years, CBT seems to be the most promising (49). After a hot discussion (95-97) in Annals of Behavioral Medicine with criticism on a review of reviewers (98), it was concluded by Manne et al (99) that CB interventions have shown sufficient evidence of treatment efficacy for cancer patients. This was supported by Fors (49) et al, who found that patients might have HRQoL benefits from CBT performed after primary breast cancer. Manne also concluded that there may be sub-groups of patients who may respond more favorably to psychological interventions. Trying to find effects of intervention in a large unselected group of patients might therefore not be successful. It is possible that future studies should be directed towards defining subgroups, where the greatest chance of benefit could be identified.

In our study, we did not evaluate the effect of each part of the programme and this will probably affect the reproducibility of the intervention. The intervention programme in our study was based on one week of intensive training and education, followed by a 4-day follow-up 2 months later. The knowledge, when we planned our study, advocated most in favour of a short-term treatment (52). This might not be the optimal design according to the results from the meta-analysis by Rehse and Pukrop (45). They identified 37 controlled trials, not all randomized, showing a positive effect from psychosocial interventions on HRQoL in adult cancer patients. However, the patient population was a mixture of men and women, with different diagnoses. Interventions with a duration of more than 12 weeks were significantly more effective than interventions of shorter duration. This has also been supported by Fors et al (49). However, regardless of intervention,

there are always factors that influence outcome and that cannot be properly controlled. Helle Ploug Hansen and co-workers stressed in a recent study that the effects of a support intervention, as measured by quantitative questionnaires cannot be properly interpreted without taking into account parameters such as human interaction, the organization or the staff, i.e. parameters not formalized in the intervention program (100)

Moreover, the relationship between the patient and the health-care provider is in itself most influential (101)

In Sweden, Swedish Council on Health Technology Assessment (SBU) a research group led by professor Jan-Otto Ottosson, studied different psyotherapeutic methods and the relative effect of the ”therapeutic alliance” between the therapist and the patient, including factors such as active participation, consideration, interest and respect, i.e. a warm and reliable relation. He concluded the findings in the following way:

”A recurrent finding is that the therapeutic alliance is of significance in different therapy forms. The (therapeutic) alliance seems to be the single factor with the greatest impact among common and unspecific factors, regardless of whether the therapist has a psycho-dynamic, existential, client-centered, behavioral or cognitive approach.”(102)

The medical community is divided, according to Carlsson and Hamrin, into “believers” and “non-believers” with respect to whether or not psychosocial factors influence breast cancer outcomes (103). No convincing results have been published in recent years in terms of survival benefits. Previous studies suggested that support intervention would prolong survival, whereas recent studies have not confirmed this (104). Smedslund (105) in a meta-analysis of psychosocial interventions on survival time in patients with different tumour diagnoses, half of which were on breast cancer, concluded that “a definitive conclusion about whether psychosocial interventions prolong cancer survival seems premature “. In our study, we could not demonstrate any difference in survival between the intervention and control groups, but the follow-up was, particularly in the case of breast cancer in all probability too short (mean 6.5 years) (Figure 8)

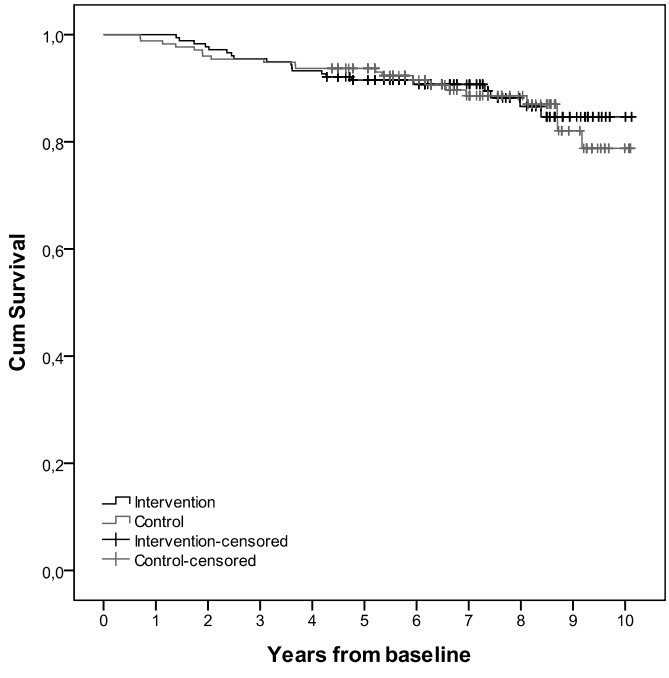


Figure 8. Kaplan-Meier curves for cumulative survival in the intervention and control groups from baseline until 23 May 2012. P-value = 0.848 for log-rank test of difference between intervention and control group.

Metastatic disease

It has been proposed that there is a survival effect of intervention on women with metastatic disease, first mentioned by Spiegel (56). However, they could not reproduce their own results in a later study (76). Goodwin also tried to reproduce this, but found that supportive-expressive group therapy did not prolong survival in women with metastatic breast cancer (106). In a Cochrane review published in 2008 (107), it was concluded that "There is insufficient evidence to advocate that group psychological therapies (either cognitive behavioral or supportive-expressive) should be made available to all women diagnosed with metastatic breast cancer. Any benefits of the interventions are only evident for some of the psychological outcomes and in the short term. The possibility of the interventions causing harm is not ruled out by the available data".

The content of support intervention

Most interventions have focused on the four first-mentioned forms of support in the Cunningham classification, whereas spiritual and/or existential therapies have almost never been applied. This is unfortunate, since a cancer diagnosis often is a trigger of a profound existential crisis, i.e. an inevitable crisis which occurs when the defences used to forestall existential anxiety are breached, allowing one to become truly aware of one´s basic situation in life (101). The basic existential challenges that are activated in such a crisis are issues about death and death anxiety, meaning and meaninglessness and man´s existential isolation. The existential core conflict that is activated by a potentially letal disease is the awareness of the inevitability of death and the wish to continue to be. Another substantial conflict is about how to create true meaning, when life is threatened: What is the real meaning and what are the real values of life? How should I live the rest of my life, now when I know that death is a possibility? A third existential conflict arises between a sudden reminder and awareness (by the cancer diagnosis) that every person is basically alone and the accentuated wish for contact, protection and need to be a part of a larger whole.

We know from the literature that such questions are central for cancer patients (108-111) and we also find from our own data (responses to open-ended questions) (23), that existential issues are of great importance (23) but seldom addressed directly in interventions. A possible reason is that there is sometimes a confusion between "spiritual" "religious" and "existential" issues. Whereas religious issues directly refer to a religious belief, and spirituality may be a part of a religious practice, existential issues relate to questions about life and death that every person must face, regardless of background. Issues of e.g. death and death anxiety, meaning and meaningless, the "why me?" and "why right now?"- questions, as well as questions of vulnerability and existential loneliness are central when facing a crisis, regardless of whether you are a believer or an atheist.

The contents of the different types of rehabilitation and whether those correspond to the patient's needs has also been discussed. Thorsen et al (41) found that supportive group sessions were most frequently offered but not needed. Women treated for breast cancer specifically requested physical therapy (43%). In recent years, several studies of different types of rehabilitation with physical elements have shown effects both on psychological and physical variables, and have shown to improve the overall quality of life (112, 113). Physical training was compared with physical training combined with CBT in a RCT. Self-managed physical training had a durable positive effect on cancer survivors' HRQoL, but the combination of physical training and CBT did not add any beneficial effect in the short or

long-term. In a review in 2010 by Spence (114) (10 studies including breast cancer patients), improvements in physical functioning, strength, physical activity levels, quality of life, fatigue, immune functioning, potential markers of recurrence and body composition were reported. However, all the studies were limited by incomplete reporting and methodological limitations.

In a Cochrane review 2012 (115), it was concluded that" exercise may have beneficial effects on HRQoL and certain HRQoL domains including cancer-specific concerns (e.g. breast cancer), body image/self-esteem, emotional well-being, sexuality, sleep disturbance, social functioning, anxiety, fatigue, and pain at varying follow-up periods. The positive results must be interpreted cautiously due to the heterogeneity of the exercise programme tested and measures used to assess HRQoL and HRQoL domains, and the risk of bias in many trials. Further research is required to investigate how to sustain positive effects of exercise over time and to determine essential attributes of exercise (mode, intensity, frequency, duration, and timing) by cancer type and cancer treatment for optimal effects on HRQoL and its domains. Thus, the same problems regarding the benefits of physical activity as with psychosocial rehabilitation remain. It is most likely that, some women can benefit from physical activity to reduce fatigue and improve quality of life while others do not (116). These needs also need to be screened to identify those with the greatest need. In another Cochrane review published in 2012 (117) was studied the effect of exercise intervention on HRQoL for people during active treatment and the review found that some studies suggested that exercise may be helpful in reducing negative outcomes and improving the quality of life in patients undergoing treatment, but the results need to be interpreted cautiously owing the risk of bias, which raises new ideas for future studies.

When we planned our study, we made the assumption that women with more severe disease, higher tumor stage, who received more intensive treatment with chemotherapy, would have more benefit of rehabilitation and therefore we stratified by chemotherapy treatment. However, there wasn't any large statistically significant difference between the stratified groups.

Regardless, many studies have reported good overall quality of life in breast cancer survivors, it has also been concluded that survivors with good quality of life are those who did not need chemotherapy, who have no comorbidity, who received sufficient emotional support from family members and have a relatively high income (118). However, all women affected by breast cancer do not need rehabilitation, and those who do, do not require the same type of intervention. It is probable that, there are some patients that may benefit from a particular type of intervention. As far back as in 1969, Paul (119) formulated a citation, that has been classic

in psychotherapy "*What* treatment, by *whom*, is most effective for *this individual* with *that* specific problem, and under *which set* of circumstances". Since it's likely that distress, which predominantly consists of depression, anxiety or anger or as a mixed state, are symptoms where needs are not always met, screening ought to be a way of identifying the patients most in need of rehabilitation (120). Bidstrup et al (120) described six screening tools for measuring distress. However, only HAD scale and "distress thermometer" (DT) have been evaluated in randomized trials. In another review, Vordermaier (121) assessed both new and well established distress screening tools and found 33 tools used in cancer care. Their conclusion was that recommendations about which tools should be used depend on the context in which the tools are implemented and the intended objectives that may vary across settings and users. Ultra-short tools such as the distress thermometer (1-4 items) are the easiest to implement in routine care settings, whereas they are not appropriate for use in research settings.

Conclusions

Support group intervention of short duration had an effect on anxiety in the short perspective, but the effect wore off in the long-term follow-up. No effect was seen on depression or different aspects of quality of life. There was a tendency for longer sick leave and more health care utilization in the group of women who underwent intervention. After long-term follow-up, women in the intervention group demonstrated less fatigue and better cognitive function, body image and future perspectives. It is possible that these effects might be explained by the use of the coping strategies taught during the intervention, but they might as well be due to chance. These findings lend little support to the use of this form of support intervention for breast cancer patients.

Future perspectives

Despite the large amount of studies on different interventions, it is still unclear if there is any profound effect on HRQoL, anxiety and depression. The disparity of results emphasizes the need for large randomized controlled studies. It is probable that not all breast cancer patients need rehabilitation and adequate screening tools need to be developed. Future studies should concentrate on identifying subgroups that could have the best benefit of intervention and specifically design studies for them.

Sammanfattning (Brief summery in Swedish)

Stödgruppsintervention hos kvinnor som behandlats för primär bröstcancer

Hälsorelaterad livskvalitet, med särskild hänvisning till ångest, depression och fatigue.

Bakgrund

Bröstcancer är den vanligaste tumörsjukdomen bland kvinnor. Tack vare förbättrad diagnostik med mammografscreening upptäcks fler tumörer tidigt. Förbättrade kirurgiska metoder med sektorresektion och sentinel node leder också till att kvinnor får mindre besvär. Den onkologiska behandlingen har också förbättrats med effektivare cytostatika, nya antikroppar, bättre strålbehandlingsmetoder och förbättrad antihormonell behandling. Allt detta har gjort att fler kvinnor botas från sin bröstcancer och de som ej botas lever längre med sin sjukdom.

Att få en bröstcancerdiagnos är för de flesta kvinnor omtumlande och orsakar ofta oro och ångest och en försämrad livskvalitet under kortare eller längre tid. Tidigare studier har visat att mellan 20-30% av alla bröstcancerdrabbade kvinnor visar symtom på ångest och/eller depression (14) jämfört med 8 respektive 6 % i en frisk svensk (15) population av kvinnor. De depressiva symtomen är mest framträdande under det första året efter diagnos och de flesta kvinnor återhämtar sig inom ett år (16) men symtom på ångest kan kvarstå i flera år (17).

Symtom som framför allt påverkar livskvalitet är oro och ångest, fatigue, minskad energi och styrka. I många studier har fatigue visat sig vara den främsta orsaken till försämrad livskvalitet. Studier har också visat att fatigue är den starkaste prediktorn för försämrad livskvalitet ett år efter diagnos hos kvinnor med bröstcancer Arndt (36). Tidigare studier har också visat att mellan 30-50 % av kvinnor med bröstcancer hade fatigue och dessa besvär kunde kvarstå i upp till 5 år. (122)

Många kvinnors liv förändras liksom deras perspektiv och värdering av livet. Många kvinnor omprioriterar sitt liv efter en cancerdiagnos och värdesätter saker på ett annat sätt, även sitt arbete.
För att förbättra kvinnors symtom och förbättra deras livskvalitet efter bröstcancerbehandling har studier gjorts på olika typer av rehabilitering (25). När vi planerade och startade vår studie fanns det dock få randomiserade studier.

Då medelåldern vid bröstcancerdiagnos är 60 år innebär detta att många är i yrkesverksam ålder. Många kvinnor är sjukskrivna kortare eller längre perioder i samband med sin diagnos och behandling. Eftersom sjukdomen är så vanlig innebär detta stora kostnader för samhället. Vad som avgör längden på sjukskrivning är inte bara sjukdom och behandling utan många andra faktorer spelar in såsom typ av arbete, utbildning, socialt nätverk, kontakt med arbetsgivare och arbetskamrater. Likaså har man i studier sett att sjukvårdskonsumtionen efter en cancerbehandling ökar (85, 86).

Det är således av stor betydelse för samhället att cancersjuka kommer tillbaka till arbetet, och för den enskilda kvinnan är det ett mått på tillfrisknande att återgå i arbete (57).

Syftet med avhandlingen var att studera effekten av en redan existerande rehabiliteringsverksamhet, på Stiftelsen Lustgården Mälardalen. Vår intention var att studera effekten på ångest, depression, livskvalitet, fatigue på kort och lång sikt samt studera om interventionen kunde ge en effekt på sjukskrivning, sjukvårdskonsumtion och hälsoekonomi.

Material och metod

Alla kvinnor som behandlades för sin första bröstcancer under tiden april 2002 till och med november 2007 informerades och tillfrågades om deltagande i studien. Inklusionskriterier var: en nydiagnostiserad primär bröstcancer, fysisk och mental förmåga att delta i gruppinterventionen och fylla i frågeformulär och en förväntad överlevnad på mer än 12 månader. Exklusionskriterier var: tidigare deltagande i grupprehabilitering och att man tidigare haft en malign sjukdom. Av praktiska skäl skedde informationen och inkluderingen i studien under strålbehandlingen. Under inklusionstiden erhöll 770 kvinnor strålbehandling för sin primära bröstcancer och 709 kom i fråga för studien. På grund av svåra syn- och hörselproblem, svår psykisk sjukdom, demenssjukdom och alkoholmissbruk exkluderades 54 stycken och på grund av att lokalerna där rehabiliteringen skedde inte var handikappanpassade exkluderades rörelsehindrade. Patienterna stratifierades efter adjuvant behandling med cytostatika eller ej. Totalt inkluderas 382 kvinnor i studien, 191 i interventions- och 191 i kontrollgruppen.

Intervention

Rehabiliteringen genomfördes inom fyra månader efter det att behandlingen avslutats (cytostatika och strålbehandling) och pågick i en vecka följt av 4 uppföljningsdagar två månader senare. Teamet på Lustgården bestod av onkologer, kuratorer, psykolog, bildterapeut, massageterapeut, dietist och en person som var utbildad i Qigong och mental visualisering. Alla hade en lång yrkeserfarenhet.

Under internatet fick deltagarna information av onkologläkaren om bröstcancer, etiologi, riskfaktorer, behandling samt fysisk och psykologisk effekt av diagnos och behandling. Man diskuterade också deltagarnas frågor.

Psykologen och kuratorn informerade om copingstrategier och psykologiska effekter och kuratorn tog även upp praktiska detaljer såsom att vara sjukskriven, försäkringar samt ekonomiska konsekvenser av att vara sjuk. Dietisten informerade om kostens betydelse.

Informations och diskussionsdelen blandades med lättare fysisk aktivitet, avslappningsövningar, qi-gong, mental visualisering och icke-verbal kommunikation (bildterapi och frigörande dans). Internatet inkluderade också gemensamma sociala aktiviteter som att gå på konserter, besöka museum och restauranger vilket också gav deltagarna möjlighet att umgås med personer med liknande erfarenheter och vistas i vacker och rofylld miljö utan att ha det vardagliga livets förpliktelser som att ta hand om familj, hem och yrkesliv.

Kontrollpatienterna följdes upp enligt sedvanliga kontrollrutiner på kirurg eller onkologi kliniken i Västerås.

Deltagarna i interventionsgruppen fick fylla i frågeformulär före interventionen, 2, 6 och 12 månader efter och kvinnorna i kontrollgruppen fyllde i frågeformulär vid motsvarande tidpunkter. Vid långtidsuppföljningen fick deltagarna fylla i samma frågeformulär som i den ursprungliga studien

Delarbete I

Björneklett HG, Lindemalm C, Rosenblad A, Ojutkangas ML, Letocha H, Strang P, Bergkvist L. A randomized controlled trial of support group intervention after breast cancer treatment: results on anxiety and depression. *Acta Oncol*. 2012 Feb;51(2):198-207. Epub 2011 Sep 19.

I arbete 1 studerade vi effekten av rehabiliteringsinternatet på ångest och depression mätt med HAD skalan (Hospital anxiety and depression scale). Ett värde mer än 10 bedömde vi talade för en klinisk signifikant depression respektive ångest.

Resultat

Ångest och depression

Det förelåg ingen skillnad mellan interventions- och kontrollgruppen vid studiens start beträffande ångest och depression. Andelen i interventionsgruppen som angav högt värde för ångest var 22 % och depression 7 %. I kontrollgruppen hade 18 % (p= 0,518) högt värde för ångest och 9 % för depression. Efter 12 månader var andelen med hög ångest nivå lägre i interventionsgruppen än i kontrollgruppen, 10 vs 19 % (p=0,055). I en regressions modell var minskningen av ångestnivån signifikant större i interventionsgruppen än i kontrollgruppen. Andelen kvinnor med höga depressionsvärden minskade något över tiden i interventionsgruppen medan den steg i kontrollgruppen vid 2 och 6 månader för att sedan minska vid 12 månader (Figur 3). Skillnaden var dock inte statistiskt signifikant.

Delarbete II

Björneklett HG, Lindemalm C, Ojutkangas ML, Berglund A, Letocha H, Strang P, Bergkvist L. A randomized controlled trial of a support group intervention on the quality of life and fatigue in women after primary treatment for early breast cancer.
Support Care Cancer. 2012 May 11. [Epub ahead of print]

I delarbete 2 studerade vi interventionens effekt på hälsorelaterad livskvalitet och fatigue och där använde vi den svenska versionen av EORTC QLQ 30 (livskvalité) och BR 23 (bröstcancer).

Fatigue mättes med den norska versionen av fatigueformuläret (FQ) (73). Fatigue formuläret är ett självskattningsformulär för bedömning av fatigue, inklusive symtom upplevda under den senaste månaden jämförda med när man senaste mådde bra. Förutom detta finns två frågor som frågar efter hur länge och hur kraftiga symtomen på fatigue var. Formuläret mäter fysisk fatigue och detta innefattar 7 frågor medan mental fatigue mäts med 4 frågor. Alla 11 frågorna innefattar total fatigue.

Resultat

Hälsorelaterad livskvalitet

Vid baslinjemätningen var det ingen signifikant skillnad mellan interventions- och kontrollgruppen men värdena på funktionsskalorna var lägre och symtomskalorna högre jämfört med friska svenska kvinnor. Vi såg en förbättring över tid på flera funktioner i båda grupperna men ingen av dessa skillnader var påverkade av interventionen utan bara av tiden.

Fatigue

Vid baslinjemätningen var det ingen statistisk signifikant skillnad mellan grupperna varken på fysisk eller mental fatigue. Medelvärdet på mental fatigue var i interventionsgruppen 5.6 och i kontroll gruppen 5.4. Medelvärdet på fysisk fatigue var i interventionsgruppen 11.1 och i kontrollgruppen 11. Båda värdena är mycket högre än i en frisk population. Fatiguevärdet sjönk från baslinjemätningen till 2 månader både i interventions- och kontrollgruppen och fortsatte att minska fram till 12 månader men det var ingen statistiskt signifikant skillnad mellan grupperna.

Delarbete III

Björneklett HG, Rosenblad A, Lindemalm C, Ojutkangas ML, Letocha H, Strang P, Bergkvist L. A randomized controlled trial of a support group intervention: Results on sick leave, healthcare utilisation and health economy. Accepted for publication in *Acta Oncol*.

I delarbete 3 har deltagarna i interventions- och kontrollgrupperna fått fylla i frågeformulär där de ska ange hur länge de har varit sjukskriva, i vilken omfattning och om det är till följd av cancersjukdomen och dess behandling. De har också fått ange hur mycket kontakt man sökt med sjukvården: familjeläkare, sjukgymnast, sjukhusspecialist och annan vårdgivare.

Resultat

Här såg vi en längre sjukskrivning i interventionsgruppen jämfört med kontrollgruppen, men skillnaden mellan grupperna var inte statistiskt signifikant. Vi kunde inte heller visa någon statistisk signifikant skillnad när det gällde sjukvårdskonsumtion, men när vi beräknade den totala kostnaden för sjukskrivning och sjukvårdskonsumtion så kunde vi visa en statistiskt signifikant högre kostnad i interventionsgruppen efter 12 månader jämfört med kontrollgruppen innan kostnaden för själva interventionen blev inräknad.

Delarbete IV

Björneklett HG, Rosenblad A, Lindemalm C, Ojutkangas ML, Letocha H, Strang P, Bergkvist L. Long-term follow-up of a randomized study of support group intervention in women with primary breast cancer. (Submitted).

I delarbete 4 har vi studerat långtidseffekten av rehabiliteringen på ångest, depression, fatigue och livskvalitet mätt med samma frågeformulär som i de två delarbetena, 5-9 år efter randomiseringen (medel 6,5 år).

Resultat

Deltagarna har fyllt i frågeformulären efter, i genomsnitt 6,5 år och svarsfrekvensen var nästan 80 %.

Vi fann en statistiskt signifikant förbättring över tid på fysisk, mental och total fatigue i interventionsgruppen jämfört med kontrollgruppen och vi såg

också en signifikant förbättring inom respektive grupp över tid. Vi har också kunnat visa en statistisk signifikant förbättring i interventionsgruppen på kognitive funktion, framtids perspektiv och kropps uppfattning mätt med EORTC QLQ 30 och BR23. Vi kunde dock inte visa någon statistiskt signifikant skillnad mellan grupperna avseende ångest och depression och den förbättring på ångest vi kunde visa efter 12 månader i interventionsgruppen i det första delarbetet kunde vi nu inte se.

Diskussion

Att få en bröstcancer väcker för de flesta kvinnor många tankar och känslor som påverkar deras livskvalitet. Många studier har genomförts på olika typer av interventioner med syfte att minska bröstcancer drabbade kvinnors symtom på bl.a. oro, ångest depression och fatigue samt att förbättra deras livskvalitet. Man har också studerat faktorer som påverkar kvinnors återgång i arbete och sjukvårdskonsumtion efter en bröstcancer diagnos. Vi har i en prospektiv randomiserad studie i en enhetlig tumör grupp, kvinnor med nydiagnostiserad bröstcancer studerat effekten av en specifik rehabilitering i Stiftelsen Lustgården Mälardalens regi.

Vi har visat att rehabiliteringen minskade ångesten under det första året men att denna effekt inte stod sig vid långtidsuppföljningen. Vi kunde inte visa någon effekt på depression sannolikt beroende på att så få kvinnor i vår studie hade symtom på depression, man låg till och med i nivå med en frisk normalbefolkning. Vi kunde inte visa någon statistiskt signifikant skillnad mellan grupperna när vi studerade sjukskrivning och sjukvårdskonsumtion, men vi kunde se signifikant högre totalkostnad i interventionsgruppen, även innan vi räknade in den faktiska kostnaden för internatet.

Vi kunde däremot inte visa någon effekt av rehabiliteringen när det gällde fatigue och livskvalitet på kort sikt under det första året vare sig med fatigue skalan (FQ) och EORTC QLQ30 men vi kunde visa en signifikant minskning av fysisk, mental och total fatigue (FQ) i långtidsuppföljningen efter att vi tagit hänsyn till det ursprungliga värdet, ålder, cytostatika behandling, utbildning, civil status och hemmavarande barn. Med EORTC QLQ30 kunde vi också visa att deltagarna i interventionsgruppen hade en bättre kognitiv förmåga kroppsuppfattning, ett bättre framtidsperspektiv vid långtidsuppföljningen. Den största effekten på fatigue såg vi hos de kvinnor som behandlats med cytostatika och detta skulle möjligen kunna bero på att dessa kvinnor under det första året var så trötta efter sin behandling att någon effekt av vår intervention inte var möjlig att upptäcka, vilket gjorde att coping och avslappning möjligen kan ha haft en mer märkbar effekt när den behandlings relaterade trötttheten avtagit.

Kvinnorna fick under rehabiliteringsinternatet mycket information om sin sjukdom, behandling samt de fick lära sig om olika typer av coping-strategier och avslappningsmetoder. Detta kan ha gjort att de efter sin hemkomst haft lättare för att hantera symtom på sin sjukdom, biverkningar av behandlingen och också haft lättare för att se framåt i tiden.

Vad vi däremot inte kunnat fånga med vår studie och som patienter ibland upplever negligeras är symtom av mer existentiell karaktär (23) och framtida forskning ska kanske fokusera på detta. Senare års forskning har också visat behovet av fysisk rehabilitering (41) och olika typer av rehabilitering med fysiskt inslag har visat ge effekt, både på psykologiska och fysiska funktioner (116) och man har också sett att kognitiv beteende terapi (KBT) visat lovande resultat (49) på livskvalitet. Sannolikt har inte alla kvinnor som behandlas för bröstcancer behov och nytta av rehabilitering och det kan möjligen vara så att man i framtiden ska använda någon form av mätinstrument för att ta reda på vem som har mest oro och ångest och därför sannolikt kan ha mest nytta av rehabilitering.

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Paper I

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ORIGINAL ARTICLE

A randomised controlled trial of support group intervention after breast cancer treatment: Results on anxiety and depression

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Abstract

Background. Previous studies have demonstrated that between 20 and 30% of women treated for breast cancer have measurable signs of anxiety and depression compared with 6% in a population of healthy women. Depression has been proposed as a predictive factor for recurrence and survival. The aim of the present study was to evaluate if psychosocial support intervention could influence anxiety and depression during the first year after diagnosis. *Material and methods*. Newly diagnosed breast cancer patients were randomised between April 2002 and November 2007 and stratified by adjuvant chemotherapy. Of 382 eligible patients, 191 + 191 patients were randomised to intervention group or control group, respectively. Control patients were subjected to standard follow-up routines. The Intervention group had support intervention at the Foundation Lustgården Mälardalen. The rehabilitation lasted one week on a residential basis followed by four days of follow-up two months later. We used the Swedish version of the HAD scale with a cut-off value greater than 10 for clinical symptoms of depression and anxiety. *Results*. Support group intervention lowered anxiety over time ($p < 0.001$) but depression was unaffected ($p = 0.610$). *Conclusion*. This prospective randomised trial of support group intervention in a large homogenous group of breast cancer women showed a statistically significant effect on lowering anxiety over time. No statistically significant effect of intervention could be seen on depression.

Breast cancer evokes psychological distress and many women react with anxiety and depression; 20–30% of breast cancer patients show measurable signs of anxiety and/or depression in the year after diagnosis [1]. The corresponding prevalence of anxiety and depression in the general population was 8% and 6%, respectively, in a healthy Swedish population [2] and in an American one [3]. The depressive symptoms are most pronounced during the first year after diagnosis, whereas most women recover within one year [4]. Symptoms of anxiety can however persist for several years [5].

Symptoms of depression have a negative influence on patients' quality of life [6] and may affect compliance to medical treatment [7], as well as recurrence, recovery and survival [8].

The impact of psychological interventions in general oncology and, more specifically, among breast cancer patients, has since been described in several studies and most of them have entailed a positive effect, but not all [9,10]. However, published studies vary considerably in terms of methodology, number of included patients, settings and results. When the present study was designed, there were few randomised studies published on the rehabilitation of cancer patients [11,12]. There was, therefore, a need for a prospective randomised study of the effects of support intervention on the psychosocial health of breast cancer patients.

The primary aim of the present study was to evaluate the effect of a special form of support intervention programme on an existing concept on anxiety and

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depression in breast cancer patients. A secondary aim was to see whether there was a difference in the levels of anxiety and depression in patients with more severe disease who had been administered chemotherapy treatment, compared with those who had not and to investigate whether the support programme was more effective in either of these subgroups. Our hypotheses were: 1. Intervention reduces anxiety, and this effect persists over time, and 2. Intervention reduces depression, and this effect persists over time.

Material and methods

Subjects

All newly diagnosed breast cancer patients between April 2002 and November 2007 presenting at the Department of Oncology at the Central Hospital in Västerås, Sweden, for postoperative radiotherapy were scrutinised for participation. The hospital is a county hospital with both medical oncology and radiotherapy. During this period, 770 patients were

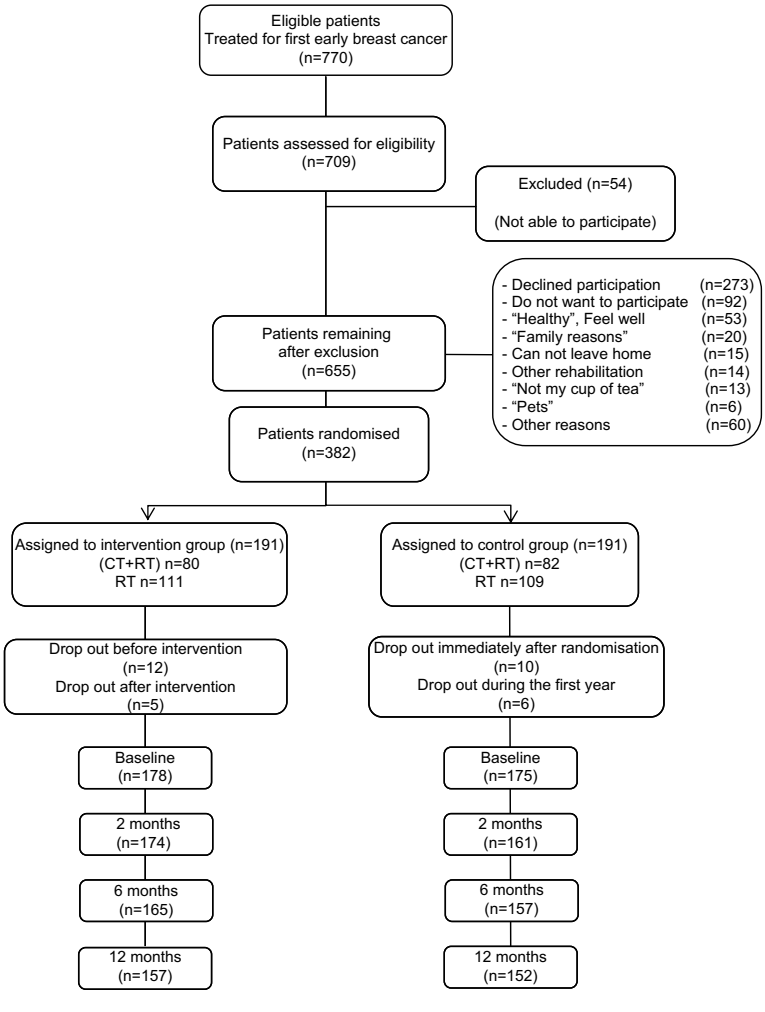

Figure 1. Flow chart of participants' progress through the randomised trial. CT, chemotherapy; RT, radiotherapy.

referred for radiotherapy and 709 were assessed for eligibility. The decision to select patients who were scheduled for radiotherapy was made for logistical reasons. However, most patients treated at the hospital were referred for radiotherapy, only a few elderly women who had undergone a mastectomy for stage I disease were excluded; see flow chart (Figure 1). The inclusion criteria were a newly diagnosed primary breast cancer, the physical and mental capability to participate in group interventions and to fill in questionnaires (for example, not demented patients, severe vision and hearing injuries, or those with serious mental illness, active alcohol abuse and because of the conference centres premises, not disabled), and an expected survival of more than 12 months. Patients who had participated in group rehabilitations previously or had a former history of any malignant disease were excluded, in total 54 patients. All those meeting the inclusion criteria were informed about the study and, after acceptance to participate; all patients gave their written informed consent. Of eligible 655 women, 382 gave their informed consent, giving an effective recruitment of 58%. The Ethics Committees at the University of Uppsala and Karolinska Institutet approved the study.

Patients were stratified by adjuvant chemotherapy and randomised in blocks of four by the use of closed envelopes. Randomisation was done by an independent research nurse, who received personal identification number from the first author, who performed the recruitment of patients. In total, 382 women were included in the study, 191 in the intervention group and 191 in the control group.

Surgery

Eighty-nine patients were treated with mastectomy and 293 with breast-conserving surgery. One hundred and sixty two underwent sentinel node biopsy only, 199 a level I-II axillary dissection and 21 patients had no axillary surgery.

Chemotherapy

In all 161 patients received chemotherapy. Standard chemotherapy was given in the form of 5-fluorouracil (600mg/m^2), Epirubicin (60–75 mg/m^2) and Cyclophosphamide (600mg/m^2) (FEC in 6–7 cycles) (n = 68). Sixteen patients had large, inflammatory or inoperable tumours and were given neoadjuvant chemotherapy with four cycles of FEC before and three cycles of FEC after surgery (n = 4) or three cycles of Epirubicin and Docetaxel and three cycles of Docetaxel (n = 12). In addition, patients were included in three different randomised studies of adjuvant or neoadjuvant treatment and were treated according to the respective study protocols.

Radiotherapy

Irradiation with (6 MV photons) was delivered to the breast in fractions of 2 Gy to a total of 50–52 Gy in all patients who had undergone breast-conserving operations (n = 293) and to the adjacent lymph node station if involvement of the axilla was present. Young patients (age below 45) were given a 10 Gy boost during the last years of the study. Patients who had undergone mastectomy due to large tumours (> 3 cm) or multifocal tumours received radiotherapy towards the chest wall in fractions of 2 Gy to 50–52 Gy (n = 82).

Antibody treatment

Patients with HER2 positive tumours were initially included in the HERA study (a randomised trial with adjuvant trastuzumab and, after August 2005, all patients with HER2 positive tumours were given adjuvant trastuzumab. A total of 15 patients received 17 cycles of adjuvant trastuzumab.

Endocrine therapy

Tamoxifen was offered to all pre-menopausal women with endocrine responsive tumours and postmenopausal women with stage I tumours. A total of 249 patients received tamoxifen treatment and 42 patients received aromatase inhibitors. The endocrine treatment usually started after radiation therapy.

The clinical characteristics of the patients were extracted from the patients' records and are presented in Table I.

The support group programme

The multimodal support-intervention programme at the Foundation of Lustgården-Mälardalen started 1992 partly inspired by the discussions in the scientific society concerning the connections between emotions, immunity and malignant diseases. It was also influenced by communications with different professionals and patients concerning what they thought would improve quality of life, or rather, would meet the needs of the patients not by that time met by the ordinary clinical procedures. The procedure indicates a reasonable degree of face validity. This led to our knowledge-information based support program supplemented with relaxation, Qi-gong and liberating dance.

In the present study the intervention took place within four months after the end of tumour-treatment and ran for seven days followed by four days follow-up two months after the initial visit.

The team leader was the director of the Foundation responsible for the time-schedules, all practical

Table I. Distribution of patients by surgical intervention, node status and tumour characteristics, menopausal status, postoperative endocrine treatment and civil status and levels of anxiety and depression at baseline. Group A and C are intervention groups given chemotherapy (A) and not given chemotherapy (C), and group B and D are non-intervention groups, with (B) and without (D) chemotherapy.

	Group			
	A (n = 81)	B (n = 80)	C (n = 110)	D (n = 111)
Age mean (min–max)	54 (30–69)	55 (38–70)	61 (34–84)	62 (38–83)
Surgery				
Mastectomy	29	32	13	15
Breast conservation	52	48	97	96
Sentinel node biopsy	16	9	68	69
Axillary clearance	65	71	31	32
No axillary dissection	0	0	11	10
Cancer in situ	0	0	12	14
Lymph nodes				
Negative	19	16	85	91
≤3	44	54	9	8
4–8	11	7	5	1
≥9	7	3	0	1
Lgll not done	0	0	11	10
Receptors				
ER+	64	63	94	95
ER−	17	17	4	7
ER not known	0	0	12	9
PR+	40	46	69	69
PR−	40	33	29	32
PR not known	1	1	12	10
Her2+	27	15	8	13
Her2−	30	35	32	31
Her2 not known	24	30	70	67
Tumour size				
T1	32	29	77	93
T2	41	43	32	17
T3	8	8	1	1
Menopause				
Premenopausal	31	24	22	18
Postmenopausal	44	52	83	91
Not known	6	4	5	2
Chemotherapy	81	80	0	0
-Preop chemotherapy	10	13		
Radiotherapy	81	80	107	107
Tamoxifen	52	52	71	74
Aromatase inhibitor	14	13	10	5
Hormone before cancer diagnose	10	8	14	24
Married	67	65	71	90
Widowed, single	14	15	40	21
Children at home	29	23	17	20

arrangements as well as taking care of the groups outside the actual supportive rehabilitation programme. The members of the team were oncologists (n = 3), social workers (n = 2), art therapist (n = 2), massage therapists (n = 2), a dietician (n = 1) as well as a person trained in Qi-gong and mental visualisation. All personnel had long occupational experience.

The guests received information from the oncologist about breast cancer, etiology, risk factors, treatments, physical and psychological effects of diagnosis and treatments. Questions from the guests were discussed.

Psychological effects and coping strategies were the responsibility of the psychologist and, to some extent the social worker, who, in addition, informed about practical-social details, such as being on the sick-list, insurances and economic consequences.

The dietician had information discussions about the importance of food and nutrition.

The informative-educational parts were mixed with physical exercise, relaxation training, Qi-gong, mental visualisation and non-verbal communication (art and liberating dance therapy).

Social activities, such as concerts, visits to museums and restaurants were provided as were the opportunities for the guests to be together with individuals with similar experiences in a beautiful and restful milieu not burdened the troubles of daily living, such as taking care of family members or keeping a household and job going. The reassembly was an opportunity to review the support-period, discuss problems after returning home, meet the team leader, dietician, the massage therapist and the companions met during the intervention.

The programme has previously been described in a pilot study of unselected patients with different tumour diagnose [13]. For a detailed description of the schedule of the rehabilitation program, please see addendum. The guests gave their opinions on the rehabilitation and their answers were continuously evaluated.

The consultants had regular guidance from a psychologist not taking part in the intervention and organised meetings were held once every six months to discuss the procedures, observations made and experiences gained.

One of the main objectives of the intervention programme was to try out different methods and to encourage the participants to continue and practice at home.

Control patients were subjected to standard follow-up routines.

Questionnaires

Study patients answered questionnaires after randomisation but before rehabilitation and after two, six and 12 months. The Swedish version of the HAD scale was used. This scale was originally designed to detect emotional disturbances in non-psychiatric patients treated in hospital clinics [14]. It is a validated scale, commonly used worldwide to discriminate between anxiety and depression [15–17].

It has been used in many breast cancer studies [18] and has been shown to have a stable factor structure and high reliability [16].

Analysis

The responses to the HAD scale were analysed as originally described [14]. The scale consists of seven items reflecting anxiety and seven reflecting depression. Each item is rated on a four point scale; 0- less than before; 1- not so much; 2- quite a lot and 3- very much, giving a maximum of 21 for depression and anxiety, respectively. Scores > 10 on either subscale indicate clinically significant depression or anxiety and subscale scores in the range of 8–10 represent borderline cases. In the statistical analysis, we focused our attention on those with high anxiety or depression scores (clinical anxiety or depression), since we considered this to be the clinically most important group. However, as a service to the reader, all values are shown in the table (Table II).

Statistical analysis

The present study is part of a randomised study covering several different aspects of rehabilitation. Power calculation was performed based on the assumption that 50% of women treated for breast cancer show some sign of psychological distress, which was reported in the literature at that time. To be able to detect a 15%-lower proportion of psychological distress between the intervention and the control group after one year, with a power of 80% and a 5% significance level, we would need a total number of 400 patients, taking in to account possible missing values.

The data are analysed according to intention-to-treat principles, i.e. all patients randomised to the intervention and control groups are analysed as representing that treatment, whether they completed it or not.

The anxiety and depression scores were treated as ordinal data variables and categorised into three levels: low (scores < 8), medium (scores 8–10), and high (scores > 10). Cross-sectional differences between the

Table II. Distribution of patients by levels of anxiety and depression at baseline, two, six and 12 months, *n* (%) of those who answered. Group A and C are intervention groups given chemotherapy (A) and not given chemotherapy (C), and group B and D are non-intervention groups, with (B) and without (D) chemotherapy.

			Group			
Time point	Variable	HAD score	A (n = 81)	B (n = 80)	C (n = 110)	D (n = 111)
Baseline	Anxiety	Low (< 8)	43 (57.3)	43 (55.8)	60 (58.3)	68 (70.1)
		Medium (8–10)	16 (21.3)	13 (16.9)	20 (19.4)	18 (18.6)
		High (> 10)	16 (21.3)	21 (27.3)	23 (22.3)	11 (11.3)
		Not answered	6 (–)	3 (–)	7 (–)	14 (–)
	Depression	Low (< 8)	62 (82.7)	53 (69.7)	79 (77.5)	84 (84.8)
		Medium (8–10)	9 (12.0)	16 (21.1)	15 (14.7)	7 (7.1)
		High (> 10)	4 (5.3)	7 (9.2)	8 (7.8)	8 (8.1)
		Not answered	6 (–)	4 (–)	8 (–)	12 (–)
2 months	Anxiety	Low (< 8)	53 (71.6)	39 (55.7)	70 (70.7)	64 (71.9)
		Medium (8–10)	13 (17.6)	13 (18.6)	16 (16.2)	12 (13.5)
		High (> 10)	8 (10.8)	18 (25.7)	13 (13.1)	13 (14.6)
		Not answered	6 (–)	11 (–)	11 (–)	22 (–)
	Depression	Low (< 8)	67 (89.3)	48 (66.7)	79 (79.8)	69 (77.5)
		Medium (8–10)	5 (6.7)	16 (22.2)	10 (10.1)	13 (14.6)
		High (> 10)	3 (4.0)	8 (11.1)	10 (10.1)	7 (7.9)
		Not answered	6 (–)	8 (–)	11 (–)	22 (–)
6 months	Anxiety	Low (< 8)	48 (69.6)	42 (60.9)	71 (74.0)	64 (72.7)
		Medium (8–10)	12 (17.4)	10 (14.5)	10 (10.4)	12 (13.6)
		High (> 10)	9 (13.0)	17 (24.6)	15 (15.6)	12 (13.6)
		Not answered	12 (–)	11 (–)	14 (–)	23 (–)
	Depression	Low (< 8)	59 (84.3)	49 (71.0)	77 (81.1)	69 (78.4)
		Medium (8–10)	10 (14.3)	11 (15.9)	12 (12.6)	9 (10.2)
		High (> 10)	1 (1.4)	9 (13.0)	6 (6.3)	10 (11.4)
		Not answered	11 (–)	11 (–)	15 (–)	23 (–)
12 months	Anxiety	Low (< 8)	53 (79.1)	41 (64.1)	75 (79.8)	64 (72.7)
		Medium (8–10)	9 (13.4)	8 (12.5)	8 (8.5)	10 (11.4)
		High (> 10)	5 (7.5)	15 (23.4)	11 (11.7)	14 (15.9)
		Not answered	14 (–)	16 (–)	16 (–)	23 (–)
	Depression	Low (< 8)	61 (91.0)	51 (81.0)	76 (81.7)	73 (83.0)
		Medium (8–10)	3 (4.5)	11 (17.5)	12 (12.9)	10 (11.4)
		High (> 10)	3 (4.5)	1 (1.6)	5 (5.4)	5 (5.7)
		Not answered	14 (–)	17 (–)	17 (–)	23 (–)

intervention and control groups at baseline, and at two, six, and 12 months of follow-up were tested with Pearson's χ^2-test. Correlations between anxiety and depression scores were calculated using Spearman's correlation coefficient (r). In order to utilise the ordinal nature of data and take care of the correlation between repeated measurements of anxiety and depression on the same subject, changes in anxiety and depression over time were analysed with multivariate generalised estimating equations (GEE) ordinal logistic regression models with unstructured working correlation matrices. Neither last-value-carried-forward (LVCF) nor imputation of missing data was applied. For patients with missing data at one or more time points, the remaining available data from the same patient at the other time points were used in the GEE estimation process. The analyses were performed both unstratified and stratified on chemotherapy treatment.

In the regression models, the three-level anxiety and depression variables were entered as response variables, with the highest level being the last ordinal category. In choosing predictor variables, a two-step-procedure was used: firstly, a full model was constructed where intervention was entered as a factor while time and interaction between time and intervention were entered as co-variates. Additionally, chemotherapy treatment and interaction between time and chemotherapy treatment were added as factors and co-variates, respectively, for unstratified analyses. Secondly, a final model was formed by deleting non-significant interaction variables from the model. Trying to improve the final model by adding age, education level, marital status or number of children in the household was unsuccessful since these variables were all non-significant. The proportional odds assumptions were tested for the full and final models with tests of parallel lines for a standard ordinal logistic regression model as well as by testing the statistical significance of the change in deviance when using a standard ordinal logistic regression model instead of a standard multinomial logistic regression model. The tests showed that the assumption could not be rejected. Linearity of time was tested by adding a quadratic time variable to the full model, but this variable was not significant for any of the outcomes, showing that the assumption of linearity could not be rejected. The statistical analyses were performed in SPSS 17/18 and R 2.13.0, with a two-sided p-value < 0.05 considered being statistically significant.

Results

Anxiety

At baseline, there were no statistically significant differences in anxiety scores between women who were allocated to the intervention and control groups, respectively.

In the intervention group, 22% had a high anxiety score, compared with 18% in the control group ($p = 0.518$). There was a decrease at two, six and 12 months in the proportion of women in the intervention group that showed signs of anxiety, whereas very small changes were seen in the control group. After 12 months, 10% in the intervention group and 19% in the control group had a high anxiety score ($p = 0.055$, Figure 2).

From the full multivariate GEE ordinal logistic regression model (Table III), it was found that, adjusted for intervention and chemotherapy treatment, the overall level of anxiety showed no significant decrease over time ($p = 0.923$). The interaction between time and chemotherapy was non-significant ($p = 0.307$), showing that chemotherapy treatment did not have a significant impact on the level of anxiety. However, the interaction between time and intervention variables showed that the anxiety level in the intervention group decreased significantly ($p < 0.001$) more than for the non-intervention group. The exclusion of the non-significant interaction between time and chemotherapy gave the final model, with only time, intervention and interaction between time and intervention, adjusted for chemotherapy treatment (Table III). This showed that there was a weak non-significant overall decrease in the anxiety level over time (OR 0.992; 95% CI 0.972–1.013; $p = 0.407$), and a significant ($p < 0.001$) additional decrease in anxiety levels over time for the intervention group, with an odds ratio of 0.946 (95% CI 0.914–0.977) per additional month, indicating that only intervention patients showed a statistically significant decreasing level of anxiety over time (Table III).

Depression

At baseline, 7% of the patients in the intervention group and 9% in the control group had a high depression score ($p = 0.818$). The proportion of women with high scores diminished slightly over time in the intervention group, whereas there was an increase in the proportion with high scores in the control group at two and six months, and thereafter a drop between six and 12 months. At 12 months, 5% in the intervention group and 4% in the control group had a high depression score ($p = 0.433$, Figure 3). The correlations between anxiety and depression scores were high, with Spearman's correlation coefficient being 0.733 and 0.717 for the intervention and control group, respectively, at baseline, 0.664 and 0.683 at two months, 0.732 and 0.700 at six months, and finally 0.751 and 0.711 at 12 months.

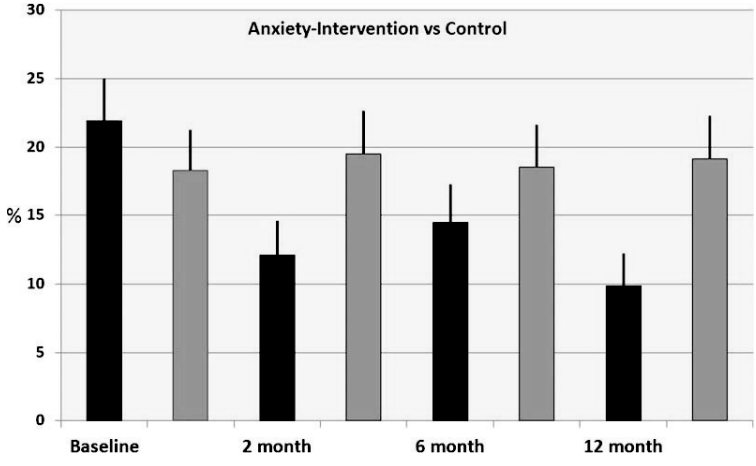

Figure 2. Anxiety intervention-control. Proportion of women with anxiety level over 10 on the HAD scale at baseline, two, six and 12 months after randomisation, for patients in intervention (dark grey bars) and control group (light grey bars), with standard error.

From the full multivariate GEE ordinal logistic regression model, it was found that neither time, nor interaction between time and intervention or between time and chemotherapy had a significant impact on lowering the depression level over time (Table III). However, after excluding the non-significant interaction terms, the final model showed that there was a statistically significant ($p = 0.036$) overall decrease in depression over time, with an odds ratio of 0.979 (95% CI 0.960–0.999) per additional month, whereas the intervention had no statistically significant effect on decreasing the level of depression over time (Table III).

When we stratified the patients into those who had received chemotherapy and those who had not, there were no significant overall effects on decreasing anxiety over time in either of the groups, but, in both groups, there was a significant effect on decreasing anxiety levels more in the intervention group than in the non-intervention group (Table IV). For depression, the interaction term between time and intervention showed to be non-significant for both the chemotherapy and the non-chemotherapy groups, implying that there was no significant impact of the intervention on depression. Deleting the interaction term showed a significant overall decreasing depression level over

Table III. Changes in anxiety and depression over time. Results from multivariate generalised estimating equations ordinal logistic regression model with three-level anxiety and depression response variables, adjusted for differences in baseline levels between intervention and chemotherapy groups. Odds ratios for being at a higher level.

		Full model†		Final model‡	
Outcome	Predictor	OR (95% CI)	P-value	OR (95% CI)	P-value
Anxiety	Time	0.999 (0.975–1.024)	0.923	0.992 (0.972–1.013)	0.407
	Time × Intervention	0.944 (0.914–0.974)	< 0.001	0.945 (0.914–0.975)	< 0.001
	Time × Chemotherapy	0.984 (0.954–1.016)	0.307	Not in model	
Depression	Time	0.994 (0.966–1.023)	0.682	0.979 (0.960–0.999)	0.036
	Time × Intervention	0.990 (0.951–1.030)	0.610	Not in model	
	Time × Chemotherapy	0.976 (0.938–1.016)	0.235	Not in model	

†Difference in deviance between standard ordinal logistic model and standard multinomial logistic model: Anxiety: 4.158, df = 5, p = 0.527; Depression: 3.811, df = 5, p = 0.577.
‡Difference in deviance between standard ordinal logistic model and standard multinomial logistic model: Anxiety: 3.329, df = 4, p = 0.504; Depression: 3.462, df = 4, p = 0.484.

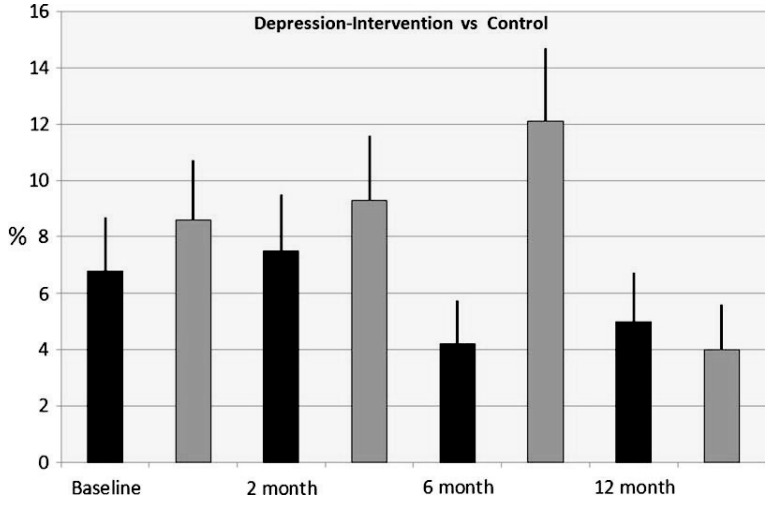

Figure 3. Depression: Intervention-control. Proportion of women with depression level over 10 points on the HAD scale at baseline, two, six and 12 months after randomisation, for patients in intervention (dark grey bars) and control group (light grey bars), with standard error.

time in the chemotherapy group but not in the non-chemotherapy group (Table V).

Discussion

Support group intervention including education about the disease and psychological reactions, mixed with art and dance therapy, Qi-gong and relaxation, was shown to positively influence the levels of anxiety among breast cancer patients over time, whereas levels of depression were unaffected by the intervention. Even if small, a lowering of the level of anxiety might be of importance for the patient. The low initial levels of depression among patients in the present study may contribute to the lack of any association between psychological support and depression. The results remained unchanged when possible confounders were included in the statistical models.

In the current study, anxiety and depression were considered as separate outcomes, and the effect of the intervention on these outcomes were estimated separately. However, given the strong correlation between the two outcomes, one may wish to consider the composite null hypothesis that anxiety and depression are simultaneously equal between the intervention and control groups. Although this question is outside the scope of this article, this null hypothesis could be tested using the Bonferroni corrected p-value < 0.025 for considering the results given in this article to be statistically significant.

The strengths of the present study are the prospective randomised design, a homogenous group of patients and a near complete follow-up (87% of those who actually participated in the study). The strength with a homogenous group of patients is that everyone has the same diagnosis of comparable stages and is of the same sex, which minimises confounding factors.

A weakness is that there was an obvious selection of patients who agreed to participate. This limits the possibility to draw conclusions about general breast cancer patients. On the other hand, such a selection will always be at hand when discussing rehabilitation. Earlier studies on drop-outs compared with study

Table IV. Changes in anxiety over time, stratified by chemotherapy status. Results from multivariate generalised estimating equations ordinal logistic regression model with three-level anxiety response variables, adjusted for differences in baseline levels between intervention groups. Odds ratios for being at a higher level.

		Full and final model†	
Treatment	Predictor	OR (95% CI)	P-value
Chemotherapy	Time	0.976 (0.947–1.005)	0.098
	Time × Intervention	0.952 (0.909–0.997)	0.036
Not chemotherapy	Time	1.005 (0.979–1.033)	0.692
	Time × Intervention	0.934 (0.895–0.974)	0.001

†Difference in deviance between standard ordinal logistic model and standard multinomial logistic model: Chemotherapy: 4.964, df = 3, p = 0.174; Not chemotherapy: 3.363, df = 3, p = 0.339.

Table V. Changes in depression over time, stratified by chemotherpy status. Results from multivariate generalised estimating equations ordinal logistic regression model with three-level depression response variables, adjusted for differences in baseline levels between intervention groups. Odds ratios for being at a higher level.

		Full model†		Final model‡	
Treatment	Predictor	OR (95% CI)	P-value	OR (95% CI)	P-value
Chemotherapy	Time	0.973 (0.942–1.006)	0.106	0.965 (0.935–0.995)	0.020
	Time × Intervention	0.976 (0.912–1.043)	0.468	Not in model	
Not chemotherapy	Time	0.987 (0.955–1.021)	0.447	0.989 (0.965–1.014)	0.373
	Time × Intervention	1.003 (0.956–1.054)	0.889	Not in model	

†Difference in deviance between standard ordinal logistic model and standard multinomial logistic model: Chemotherapy: 0.721, df = 3, p = 0.868; Not chemotherapy: 1.524, df = 3, p = 0.677.
‡Difference in deviance between standard ordinal logistic model and standard multinomial logistic model: Chemotherapy: 0.118, df = 2, p = 0.943; Not chemotherapy: 1.449, df = 2, p = 0.485.

patients indicates that those cancer patients who actually accept participation are those who have the highest needs, i.e. those with a higher degree of distress [19]. Many patients preferred not to participate due to other engagements in their lives to which they assigned higher priority. Because of the practical arrangements of the intervention (residential basis for one week), many women with families, children, pets and old and sick husbands chose to remain with their families instead. Other women chose not to participate in this study due to reasons such as "I feel well", "I don't need support ", and "I have already gone back to work". Yet another reason for not participating in our study was that they did not want to meet other sick women with a poorer prognosis.

Another weakness of the study is the reproducibility of treatment. The concept was based on several different dimensions including Qi-gong, art and dance therapy which are difficult to standardise. However, we tested the whole concept, and irrespective of the variations between different therapists and methods, the levels of anxiety decreased significantly over time only in the intervention group.

Our results are in line with a meta-analysis by Sheard and Maguire [20] in which they separately analysed the effect of psychological interventions on anxiety and depression among cancer patients. They included 19 studies measuring anxiety and 20 measuring depression and found a clinically significant effect for anxiety but not depression. This has been confirmed in later studies [21,22].

In a recently published review article by Fors et al. [23] they found limited documentation on the efficacy of psychosocial rehabilitation interventions among breast cancer patients, which suggest that despite the large amount of intervention studies it is difficult to prove any positive effect. This is further supported in a recent study by Boesen [24], in which they could not find any statistically significant effect of the intervention on any of the psychosocial questionnaire outcomes.

In the future screening by HAD, prior to intervention, would be an option to select patients and obtain those with the highest anxiety and depression scores and see whether they drive more benefit from the intervention. But this remains to be proven. However, HAD as well as other self-report measures, have well-known shortcomings. As regards HAD, the optimal cutoff scores vary depending on study and patient population and there is a risk both for under-detection and for false positive rates when compared to clinical interviews and examination using DSM IV criteria [25]. This is partly due to the fact that different patients can achieve similar summary scores from strongly endorsing only a few items or from weakly endorsing many items. It is also noteworthy that HAD (in contrast, e.g. to Beck Depression inventory or Zung Self-Rating depression scale) removes the somatic symptoms of depression (weight loss or gain and fatigue), which affects the outcome.

It has been discussed whether signs of anxiety or depression influence the prognosis of breast cancer. Falagas et al. [8] analysed 31 studies examining the association of various psychosocial parameters on survival and 25 of these showed an effect. They also identified six studies examining if psychological intervention could influence disease outcome. Two of those showed an effect, whereas four did not. In a later study, Groenvold [26] showed that low levels of psychological distress and low fatigue independently predicted longer recurrence free survival and overall survival.

Even if we did not specifically study the prognostic effects from support intervention, it seems unlikely, considering the minor effect found only on

anxiety levels, that support group intervention in the present form would influence the prognosis.

Conclusions

This prospective randomised trial of support group intervention in a large homogenous group of women treated for primary breast cancer showed a significant effect of intervention on lowering anxiety over time. No statistically significant effect of the intervention was observed on depression levels.

Acknowledgements

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Supplementary material available online

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Paper II

Support Care Cancer
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ORIGINAL ARTICLE

A randomized controlled trial of a support group intervention on the quality of life and fatigue in women after primary treatment for early breast cancer

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Abstract
Background When diagnosed with breast cancer, most women's lives change as well as their perspectives on and appreciation of life. The aim of the present study was to evaluate whether psychosocial support intervention could influence health-related quality of life (HRQOL) and fatigue during the first year after diagnosis.
Material and methods Of 382 patients with newly diagnosed breast cancer, 191 patients were randomized to an intervention group and 191 patients were randomized to a routine control group. The intervention group received support intervention that lasted 1 week on a residential basis, followed by 4 days of follow-up 2 months later. The support intervention included informative educational parts, relaxation training, mental visualization, and nonverbal communication. HRQOL was measured using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-BR23 questionnaires and fatigue with the Norwegian version of the fatigue scale at baseline and at 2, 6, and 12 months after intervention.
Result There was a time-dependent improvement in both functional and symptom scales between baseline and 12 months as measured by the EORTC QLQ-C30 and BR23 questionnaires and there was a decrease in fatigue between baseline and after 2 months with further improvement up to 12 months in both groups, but there were no differences between the intervention and control groups at any point in time.
Conclusion HRQOL improves and symptoms of fatigue decrease over time, but we could not see any additional effect from the rehabilitation program in this setting.

Keywords Support intervention · Breast cancer · Health-related quality of life · Fatigue · EORTC QLQ-C30 and BR23 · The Norwegian version of the fatigue scale

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Introduction

When diagnosed with breast cancer, most women's lives change as well as their perspectives on and appreciation of life. Treatment with surgery, chemotherapy, and radiation therapy also adds treatment-specific symptoms that affect the quality of life (QOL). Health-related quality of life (HRQOL) has been defined as "a global concept, conceived

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to reflect the totality of human well-being, including (but not limited to) physical, psychological, social, economic and spiritual domains. The notion of health-related quality of life (HRQOL) addresses QOL as it is affected by disease and treatment" [1].

Numerous studies have been carried out to investigate HRQOL after breast cancer diagnosis and treatment, and a large number of instruments have been developed to measure QOL, as summarized by Montazeri [2]. Out of 477 papers on QOL in breast cancer patients, 37 covered supportive care topics and 15 of these studies highlighted the effect of some form of intervention, mental or physical. However, the results varied a lot, and there were few methodologically strict and controlled studies.

Symptoms that primarily affect HRQOL are distress, fatigue, reduced energy, and a loss of stamina. In many studies, fatigue seems to be the predominant cause of a reduced QOL. Arndt et al. [3] found that fatigue was the strongest predictor of impaired QOL at 1 year after diagnosis. Cancer-related fatigue has been defined by the National Comprehensive Cancer Network as "a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning" [4]. Thirty to 50 % of patients have problems with fatigue, which may persist for up to 5 years [5].

Since most women survive breast cancer and those who are not cured live a lot longer than before, it is of great importance to find methods to improve HRQOL [6]. Social support and intervention have been found to be successful in some studies on QOL, as described in a review by Rehse and Pukrop [7]. They concluded that psychosocial interventions reveal a positive impact on QOL in cancer patients and also showed that educational programs were more effective than other types of intervention. However, in this review, not all studies were randomized, both men and women were included (intervention more profitable in men); there were great differences in methodology, patient recruitment, and diagnoses. In another review by Newell et al. [8] on psychological therapies for cancer patients, they could only tentatively recommend interventions to improve QOL.

When we designed our study, there were few randomized studies on the effect of psychosocial intervention on QOL after a breast cancer diagnosis [9, 10]. The primary aim of our study was to investigate the effect of support group intervention in a homogeneous group of primary breast cancer patients on HRQOL as measured with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and BR23 and fatigue measured with the Norwegian fatigue scale. A secondary aim was to stratify into two groups, viz. those who had had a more severe disease, which entailed intensive treatment with chemotherapy, and those who had not.

The present study is part of a randomized study covering several different aspects of rehabilitation, anxiety and depression (manuscript in print), QOL, fatigue, health economy, and health care utilization (unpublished data).

Materials and methods

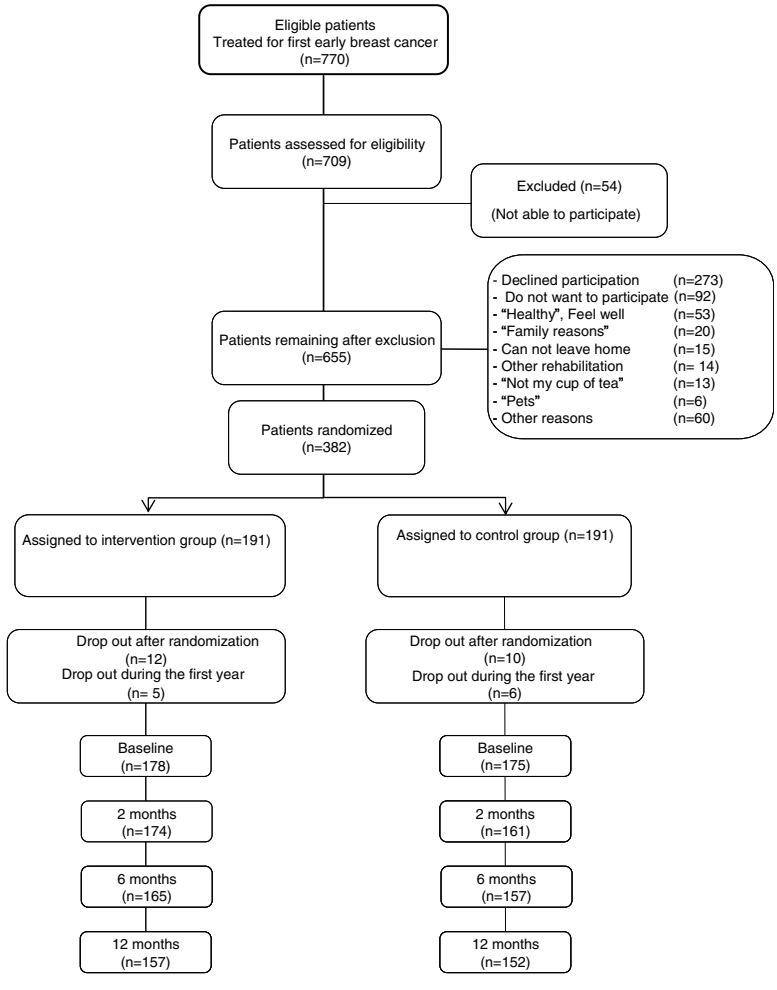
Subjects

Women with a newly diagnosed breast cancer at the Central Hospital in Västerås, Sweden between April 2002 and November 2007 were included in the study. Criteria for inclusion were a newly diagnosed primary breast cancer, the physical and mental ability to participate in group interventions and to fill in questionnaires, and an expected survival time of more than 12 months. Exclusion criteria were patients who had participated in group rehabilitations previously or had a former history of any malignant disease. Patients were, for practical reasons, included during their adjuvant treatment with radiotherapy and all women with primary breast cancer were considered for inclusion in the study. During this period, 770 women received radiotherapy for their primary breast cancer and 709 were assessed for eligibility, 54 of whom were excluded due to severe visual or auditory impairment, serious mental illness, dementia, active alcohol abuse, and due to the conference center premises, physical disability. Most women were treated with radiotherapy during this period, although a few, mostly elderly women (more than 65 years) who had undergone a mastectomy, were not treated with radiotherapy according to regional treatment guidelines. All women who met the inclusion criteria were informed about the study, and after acceptance to participate, all women gave their written informed consent. In total, 382 women accepted to participate and 273 declined participation, see flowchart (Fig. 1). One hundred and ninety-one women were allocated to the intervention group and 191 to the control group. Of those randomized patients, 33 dropped out during the first year, 12 from the intervention group and 10 from the control group immediately after randomization. Five in the intervention group participated in the first rehabilitation week but dropped out thereafter, and six in the control group dropped out during the first year (Fig. 1). The Ethics Committee at the University of Uppsala approved the study. Patients were randomized in blocks of four using closed envelopes, after stratification according to their primary treatment, viz. those who had received chemotherapy and those who had not.

Treatment

The various surgical and oncological treatments, together with the clinical characteristics of the patients, were extracted from the patients' records and are shown in Table 1.

Fig. 1 Flowchart of the study



Support intervention

The multimodal support intervention program at the Foundation of Lustgården Mälardalen started in 1992 and was inspired by the discussions in the scientific community concerning the connections between emotions, immunity, and malignant diseases. Professional persons (oncologists, surgeons, social workers, and psychologists) as well as patients were involved in trying to identify methods that would improve QOL and would meet the needs of the patients, which were not, at that time, met in ordinary clinical practice. The procedure indicates a reasonable degree of face validity. This led to a knowledge information-based support program supplemented with relaxation, qigong, and liberating dance. The intervention concept was fully developed and tested in a pilot study [11] before the present study started. The intervention took place within 4 months after the end of adjuvant treatment (chemotherapy and radiotherapy) and ran for 7 days, followed by a 4-day follow-up 2 months after the initial visit. Trastuzumab and long-term endocrine treatment could be ongoing.

The team leader was the director of the foundation and was responsible for the time schedules, all practical arrangements, as well as taking care of the groups outside the actual supportive rehabilitation program.

The team members were oncologists ($n=3$), social workers ($n=2$), a psychologist ($n=1$), an art therapist ($n=2$), massage therapists ($n=2$), a dietician ($n=1$), as well as a person trained in qigong and mental visualization. All personnel had long occupational experience.

Table 1 Patient demographics, disease characteristics, and treatment

	Group	
	Intervention (n=191)	Control (n=191)
Age (years)	57.5 (30–84)	58.5 (38–83)
Breast surgery		
Mastectomy	42	47
Breast conservation	149	144
Axillary surgery		
Sentinel node biopsy	84	78
Axillary clearance	96	103
No axillary dissection	11	10
DCIS or LCIS	12	14
Invasive carcinoma	179	177
Lymph nodes		
Negative	104	107
≤3	53	62
4–8	16	8
≥9	7	4
Axillary surgery not performed	11	10
Receptors		
ER+	158	158
ER−	21	24
ER not known	12	9
PR+	109	115
PR−	69	65
PR not known	12	11
Her2+	35	28
Her2−	62	66
Her2 not known	94	97
Tumor size (cm)		
≤2	109	122
>2	82	69
Menopause		
Premenopausal	53	42
Postmenopausal	127	143
Not known	11	6
Chemotherapy	81	80
Radiotherapy	188	187
Tamoxifen	123	126
Aromatase inhibitor	24	18
Hormone before cancer diagnosis	24	32
Marital status		
Married	137	155
Widowed, single	54	36
Children at home	46	43

The guests received information from the oncologist about breast cancer, etiology, risk factors, treatments, and physical and psychological effects of diagnosis and treatments. Questions from the guests were discussed.

The psychologist informed about psychological reactions to a serious disease and different coping strategies, as did social workers, who in addition informed about practical, social details such as being on the sick list, insurances, and economic consequences of illness. The dietician discussed the importance of food and nutrition.

The informative education parts were mixed with mild physical exercise, relaxation training, massage, qigong, mental visualization, and nonverbal communication (art and liberating dance therapy).

The intervention also included social activities such as concerts and visits to museums and restaurants which also gave the participants the opportunity to be together with individuals with similar experiences in a beautiful and restful milieu and unencumbered by the troubles of daily living, such as taking care of family members, keeping a household, and work commitments. The program has previously been described in a pilot study of unselected patients with different cancer diagnoses [11]. The rehabilitation was evaluated by the guests and their answers were continuously monitored.

The consultants received regular guidance from a psychologist who did not take part in the intervention. Meetings were held once every 6 months to discuss the procedures, observations made, and experiences gained. Control patients were subjected to standard follow-up routines.

The present study is part of a randomized study covering several different aspects of rehabilitation, anxiety and depression [12], and health economy and health care utilization (unpublished data).

Evaluation of health-related quality of life

Intervention and control patients answered questionnaires before rehabilitation and after 2, 6, and 12 months. HRQOL was measured using the Swedish version of the EORTC QLQ-C30 (quality of life) and BR23 (breast cancer) [13]. This is a 30-item standardized measure composed of multi-item scales and single items that reflect the multidimensionality of the QOL construct. It includes a global health and QOL scale (two items), five functioning scales (physical, role, emotional, cognitive, and social) of combined items, three multi-item symptom scales (fatigue, pain, and emesis), and the remaining single items assess additional symptoms commonly reported by cancer patients (dyspnea, sleep disturbance, appetite, diarrhea, and constipation) and, finally, the financial impacts of the disease and treatment. The breast cancer module BR23 includes 23 breast cancer-specific questions grouped into the functioning scale (i.e., body image, sexuality, and future perspective) and the symptom scales and a single item assessing systemic side effects, arm

symptoms, breast symptoms, and hair loss. The scoring of the QLQ-C30 and QLQ-BR23 items were performed in accordance with the EORTC scoring manual. All scores were linearly transformed to a 0- to 100-point scale. In both instruments, high functioning scores represent better functioning and QOL, whereas high symptomatic scores indicate more severe symptoms. A cutoff value of 50 has been suggested by Koller and Lorenz to indicate clinically significant impairments [14] and those cutoff values were used in this paper.

Fatigue was measured by the Norwegian version of the fatigue questionnaire (FQ) [15]. The FQ is a self-report instrument for the assessment of fatigue, including symptoms experienced during the last month compared with how the subject felt when last feeling well. Additionally, two items ask about the duration and the extent of fatigue. FQ measures physical fatigue (PF) which encompasses seven items, while mental fatigue (MF) encompasses four items. All 11 items are designated as total fatigue (TF). Each item has four response choices. Likert scoring (0, 1, 2, and 3) is used for the construction of PF, MF, and TF. Higher scores imply more fatigue. The FQ has originally been validated in primary care and has shown good face and discriminative validity [16], but has also been used on cancer patients [15].

Statistics

Power calculation was performed based on the assumption that 50 % of breast cancer patients experience some kind of psychological distress during the first year of disease. To be able to detect 15 % point differences in psychological distress between the intervention and the control group after 1 year, with a power of 80 % and a significance level of 5 %, we would need a total number of 340 patients. In order to allow for at least a 10 % dropout rate, we aimed for 400 patients.

Linear mixed effect models evaluated longitudinal changes within and between groups for QOL. Random subject effects were estimated for the intercept and slope for time (interval between questionnaires in months). In order to test whether outcomes for the two groups varied in time, an interaction term was included between time and intervention.

All p values were two-sided and statistical significance was considered to be present at $p<0.05$. The linear mixed effect models were performed with the statistical software package SAS and further analyses were performed with the R statistical software package.

Results

Quality of life

At baseline, there were no significant difference between the intervention and control groups, but the levels on the functional scales were lower and levels on the symptomatic scales were higher (Tables 2 and 3) when compared with data from healthy Swedish women [17].

In a mixed linear multivariable regression model, there was a statistically significant effect over time on the global health score (F value=4.28, p=0.0051), role functioning (F value=7.07, p=0.0001), emotional functioning (F value=7.70, $p<0.0001$), and social functioning (F value=11.12, $p<0.0001$) in both the intervention and control groups. There was also an effect over time on the symptom scales: fatigue (F value=13.58, $p<0.0001$), nausea and vomiting (F value=5.16, p=0.0015), insomnia (F value=3.80, p=0.0099), and financial difficulties (F value=5.41, p=0.0011). Similar time-dependent effects were seen on the breast scale (BR23) on body image (F value=10.95, $p<0.0001$), sexual functioning, future perspective (F value=10.79, $p<0.0001$), systemic side effects (F value=4.46, p=0.0040), and breast symptoms (F value=38.95, $p<0.0001$), but none of these differences were affected by intervention, only by time.

There were no significant effects of intervention (compared with controls) on HRQOL as measured by the EORTC QLQ-C30 and BR23, either for the whole intervention group or for the patients who had received chemotherapy and those who had not (Tables 2 and 3).

Fatigue

At baseline, there were no statistically significant differences between the intervention and control groups, either as regards MF or PF. The average level of mental fatigue was 5.6 in the intervention group and 5.4 in the control group. The average level of PF was 11.1 in the intervention group and 11.0 in the control group. However, this is a much higher value than in a healthy population [18]. There was a decrease in fatigue from baseline to 2 months both in the intervention and control groups and the fatigue score continued to decrease over time up to 12 months in both groups, but the differences between the groups were not statistically significant (Fig. 2).

Patients who had received chemotherapy scored higher on both MF and PF both in the intervention and control groups, but there were no statistically significant differences between the intervention and control groups at any point in time.

Discussion

In this randomized controlled trial (RCT), the support group intervention was not shown to have any statistically significant effects on HRQOL, as measured by the EORTC QLQ-C30 and BR23, or fatigue, when measured by the Norwegian version of the fatigue scale, which, of course, does not

Table 2 EORTC QLQ-C30 mean scores from time of baseline in the experimental and control groups using a linear mixed model adjusted for marital status, number of children, and level of education

EORTC QLQ-C30		Time				***p* value**
Outcome	Independent	Baseline	2 months	6 months	12 months	
QLQ	Intervention	62.6	66.3	67.5	69.7	0.6442
	Control	60.2	65.0	63.0	64.6	
PF	Intervention	76.5	79.1	80.2	76.5	0.7580
	Control	76.5	78.3	77.8	77.9	
RF	Intervention	70.5	77.3	79.6	80.1	0.4949
	Control	68.7	80.4	76.8	76.2	
EF	Intervention	66.8	71.8	74.4	77.3	0.3538
	Control	68.0	73.9	71.5	74.4	
CF	Intervention	72.7	73.6	75.1	75.6	0.8727
	Control	75.2	77.0	78.1	76.1	
SF	Intervention	74.3	81.4	81.4	83.2	0.8654
	Control	73.3	83.5	82.2	83.4	
FA	Intervention	42.1	33.4	31.9	30.2	0.9066
	Control	42.7	34.3	34.7	32.9	
NV	Intervention	7.9	5.7	3.9	4.0	0.2018
	Control	6.7	4.1	5.8	4.1	
PA	Intervention	30.1	24.9	25.8	22.3	0.4541
	Control	30.5	22.8	26.4	27.2	
DY	Intervention	28.0	25.8	28.0	24.5	0.8196
	Control	30.4	26.3	26.9	26.4	
SL	Intervention	40.8	38.0	33.8	29.7	0.5454
	Control	41.4	37.6	39.1	35.2	
AP	Intervention	10.3	7.7	7.6	6.0	0.8282
	Control	11.1	7.1	9.6	7.1	
CO	Intervention	9.8	10.2	8.0	6.6	0.4450
	Control	11.1	7.6	9.5	8.4	
DI	Intervention	10.9	7.2	9.0	9.1	0.8997
	Control	9.9	7.5	9.7	10.1	
FI	Intervention	19.5	18.8	18.9	14.7	0.1631
	Control	22.7	14.5	17.1	13.7	

QLQ global health status, *PF* physical functioning, *RF* role functioning, *EF* emotional functioning, *CF* cognitive functioning, *SF* social functioning, *FA* fatigue, *NV* nausea and vomiting, *PA* pain, *DY* dyspnea, *SL* insomnia, *AP* loss of appetite, *CO* constipation, *DI* diarrhea, *FI* financial impact

Table 3 EORTC BR23 mean scores from time of baseline in the experimental and control groups, using a linear mixed model adjusted for marital status, number of children, and level of education

EORTC QLQ-BR23		Time				*p* value
Outcome	Independent	Baseline	2 months	6 months	12 months	
BRBI	Intervention	70.1	79.4	80.3	81.2	0.9467
	Control	69.1	77.5	77.3	78.1	
BRSEF	Intervention	21.1	24.0	26.1	27.7	0.9226
	Control	18.1	18.5	21.8	23.2	
BRSEE	Intervention	60.3	61.0	60.5	57.7	0.8746
	Control	58.6	58.7	61.7	59.5	
BRFU	Intervention	50.9	55.5	61.9	64.7	0.3183
	Control	49.6	56.9	55.6	60.2	
BRST	Intervention	23.1	20.1	17.8	18.4	0.4744
	Control	23.9	21.5	22.2	20.7	
BRBS	Intervention	34.9	26.4	22.8	16.6	0.4087
	Control	34.4	23.4	23.1	19.1	
BRAS	Intervention	19.0	25.4	23.3	20.5	0.1245
	Control	23.4	22.1	24.6	23.6	
BRHL	Intervention	44.0	32.3	27.6	35.3	0.1176
	Control	51.2	14.7	45.1	36.7	

BRBI body image, *BREF* sexual functioning, *BREE* sexual enjoyment, *BRFU* future perspective, *BRST* systemic therapy side effects, *BRBS* breast symptoms, *BRAS* arm symptoms, *BRHL* upset by hair loss

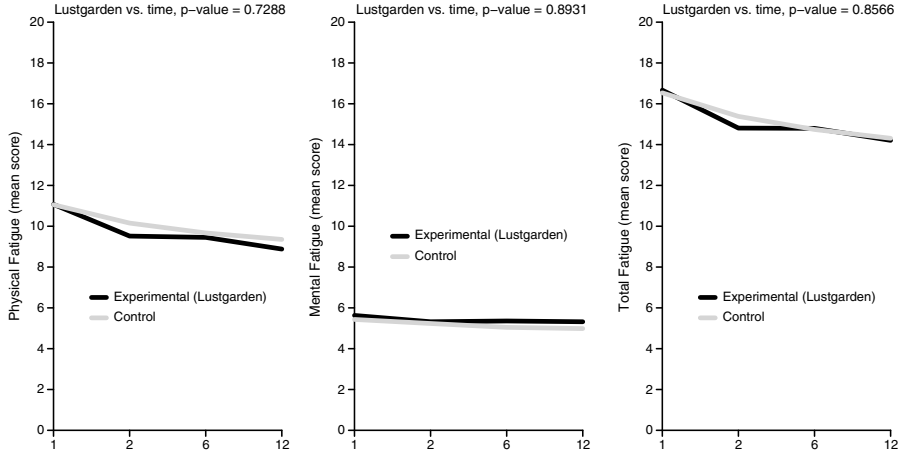


Fig. 2 Comparison between the intervention and control groups regarding PF, MF, and TF

preclude the possibility of other effects, not covered by the questions in the instruments used in this study.

The strengths of the present study are the design, a prospective RCT in a group of women with primary breast cancer, and a near complete follow-up (87 %) of those who actually participated in the study.

A weakness is the selection of patients who agreed to participate. This limits the possibility of drawing conclusions about breast cancer patients in general. On the other hand, such selection will always be present when discussing rehabilitation and previous studies on dropouts compared with study patients, indicating that cancer patients who actually accept participation are those who have the highest needs [19–21]. One indication of this is that five women (mean age, 52 years) in the control group dropped out immediately after randomization because they wanted to participate in the intervention. No other differences between dropout patients and those who completed the study were noted.

We studied the effect of a preexisting comprehensive concept for rehabilitation containing different methods of intervention developed by the initiators and professionals in collaboration with the patients according to patient wishes and needs. We did not evaluate the effect of each part of the program and this will probably affect the reproducibility of the intervention. However, all patients followed the complete program and participated in the different sessions on an equal basis, and the purpose of the study was to evaluate the effects of the complete program, not the individual components. The intervention program in our study was based on 1 week of intensive training and education, followed by a 4-day follow-up 2 months later. This might not be the optimal design according to the results from the meta-analysis by Rehse and Pukrop [7]. They identified 37 controlled trials, not all randomized, showing a positive effect from psychosocial interventions on QOL in adult cancer patients. However, the patient population was a mixture of men and women, with differing diagnoses and diverging programs. The best effects were seen in men and after a prolonged intervention that lasted for at least 12 weeks. This makes a direct comparison with our results for a homogeneous group of women with a short intervention program difficult. The design of our intervention, with residential intervention for 7 days followed by four follow-up days in residential form, might be cost-intensive, but participants outside the study were often given grants from various foundations. In addition, comparisons with other studies are often not possible to carry out since it is rarely stated what interventions cost. A health economic analysis of our intervention program with sick leave and health care consumption will be performed and presented in a coming paper.

Our intervention was, with few exceptions, only psychoeducational with little or no physical activity, which means that you could not expect any effect on the physical parameters. In addition, the treatment of breast cancer patients in Sweden today can be considered good, with a lot of emphasis put into psychosocial support in the primary handling of the patients. Therefore, the addition of a brief extra support intervention might not be expected to provide any great effect. Mandelblatt et al. [22] found that the process of care, and not the therapy itself, seems to be the most important determinant of long-term QOL in a study which, however, only included women aged more than 65 years.

There exists a large number of studies concerning HRQOL in breast cancer patients, as summarized by Montazeri in a

bibliographic review [2]. He identified 37 articles on the effect of supportive care on QOL, most of which showed positive effects. Since this survey covers a very long time scale (1974–2007), one can see how the QOL studies developed over the years. Older studies (1970s and 1980s) usually only measured the QOL of patients, related to symptoms and side effects [23–25], and in the early 1990s, intervention studies became more common [26]. However, few of the studies were randomized [27–29], 10 included physical activity and 13 included some kind of drug therapy as well. RCTs became more common in the early 2000s, when we started our study, and studies with more physical activity have become more common in recent years. Nonrandomized studies have also been performed in recent years and Antoni et al. [30] found an improvement after intervention.

The difference in outcome between randomized and nonrandomized trials stresses the importance of performing randomized studies. The absence of a randomized comparison group makes it impossible to disentangle the effect of time and intervention, as illustrated by our study. In the present study, we found an improvement over time for many dimensions of QOL in both the intervention and control groups, but no distinguishable effect of the intervention. This is in contrast with the findings of Dolbeault et al. [31], who in an RCT, found an effect of psychoeducational intervention on emotional and role functioning, as well as in health status and fatigue in breast cancer women. Their randomization was performed after an interview to identify eligible patients, making their patient choice selected.

Our results corroborate a recently published review by Fors et al. [32] that could not demonstrate any effect of psychosocial intervention on breast cancer patients. They identified 54 studies, in all 18 RCTs out of which 3 RCTs (n=881) specifically examined the effect of psychosocial rehabilitation on QOL and no treatment effects were found, whereas they found a short-term benefit as regards fatigue. In an earlier review of reviews [33] of psychological interventions for distress, it was concluded that "there is no convincing evidence of broadly effective psychological interventions."

In our study, we chose to include women of all ages in the same intervention. It has been shown that younger women (<50 years) have more psychosocial symptoms and impaired QOL than older women and have also been shown to benefit more from psychosocial rehabilitation than older patients [39], possibly due to a more pronounced need of existential support. Older patients, unlike younger patients, have more physical needs, depending on more prominent physical symptoms and comorbidities [40] A small decline in physical activity or moderate fatigue can be devastating for fragile elderly women [22] and, therefore, they probably have different rehabilitation needs [34–38]. Our rehabilitation program did not differentiate the treatment according to age, which could have diluted any possible effects of intervention.

Our interventions were mainly based on psychosocial support with no or minimal physical content. In contrast, Fillion et al. [41] showed in an RCT that intervention that combines stress management, psychoeducation, and physical activity resulted in an improvement on fatigue, energy levels, emotional distress at the 3-month follow-up, and physical QOL at post-intervention, compared with a control group. Heim et al. [42] found in an RCT that structured physical training during rehabilitation and thereafter can improve symptoms of chronic fatigue and QOL in breast cancer patients. Korstjens et al. [43] concluded, in a study on physical and psychosocial rehabilitation, that significant improvements in all outcome variables of QOL and their results indicated that physical rehabilitation was essential for improvement of psychological parameters, but this study was not randomized. van Weert et al. [44] found that multidimensional rehabilitation in a study with groupwise randomization with individual exercise, sports, psychoeducation, and information had a statistically significant and clinically relevant beneficial effect on HRQOL compared with monodimensional intervention. However, in both these trials, they included all types of cancer, making it difficult to draw conclusions regarding female breast cancer patients, and they had no control group, which makes it difficult to determine whether the effect was due to intervention or a normal restoration after the diagnoses and treatment. To summarize current knowledge, there is a Cochrane report showing that exercise appears to have some benefit in the management of fatigue, both during and after cancer treatment [45].

Conclusion

We conclude that we could not show any effect of support intervention according to this concept with residential intervention for 1 week and 4 days of follow-up on HRQOL or fatigue. Other types of intervention need to be tested in the future, such as prolonged intervention over time, intervention with a different content, intervention adjusted to different age groups, or perhaps intervention with more physical activities. There is also a need to define valid outcome measurement for such interventions. Many QOL instruments, such as QLQ-C30, focus mainly on physical activities, which may not be optimal for psychosocial rehabilitation projects. It also needs to be pointed out that, despite anticipated difficulties, support intervention programs need to be tested within the framework of randomized clinical trials due to the obvious risks of selection bias and a time-dependent effect on QOL after a breast cancer diagnosis.

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Conflict interest None of the authors have declared any conflict of interest.

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Paper III

A randomized controlled trial of support group intervention after breast cancer treatment: Results on sick leave, health care utilization and health economy.

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Abstract

Background

More than 50% of breast cancer patients are diagnosed before the age of 65. Returning to work after treatment is, therefore, of interest for both the individual and society. The aim was to study the effect of support group intervention on sick leave and health care utilization in economic terms.

Material and Methods

Of 382 patients with newly diagnosed breast cancer, 191 + 191 patients were randomized to an intervention group or to a routine control group respectively.

The intervention group received support intervention on a residential basis for one week, followed by four days of follow-up two months later. The support intervention included informative-educational sections, relaxation training, mental visualization and non-verbal communication. Patients answered a questionnaire at baseline, 2, 6 and 12 months about sick leave and health care utilization.

Result

There was a trend towards longer sick leave and more health care utilization in the intervention group. The difference in total costs was statistically significantly higher in the intervention group after 12 months ($p= 0.0036$)

Conclusion Costs to society were not reduced with intervention in its present form.

Key words: Support intervention, breast cancer, return to work, sick leave, health care utilization, health economy

Introduction

Breast cancer is the most common malignant disease in women (excluding non-melanoma skin cancer). Annually 1.3 million women are diagnosed on a worldwide basis, while in Sweden 7,300 women are diagnosed. The prognosis is generally good; approximately 90% are alive after 5 years, and 80% after 10 years. More than half of the women are diagnosed before the age of 65 and, thus, on full- time work. In Sweden, more than 80% of women are employed. Returning to work after initial treatment is, therefore, in the interest of both the individual and society. For the individual woman, returning to work is a measure of normalization and recovery (1). For society, sick leave means loss of production and costs for health insurance. We know from an extensive meta-analysis that breast cancer survivors are more likely to be unemployed than healthy control participants (2). As reviewed by de Boer et al, proposed mechanisms are job discontinuation, difficulty combining treatment with full-time work and physical or mental limitations (2). Still, the majority of breast cancer survivors return to work. Bouknight (3) found that more than 80% returned to work within 18 months, but obviously, some survivors do not(4) .

Several factors have been found to be associated with returning to work, such as chemotherapy (5, 6) age (7), education (6, 8, 9) and income (3), but very few randomized controlled studies have been carried out into interventions aimed at reducing the proportion of patients not returning to work (10). We have previously presented results from a prospective randomized controlled study of a support group intervention programme, with the main objective of studying possible effects on mood, fatigue and quality of life (11, 12). A secondary aim of that study was to investigate possible effects on sick leave and health care utilization.

The aim of the present analysis was, within the framework of a prospective randomized controlled trial, to study the effect of support intervention, after breast cancer treatment, on sick leave, health care utilization and health economy in women with primary breast cancer. Our hypothesis was that the intervention would have a possible beneficial effect on the women's symptoms, with less anxiety, depression and fatigue and better quality of life (13, 14). This effect would, in turn, lead to a shorter sick leave and a quicker return to work, with a corresponding reduction in the consumption of medical care and, finally, emanating in lower costs for society, however this assumption has little evidence. Fors et al (15) had in their review intended to study work disability, however they could not find any studies with these outcome measures.

Material and method

Subjects

All women with a newly diagnosed primary breast cancer were, during their postoperative radiotherapy, considered for participation. They were included between April 2002 and November 2007 at the Department of Oncology at the Central Hospital in Västerås, Sweden. During this period, 770 patients were referred for radiotherapy and 709 were assessed for eligibility. Patients were, for logistical reasons, recruited during their treatment with radiotherapy. Most patients treated at the hospital were referred for radiotherapy, but, according to current regional guidelines, a few elderly women merely underwent a mastectomy [see flow chart (Fig.1)]. The inclusion criteria in the study were a newly diagnosed primary breast cancer, no previous malignancy, the physical and mental capability to participate in group interventions and to fill in questionnaires and an expected survival time of more than 12 months. Due to the characteristics of the residential premises, patients with a physical disability were excluded. We also had to exclude patients with severe visual or hearing impairments, serious mental illness, dementia or active alcohol abuse, due to their

inability to participate in the intervention. Patients who had participated in group rehabilitations were also excluded in total, 54 patients. In the total group, the patients were between 30-84 years, which means that the issue of sick leave is not relevant to the entire group. We, therefore, limited the analyses to those who were under the age of 65 at the time of the intervention, which is the general age of retirement in Sweden.

All those fulfilling the inclusion criteria were informed about the study and, after acceptance to participate, all patients provided their written informed consent. The Ethics Committee at the University of Uppsala approved the study and patients were treated according to the Declaration of Helsinki.

Patients were stratified according to adjuvant chemotherapy and randomized in blocks of four by the use of closed envelopes. In total, 382 women were included in the study, 191 in the intervention group and 191 in the control group. See Figure 1.

Support intervention

The support-intervention programme at the Foundation of Lustgården Mälardalen resort started in 1992 and was developed by discussions in the scientific community concerning the connections between emotions, immunity and malignant diseases. Professional persons, e.g. oncologists, surgeons, social workers, psychologists as well as patients were involved in the process that sought to identify what they thought would improve quality of life, or rather, what would meet the needs of the patients, which were not at that time met by ordinary clinical practice. The procedure was implemented in order to achieve a reasonable degree of face validity. This led to an information- based support programme supplemented with relaxation, qi-gong and liberating dance. The intervention concept was fully developed and tested in a pilot (16) study before the present study was initiated.

The intervention took place within four months of ending adjuvant treatment (chemotherapy and radiotherapy) and comprised a seven-day stay at the Foundation of Lustgården Mälardalen resort, where the participants took part in the support programme, followed by a four- day follow-up two months after the initial visit. Trastuzumab and long-term endocrine treatment could be on-going.

Control patients were subjected to standard follow-up routines at the Department of Oncology or Surgery.

Questionnaires and Analyses

Study patients answered questionnaires at baseline (after randomization but before intervention) as well as 2, 6 and 12 months after the intervention. We used a questionnaire, that we formulated (see appendix) with questions about family situation (single, married, cohabiting, divorced, children at home etc.), and open questions about occupation, sick leave and health care utilization.

Sick leave

The questions explored whether the patient was currently on sick leave and to what extent, as well as how many days the patient had been on sick leave during the last 12 months. For calculations about the number of participants as well as the number of days on sick leave, we did not include women who at baseline stated that they were retirees, early retirees or had unpaid work. For the calculation of the cost of sick leave, we included all women who at the time of answering the questionnaire indicated that they had been on sick leave for at least one day during the last 12 months. Based on these self-reported data, we calculated an estimate of the costs for the sick leave period. Since no data on the participants' actual incomes were

available, it was decided that the costs for sick leave should be based on an average monthly income of 2,900 EURO (25,000 SEK). According to the Swedish social security regulations during the years covered in the present study, this amounted to a sickness benefit of €73.62 (631 SEK) per day. Most women were on sick leave during the intervention, which, in most cases occurred in close proximity to the treatment. However, we lack detailed information.

The Swedish regulation on sickness absence

The social insurance system in Sweden is publicly funded and covers all who reside or work in Sweden, providing financial protection for persons with a disability or in connection with an illness. The first 14 days of a sick leave period are paid by the employer. The sickness benefit is approximately 80 % of the individual's income. You may be on the case of a sick leave for a maximum of 364 days during a 15- month period, but in severe disease such as cancer, this period can be extended. Disability pension can be granted if work capacity is permanently reduced by at least a quarter. One cannot, according to Swedish labour laws, be dismissed from work due to illness.

Health care utilization

Regarding health care utilization, the participants were asked separate questions about whether they had visited a general practitioner, a medical specialist, or a physiotherapist or performed any other health care visits. If the answer was affirmative, the participants were asked how many times they had visited each particular medical speciality during the last 12 months. In the calculations of health care consumption, we used the reported number of visits to any health care provider during the study period. For calculation of the costs for the different health care services, we used the calculated costs of a visit to a health care provider

at the Västmanland County Hospital, Västerås in the year 2005, which was 192 EURO for a doctor's appointment in primary care, 471 EURO for consultations by medical specialists and 87 EURO for visits to a physiotherapist (data from the financial unit at the hospital). However, we lack information about the cost of other health care visits and, therefore, this is not included in the economic calculation.

Total cost

The health economic cost was calculated separately as the sum of the cost of sick leave and the cost of health care utilization, with or without the cost of the intervention, 2,300 EURO, which was the actual cost that we were charged, and included food, lodgings, personnel costs and other expenses for the boarding.

No calculation of the costs for society in terms of loss of production or filling of vacancies could be performed.

Power analysis

The present study is part of a randomized study covering different aspects of rehabilitation. Power calculation was performed based on the assumption that 50% of women treated for breast cancer show some sign of psychological distress (17), which was reported in the literature at that time. To be able to detect a 15% lower proportion of psychological distress between the intervention and the control group after one year, with a power of 80% and a 5% significance level, we would need a total number of 340 patients. In order to allow for at least a 10% drop-out rate we aimed for 400 patients.

Statistical analysis

Differences between the intervention and control groups were tested with Pearson's χ^2-test for categorical variables, except in one case when the assumptions behind Pearson's χ^2-test were not fulfilled and Fisher's exact test had to be used instead. The Mann-Whitney test was used for discrete variables, and since not all continuous variables could be considered to be normally distributed, the Mann-Whitney test was used also for continuous variables. In the questionnaire, the number of days on sick leave during the last 12 months was categorized as 0, 1-2, 3-7, 8-14, 15-30, 31-60, 61-90, 91-180, 181-365 or >365 days. For the analyses in this study, each category was replaced with the median of the category's lowest and highest values and >365 days set to 365 days. The health economic cost of sick leave was then calculated as number of days on sick leave times €73.62. The number of days on sick leave as well as the health economic cost of sick leave were then treated as continuous variables. The number of visits to each specific kind of health care provider was categorized as 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or >10 visits. For the analyses in this study, the category >10 visits was set to 11 visits. The economic cost of health care utilization was then calculated as the sum of i. the number of visits to a doctor in primary care €192 (1374 SEK), ii. the number of visits for consultations by medical specialists €471 (3360 SEK), and iii. the number of visits to a physiotherapist €87 (620 SEK). The number of visits to each specific kind of health care provider was analyzed as a discrete variable, while the economic cost of health care utilization was treated as a continuous variable. Statistical analyses were performed with IBM SPSS Statistics and R, with p-values <0.05 considered statistically significant.

Results

Primary treatment

Two hundred and ninety-three patients were treated with breast-conserving surgery and 89 underwent a mastectomy. One hundred and sixty underwent sentinel node biopsy only, 198 a level I-II axillary dissection and 24 patients had no axillary surgery. Chemotherapy was administered to 161 patients, either pre- or postoperatively. Radiotherapy was delivered to 375 patients - to the breast in all patients who had undergone breast-conserving operations and to adjacent lymph node stations if involvement of the axilla was present. Antibody treatment was used in patients with HER2-positive tumours and endocrine therapy to most endocrine responsive patients. For further details on primary treatment, see (12). The clinical characteristics of the patients were extracted from the patients' records and are to be found in Table 1.

Response rate

The response rate was 92% at baseline, 88% at 2 months, 84% at 6 months and 81% at 12months se flow chart (figure 1).

Sick leave

At baseline (time for randomization), 121 (63.4%) in the intervention and 115 (60.2%) in the control group (p=0.528) were employable (defined as not retired, no early-age disability, and no unpaid employment).Of these, 20 were unemployed, 10 in the intervention group and 10 in the control group.

Of those that were employable at baseline, 71 (64.5%) in the intervention group and 65 (63.7%) in the control group were on sick leave (p=0.901). At 2, 6 and 12 months, 47 (44.3%) and 42 (45.7%) (p=0.853), 38 (36.2%) and 29 (32.6%) (p=0.599), 26 (27.1%) and 22 (25.3%)

(p=0.783) were on sick leave in the intervention and the control groups, respectively. The differences between the groups were, thus, not statistically significant (Figure 2).
At baseline, women treated with chemotherapy in the intervention group had, on average, been on sick leave for 241 days during the previous 12 months compared with 234 in the control group. The accumulated sick leave for the previous 12-month period increased slightly in both the intervention and control group until the 2 month cut-off, but, thereafter, the proportion of women on sick leave decreased up to the 12- month follow-up in both groups. The differences between the groups were not statistically significant (Table 2).

Women not treated with chemotherapy in the intervention group, had on average only been on sick leave for 84 days compared with 86 days during the previous 12 months in the control group (p=0.539). This increased slightly in the intervention group up to the 6- month follow-up. In the control group, there was a decrease at 2 months and an increase at 6 months but a significant decrease in both groups up to 12 months. There was no significant difference between the groups at any point in time (Table 2).

Health care utilization

There was no statistically significant difference between the groups regarding the number of visits to medical specialists, general practitioners or physiotherapists at any time after the intervention period. There was no significant difference between the groups regarding contacts with other health care providers (e.g. chiropractors, naprapaths and masseurs) at baseline or at 2 months but, of those treated with chemotherapy, women in the intervention group consulted other health care providers more often than women in the control group after six and 12 months (p=0.006 and p=0.015, respectively) (Table 3).

Health economics.

The total costs for sick leave and consumption of health services at each follow-up during the study period decreased in both the intervention and control group from baseline to the 12-month follow-up. The total costs for the intervention group were higher at all points in time and the differences between the groups reached statistical significance after 12 months (Mann-Whitney p=0.036) (Table 4), Fig. 3-5.

Adding the cost of the intervention made the cost for the intervention group statistically significantly higher at all times of measurement.

Discussion

This prospective randomized trial of the effects of support intervention in women with primary breast cancer showed no positive effects of the intervention on sick leave, health care utilization and health economy. On the contrary, there was a tendency for women undergoing the intervention to have a longer sick-leave period and to seek other health care providers more often when compared with control patients. The total cost of sick leave and consumption of health services was statistically significantly higher for the intervention group after 12 months, and it was also higher, but not significantly higher at any measured time, even before the cost of the intervention has been included. This is contrary to the results of Simpson et al (18), who found a 23.5 % cost reduction after a psycho-social intervention, but they only studied the effect of the intervention on the cost of health care consumption. Analyses of whether positive effects on anxiety (12) or other psychosocial or existential effects outweigh the increased costs were beyond the scope of this article.

The reasons for the lack of a positive effect could be multifactorial. The intervention could have been too short to alleviate patients' symptoms (19), or the content of the intervention

might have been suboptimal to demonstrate any direct impact on sick leave and health care consumption. There exists only a few previous studies for comparison, since intervention studies rarely measured sick leave or had return to work as an outcome (10). A recently published Cochrane review demonstrated low quality evidence for psychological interventions on return to work rates and a moderate quality evidence for multidisciplinary interventions involving physical, psychological and vocational components (20). Another important aspect may be that the intervention actually influenced the patients' thoughts and feelings and created a need for sick leave to handle and cope with their anxiety. This was also discussed in an article by Damjaer (21) et al where they studied early retirement after breast cancer. During the intervention, many women had the opportunity to focus on themselves for the first time in their life and not take care of family and relatives. This may have led to a change of priorities in favour of a longer sick leave (7).

Another weakness in our study may be that women themselves had to state their sick leave and we did not collect the data from any official record. On the other hand, the women in this study were asked to indicate the extent to which they had been on sick leave due to their breast cancer. This distinction might be difficult to disentangle from a register. Women may, however, have interpreted this question differently. Some may have regarded the whole sick leave period as caused by breast cancer and treatment while others may have interpreted it as fatigue or depression. This distinction is probably difficult to disentangle even if you study the sick leave records since the same may apply to doctors issuing the certificates. One could, therefore, argue that any sick leave period during the follow-up should be regarded as caused by breast cancer.

Another weakness is that we lack information about the income of the women and, therefore, had to estimate this as the average income in Sweden. It is well known that breast cancer is more frequent in women from higher social classes. However, for comparison, of the two

randomized groups the exact level of income does not matter. We also lack data on women's health before the breast cancer diagnosis, which can also be regarded as failing. Petersson (22) et al showed that women with poorer health before diagnosis had longer sick- leave periods.The study participants had, during the intervention, received an opportunity to try different methods of alleviating symptoms, such as massage, relaxation and qigong. This may have contributed to women in the intervention group who received chemotherapy to search for other health care providers such as massage therapists.

Bouknight (3) showed that work-place adjustments played an important role in breast cancer patients' return to work, which has also been shown by Pryce (23) in a study of patients with different cancer diagnoses. Perhaps this is a better way forward, having a multimodal approach and working closely with employers, when planning for patients' return to work. Previous studies have put forward the idea that interventions to help patients return to work should be individually tailored and conducted in close co-operation with occupational health experts and employers (24, 25) and studies on this are on-going and should be investigated further.

Since we could not see any faster return to work or reduced number of physician and physiotherapist visits in the intervention group, we were not able to show any economic gain from this type of this intervention, rather a higher cost. The question is, of course, whether other types of intervention with more physical elements would be more cost- effective but. Haines (26) et al could not show any efficacy and economic efficiency of a multimodal physical activity programme. In a study by Lemieux (27) on psychosocial intervention in metastatic breast cancer patients, they could not show any decrease in health care system resource utilization.

The cost of our intervention was, when we conducted our study, 2300 € per patient and, thus the economic net effect of this type of rehabilitation is negative.

Conclusion

We conclude that we could not show any positive economic effect of support intervention on sick leave and, health care in this setting, with residential intervention for one week and four days of follow-up. In fact we saw a tendency towards longer sick leave and more health care utilization and we could show that the total cost in the intervention group was actually higher and that this difference was statistically significant after twelve months. Future randomized studies with sick leave as outcome measures, should be work-directed, in closer co-operation with employers and insurance agencies, to make it easier for cancer patients to return to work.

Conflict of interest statement

None of the authors have declared any conflict of interest.

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Table 1 Distribution of patients according to surgical intervention, node status, tumour characteristics, menopausal status, post-operative endocrine treatment and civil status at baseline.

	Group		
	Intervention *(n=191)*	**Control** *(n=191)*	**P-value**
Age, mean (range)	57.5 (30-84)	58.5 (38-83)	0.360
≤40 år	12	8	0.776
41-50 år	34	34	
51-65 år	106	105	
≥ 65 år	39	44	
Surgery			
Mastectomy	42	47	0.545
Breast conservation	149	144	
Sentinel node biopsy	85	80	0.606
Axillary clearance	95	103	0.413
Neither axillary dissection ,nor sentinel node	11	10	0.822
Cancer in situ	12	14	0.685
Lymph nodes			
Negative	104	107	0.370
≤3	53	62	
4-8	16	8	
≥9	7	4	
Lgll not done	11	10	
Receptors			
ER+	158	158	0.730
ER-	21	24	
ER not known	12	9	
PR+	109	115	0.800
PR-	69	65	
PR not known	13	11	
Her2+	15	10	0.585
Her2-	82	84	
Her2 not known	94	97	
Tumour size			
≤2 cm	109	122	0.174
>2 cm	82	69	
Menopause			
Pre-menopausal	53	42	0.158
Post-menopausal	127	143	
Not known	11	6	
Chemotherapy	81	80	0.918†
Radiotherapy	188	187	1.000‡
Tamoxifen	123	126	0.747
Aromatase inhibitor	52	42	0.235
Hormone before cancer diagnosis	24	32	0.247
Civil status			
Married, cohabiting	136	151	0.076
Single, divorced, widow	55	40	
Have children living at home	47	43	0.629
Education level			
Elementary school	60	59	0.857
High school	42	46	
College/University	77	71	
Missing	12	15	

† Randomization stratified on this variable.

‡P-value from Fisher's exact test.

Table 2. Sick leave: Mean days on sick leave during the last 12 months following randomization in women of working-age. Retirees, early retirees or women with unpaid work are excluded. Comparison between intervention and control group, Patients are stratified according to treatment with chemotherapy.

		Sick leave						
		Intervention			Control			Mann-W
	Time	n=	Mean(days)	sd	n=	Mean(days)	sd	p value
Chemo-therapy	0 Month	57	241.4	±88.1	56	233.8	±82.3	0.401
	2 Month	58	246.6	±97.7	50	252.8	±98.7	0.646
	6 Month	56	240.5	±125.6	46	208.7	±119.3	0.164
	12 Month	48	154.8	±153,4	45	123.3	±148.8	0.319
Not Chemo-therapy	0 Month	51	84.5	±91.4	44	85.8	±75.5	0.539
	2 Month	48	86.2	±85.4	40	79.1	±81.2	0.949
	6 Month	49	93.4	±108.4	38	89.9	±99.7	0.959
	12 month	45	49.0	100.8	40	40.0	±87.7	0.399

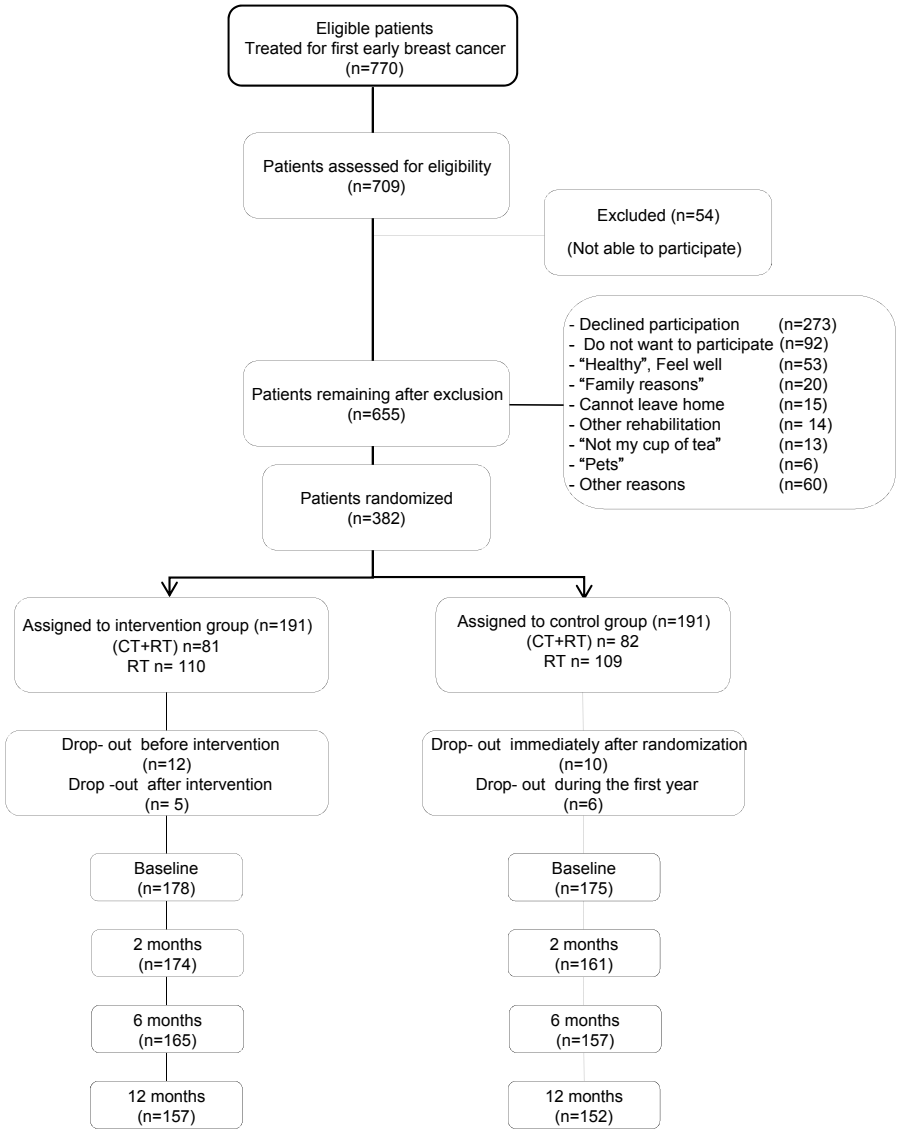
Table 3. Health care utilization: Average number of visits to general practitioners, hospital specialist, physiotherapists and other health care providers for the 12 months following randomization. Intervention group vs. control group at baseline, 2, 6 and 12 months after randomization. Patients are stratified according to treatment. M-W=Mann-Whitney

			Healthcare utilization						
			Intervention			Control			M-W
			n=	Mean	sd	n=	Mean	sd	p value
Chemotherapy	0 Month	Gen.prac	71	0,9859	±1,57201	70	1,2857	±2,27872	0,904
		Specialist	66	4,8333	±4,8185	66	4,8636	±4,84811	0,94
		Physiother.	74	1,027	±2,4605	64	1,0938	±2,64106	0,862
		Other	63	1,9524	±2,52362	59	1,4746	±2,47996	0,331
	2 Months	Gen.prac	72	1,1806	±1,99525	62	1,1613	±2,36916	0,497
		Specialist	66	4,576	±4,671	64	3,531	±4,125	0,173
		Physiother.	70	1,3571	±2,67048	60	2,1333	±4,05248	0,738
		Other	70	0,6286	±2,11394	62	0,5	±1,81749	0,459
	6 Months	Gen.prac	69	1,5797	±2,71383	64	1,1719	±1,93181	0,799
		Specialist	71	2,916	±3,652	61	2,279	±3,204	0,233
		Physiother.	68	2,3235	±3,94908	65	2,1538	±3,70064	0,71
		Other	71	1,2254	±2,88938	61	0,1639	±0,82017	**0,006**
	12 Months	Gen.prac	66	1,4394	±2,30136	61	1,1311	±1,727	0,603
		Specialist	63	1,952	±2,524	59	1,475	±2,48	0,079
		Physiother.	65	2,6154	±4,09532	60	2,0333	±3,77308	0,402
		Other	64	1,2969	±3,09982	56	0,25	±1,49241	**0,015**
Not Chemotherapy	0 Month	Gen.prac	98	1,051	±2,13644	89	1,0112	±1,99713	0,986
		Specialist	90	2,4778	±3,20543	87	1,7586	±2,91733	0,051
		Physiother.	96	0,6771	±2,36863	93	1,0645	±2,72989	0,128
		Other	89	0,7978	±1,31581	81	0,8148	±1,60555	0,828
	2 Months	Gen.prac	94	0,8191	±1,30312	84	1,0238	±1,94488	0,672
		Specialist	92	2,0543	±2,694	80	1,725	±2,882	0,125
		Physiother.	96	0,5521	±1,86305	88	0,8182	±2,41901	0,987
		Other	92	0,1957	±1,18821	86	0,2674	±1,39262	0,633
	6 Months	Gen.prac	91	1	±1,63299	85	1,4706	±2,50518	0,559
		Specialist	93	1,882	±2,734	81	1,617	±2,634	0,506
		Physiother.	92	1,1522	±3,0162	81	1,0988	±2,80002	0,893
		Other	89	0,4045	±1,62172	77	0,1818	±1,02247	0,28
	12 Months	Gen.prac.	89	0,8764	±1,67074	82	1,122	±2,28463	0,883
		Specialist.	89	0,798	±1,316	81	0,815	±1,605	0,542
		Physiother.	93	1,086	±2,90672	84	0,9524	±2,55496	0,902
		Other	93	0,3011	±1,63378	80	0,25	±1,2376	0,701

Table 4. Total cost of sick leave and health care utilization (SEK) for the 12 months following randomization. Intervention group compared with control group.

	Intervention		Control		
Time	N	Mean±SD	n	Mean±SD	P-value†
0 month	143	86511.1±83014.0	141	78071.5±82415.9	0.172
2 months	146	85748.5±86165.8	130	80861.1±89899.4	0.407
6 months	148	78075.2±90088.7	128	67639.0±80454.3	0.240
12 months	141	49450.7±83196.7	132	38074.0.±72259.0	0.036
Difference 0-12 months	112	33098.8±74681.1	114	41231.1±64549.2	0.222

† P-values from Mann-Whitney test



1.

Figure1. Flow chart of participants' progress through the randomized trial.

CT=Chemotherapy RT=Radiotherapy

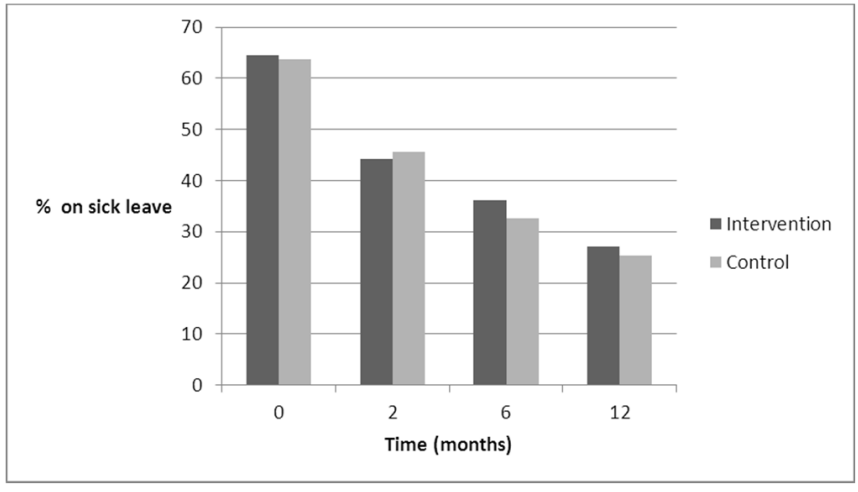


Figure 2. Proportion of women of working-age on sick leave, at baseline, 2, 6 and 12 months post intervention. Women with retirement pension, disability pension and women with temporary disability are excluded.

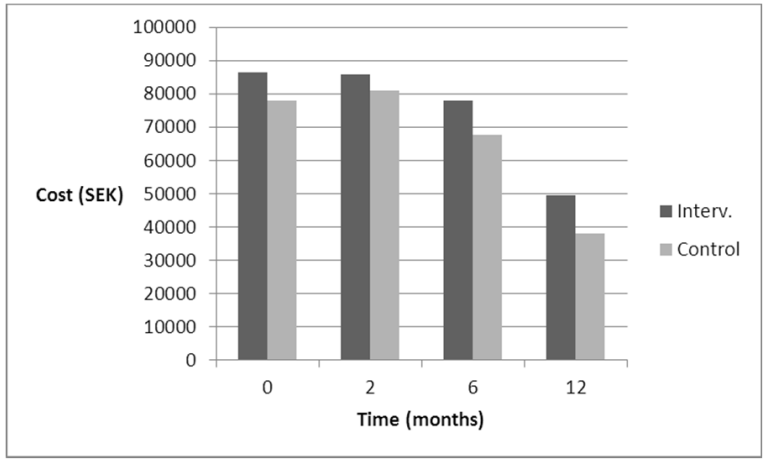


Figure 3. Total cost of sick leave and health care utilization (SEK) for the 12 months following randomization for the whole study population. Cost of intervention not included

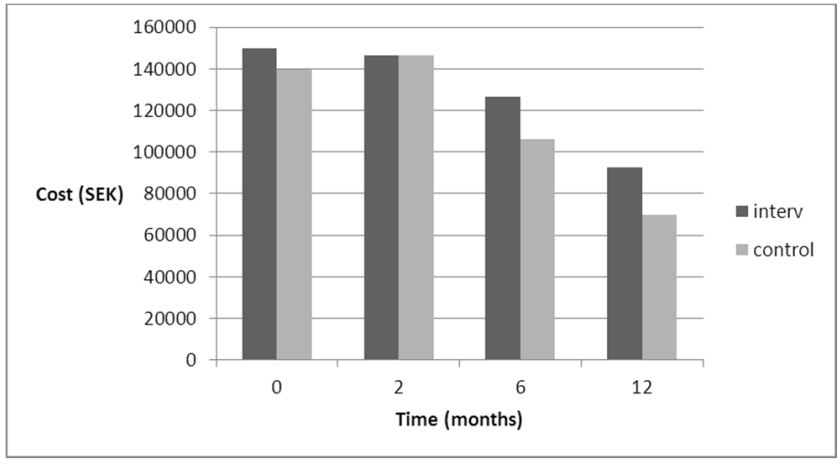


Figure 4. Total cost of sick leave and health care utilization during the last 12 months for the 12 months following randomization for women treated with chemotherapy. Cost of intervention not included

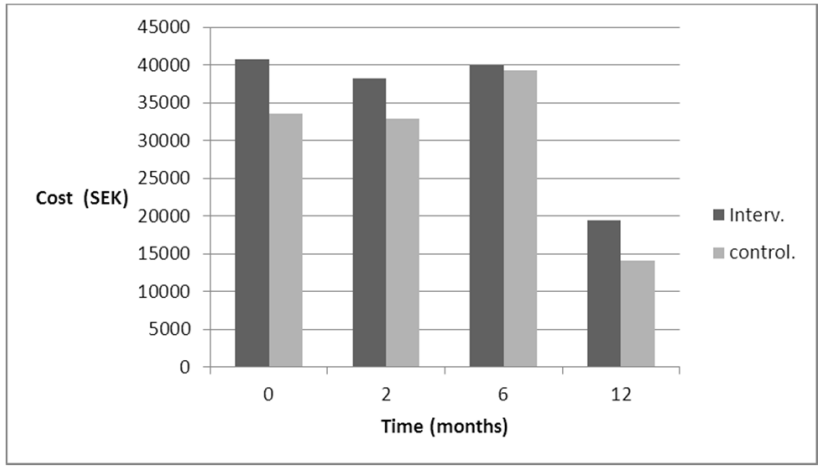


Figure 5. Total cost of sick leave and health care utilization for the 12 months following randomisation at each measuring point for women not treated with chemotherapy. Cost of intervention not included

Addendum

Attached you will find a number of issues concerning your personal situation and your health and quality of life. Please read each question, follow the instructions and select the answer that best matches your situation. It is important that you try to answer all the questions.

1. I am

O Single
O Married/Co-habiting
O Divorced
O Widowed

2. I live together with

O Spouse / Partner
O Spouse / partner, children
O Other relatives
O Other people
O Alone

3. I have children living at home

O Yes
O No

4. The children are in the following age groups

O 0-6
O 7-12
O 13-18
O Older than 18

5. Which is your highest level of education?

O Primary/Basic School
O 6 th form
O University education or equivalent

6. What is your principal occupation? Tick the option that is relevant right now

O Professionally employed
O Unemployed
O Student
O Retired
O Unpaid work (home-making)
O Other _____,

7. Is your economy affected by your illness?

O Yes.
O No

8. What Parts of the socio-economic net-work do you need today?

O Home help
O Physiotherapist
O Social welfare counsellor
O Social assistance
O Contact with primary care
O Others. _____, _____

9. How many days have you been on sick leave because of your symptoms over the past 12 months?

O 0 days ,O 1-2 days ,O 3 ~ 7 days ,O 8-14 days ,O 15-30 days
O 31-60 days ,O 61-90 days, O 91-180 days , O 181-365 days ,O more than 365 days

10. Are you on sick leave today?

O Yes
O No
If yes, to what degree?
O 25%, O 50%, O 75%, O 100%

11. Do you have sick leave compensation today?

If yes, to what degree?
O 25%, O 50%, O 75%, O 100%

12. Have you been awarded a disability pension?

O Yes
O No
If yes, to what degree?
O 25%, O 50%, O 75%, O 100%

13. Have you sought treatment because of your symptoms over the last 12 months?

Family doctor
O No
O Yes

If Yes, number of times

O	O	O	O	O	O	O	O	O	O	O
1	2	3	4	5	6	7	8	9	10	>10

Medical specialist
O No
O Yes

If Yes, number of times

O	O	O	O	O	O	O	O	O	O	O
1	2	3	4	5	6	7	8	9	10	>10

Physiotherapist.
O No
O Yes

If Yes, number of times

O	O	O	O	O	O	O	O	O	O	O
1	2	3	4	5	6	7	8	9	10	>10

Other (Chiropractor, Naprapath or the like)
O No
O Yes

If Yes, number of times

O	O	O	O	O	O	O	O	O	O	O
1	2	3	4	5	6	7	8	9	10	>10

Paper IV

Long-term follow-up of a randomized study of support group intervention in women with primary breast cancer

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Abstract

Background

Despite a fairly good prognosis, many breast-cancer patients suffer from symptoms such as anxiety, depression and fatigue, which may affect health-related quality of life and may persist for several years. The aim of the present study was to perform a long-term follow-up of a randomized study of support group intervention in women after primary breast cancer treatment.

Materials and Methods

Three hundred and eighty two women with primary breast cancer were randomized to support group intervention or control group, 181 in each group. Women in the intervention group participated in one week of intervention followed by 4 days of follow–up two months later. This is a long-term follow-up undertaken, in average, 6.5 years after randomization. Patients answered the questionnaires EORTC-QLQ 30, BR 23, HAD and the Norwegian version of the fatigue scale (FQ).

Results

After adjusting for treatment with chemotherapy, age, marriage, education and children at home, there was a significant improvement in physical, mental and total fatigue (FQ), cognitive function, body image and future perspective (EORTC QLQ 30 and BR23) in the intervention group compared with controls. The proportion of women affected by high anxiety and depression scores were not significantly different between the groups.

Conclusion

Support intervention significantly improved cognitive function, body image, future perspective and fatigue, compared with to the findings in the control group.

Key words Long-term follow-up, support group intervention, breast cancer, anxiety, depression, fatigue, and health- related quality of life

Background

Despite a fairly good prognosis for breast-cancer patients after treatment (90% are alive after 5 years, and 80% after 10 years), many women suffer from symptoms such as anxiety,

Despite a fairly good prognosis for breast-cancer patients after treatment (90% are alive after 5 years, and 80% after 10 years), many women suffer from symptoms such as anxiety, depression and fatigue, which may affect health- related quality of life and may persist for several years. Twenty to thirty percent of breast cancer patients show measurable signs of anxiety and/or depression during the year after diagnosis (1). Breast cancer patients have also been shown to have higher levels of depressive symptoms than other cancer patients (2). The depressive symptoms are most pronounced during the first year after diagnosis, but studies have also shown that up to 15% suffer from depressive symptoms 5 years after diagnosis (3) and symptoms of anxiety can persist for several years (4).

In addition, studies have also shown that breast cancer patients have a great need of support for many years after diagnosis (1).

Symptoms of depression have a negative influence on patients' quality of life (5) and might also affect recurrence, recovery and even survival (6, 7). Symptoms that primarily affect health- related quality of life (HRQoL) are distress, fatigue, reduced energy and a loss of stamina.

Fatigue seems to be the predominant cause of a reduced quality of life. Thirty to 50% of breast cancer survivors have problems with fatigue ,which may persist for up to 5 years (8) Arndt et al (9) found fatigue to be the strongest predictor of impaired quality of life at one year after diagnosis and Meeske (10) found that 41 % of breast cancer survivors were fatigued 2-5 years post diagnosis. Reinertsen (11)found that women may experience fatigue up to 10 years after multimodal treatment, with about one third having chronic fatigue (CF) and about one fourth having persistent fatigue (PF). Reidunsdatter (12) concluded that fatigue and breast symptoms increased during radiotherapy (RT)and that extended RT was a predictor of

increased fatigue. Furthermore symptoms that often affect breast cancer patients, but are often neglected are those of an existential character (13).

In order to improve cancer symptoms as distress, anxiety, depression and reduced HRQoL in women treated for breast cancer, many different types of psychological interventions have been described. The short-term results have been divergent and the most recent studies have not shown any effect (14-17).

There are few studies with a longitudinal follow-up. Ganz (18) found that long-term disease-free survivors with no adjuvant therapy reported good health- related quality of life, but those who received adjuvant therapy had poorer functioning in several dimensions of HRQOL.

Since many women have symptoms of their breast cancer and treatment that persist for years after treatment, there is a need of studies with long-term follow-ups (14, 19).

The aim of the present study was to analyze the long- term effect of support intervention on different aspects of HRQoL, anxiety, depression and fatigue.

Material and methods We have previously presented results from a randomized controlled study on support group intervention in primary breast cancer (17, 20),All newly diagnosed breast cancer patients between April 2002 and November 2007 presenting at the Department of Oncology at the Central Hospital in Västerås, Sweden, for postoperative radiotherapy were scrutinized for participation. See flow chart (Fig.1). The inclusion criteria were a newly diagnosed primary breast cancer, the physical and mental capability to participate in group interventions, able to fill in questionnaires Individuals with dementia (for example demented persons, severe visual and auditive impairments, serious mental illness, active alcohol abuse and because of the conference centres' premises physical disabled were excluded), and an expected survival of more than 12 months. We also excluded patients who had participated in

group rehabilitations previously or had a former history of any malignant disease, in total 54 patients. All meeting the inclusion criteria were informed about the study and all patients gave their written informed consent. The Ethics Committee at the University of Uppsala approved the original study and the follow-up study and patients were treated according to the Helsinki declaration.

Patients were stratified into those who had received adjuvant chemotherapy and those who had not, and randomised in blocks of four by the use of closed envelopes. In total, 382 women were included in the study, 191 in the intervention group and 191 in the control group.

Women in the intervention group participated in a one- week support intervention program with four days of follow-up after two months on a residential basis at the Foundation of Lustgården, Mälardalen. During the intervention, the patients received information about cancer aetiology, risk factors, treatment, physical and psychological effects and coping strategies. The theoretical -educational lectures and group discussions were intermixed with physical exercise, relaxation, Qi-gong, and non –verbal communication (art- and dance therapy). The programme has previously been described in detail (20).

Control patients underwent standard follow-up routines at the Department of Oncology or Surgery. All answered questionnaires at baseline (after randomization but before intervention), and after 2, 6 and 12 months.

We have now conducted a long- term follow-up of participants in this study.

All women in the earlier study, except those assigned by medical records to be suffering from dementia or not deemed able to complete a questionnaire, were informed by letter about the follow-up study and, after acceptance to participate, all patients gave their written informed consent

Questionnaires and Analyses

Study and control patients received the same questionnaire as those used in the previous study, on short-term effects. We used the Swedish version of the HAD scale to measure symptoms of anxiety and depression. It is a validated scale, commonly used worldwide to discriminate between anxiety and depression (21-23). The responses to the HAD scale were analysed as originally described (24). The scale consists of seven items reflecting anxiety and seven reflecting depression. Each item is rated on a four- point scale; 0- less than before; 1- not so much; 2- quite a lot and 3- very much, giving a maximum of 21 for depression and anxiety, respectively. Scores >10 on either subscale indicate probable cases of depression or anxiety and subscale scores in the range of 8-10 represent possible cases(21, 24) . In the statistical analysis we considered only those with high anxiety score (probable anxiety or depression).

In order to measure Health related Quality of life we used EORTC QLQ 30 and BR 23 questionnaires. The EORTC QLQ 30 is a 30-item standardized assessment, composed of multi-item scales and single items that reflect the multidimensionality of the quality of life construct. It includes a global health and quality of life scale (two-items), five functioning scales (physical, role, emotional, cognitive, and social) of combined items, three multi-item symptom scales (fatigue, pain and emesis) and the remaining single items assess additional symptoms commonly reported by cancer patients (dyspnoea, sleep disturbance, appetite, diarrhoea, constipation) and finally, the financial impacts of the disease and treatment. The breast cancer module BR 23 includes 23 breast cancer specific questions grouped into the functioning scale (i.e., body image, sexuality, and future perspective) and the symptom scales and single items assess systemic side-effects, arm symptoms, breast symptoms, and hair loss. The scoring of the QLQ-C30 and QLQ-BR 23 items were performed in accordance with the EORTC scoring manual. All scores were linearly transformed to a 0-100-points scale. In both

instruments, high functioning scores represent improved functioning and HRQOL; whereas high symptomatic scores indicate more severe symptoms.

Fatigue was measured by the Fatigue Questionnaire (FQ), initially developed by Chalder (25), translated and validated by Loge(26) and used in cancer patients (27) and now translated to Swedish, although not formally validated, as the Swedish and Norwegian languages are mutually understandable and the populations are similar.

The FQ is a self-report instrument for assessment of fatigue, including symptoms experienced during the past month compared with how the subject felt when last feeling well. Additionally, two items ask about the duration and the extent of the fatigue. FQ measures physical fatigue (PF) and encompasses seven items, while mental fatigue (MF), encompasses four items. All 11 items are designated total fatigue (TF). Each item has four response choices. Likert-scoring (0, 1, 2, 3) is used for the construction of PF, MF and TF and the scores are summated resulting in score ranges of 0-28 for PF, 0-16 for MF and 0-44 for TF. Higher scores imply more fatigue. The FQ has originally been validated in primary care and has shown good face and discriminative validity (25).

The questionnaires were sent to women in the original study group after 3.6-9.5 years (mean 6.54) in the intervention group and 3.7-9.6 years (mean 6.52) in the control group (p=0.921).

We compared our results in this long-term follow-up study with our results in the initial study, at baseline and at 12 months and in relation to support-intervention or control patients.

Statistical analysis

The outcome variables of interest were anxiety and depression, fatigue (physical, mental and total) as measured by FQ and quality of life as measured with the 15 scales of EORTC QLQ-C30 and the 8 scales of EORTC QLQ-BR23. Anxiety and depression were analyzed as binary categorical variables (anxiety/depression or not, defined as HAD>10 or not), while the outcome variables from the FQ, EORTC QLQ-C30 and EORTC QLQ-BR23 scales were analyzed as continuous variables.

Results for categorical variables are presented as frequencies and percentages, while continuous variables are presented as means and standard deviations (SD). Differences between intervention and control groups were tested univariately with Pearson's χ^2-test for categorical variables and Mann-Whitney's *U*-test for continuous variables. Fisher's exact test was used for categorical variables in a couple of cases where the assumptions underlying Pearson's χ^2-test were not fulfilled. Univariate tests of differences between baseline or the 12 month follow-up on the one hand and long-term follow-up on the other within the intervention or control group, respectively, were performed using McNemar's test for categorical variables and Wilcoxon's signed rank test for continuous variables. The choice of using the non-parametric Mann-Whitney's *U* and Wilcoxon's signed rank test for continuous variables instead of the corresponding parametrical tests was based on the authors' assessment that the continuous variables were not normally distributed.

In the multivariate analyses, the differences between intervention and control groups were examined using linear regression analysis when the outcome variable was continuous and binary logistic regression analysis when the outcome variable was categorical, adjusting for

baseline levels of the outcome variable as well as chemotherapy treatment, age, marriage status, education level and having children living at home. The statistical analyses were performed in IBM SPSS Statistics 20. For all statistical tests, a two-sided p-value of<0.05 was considered statistically significant.

Results

Of the 382 women included in the study at baseline, 39 (10.2%) had died,[23 (12.0%) in the intervention group and 16 (8.4%) in the control group (p=0.237)]. Furthermore, 12 (3.5%) of the women still alive, [7 (4.2%) in the intervention group and 5 (2.9%) in the control group (p=0.509)], were assessed to be in too poor health to be able complete in the questionnaires. The questionnaires were thus sent to 331 (86.6%) of the 382 participants included at baseline; 261 (78.9%) of these responded. The response rate was significantly higher (p=0.030) in the intervention group (n=135, 83.9%) than in the control group (n=126, 74.1%) (Figure 1). The mean (SD) time of follow-up was 6.54 (1.58) years for the intervention group and 6.52 (1.68) years for the control group (p=0.921).

Anxiety

At the long-term follow-up, n=16 (11.9%) of women in the intervention group had high HAD-anxiety scores compared with n=18 (14.4 %) in the control group (p=0.558 for difference between groups at follow-up). After adjusting for baseline anxiety levels, chemotherapy treatment, age, marriage status, education level and having children at home in a multivariate binary logistic regression model, the difference between the groups was still not statistically significant (OR=0.678; 95% CI: 0.282-1.628; p=0.385; Nagelkerke R^2=0.279).

When comparing anxiety levels between baseline and follow-up within groups, there was an improvement in both the intervention and the control groups. Further more, there was also an improvement in the control group but not the intervention group between anxiety levels at 12 months and follow-up at a mean of 6.5 years from baseline (Figure 2).

Depression

In the intervention group, n=7 (5.2 %) had high depression scores at follow-up, compared with=7 (5.7 %) in the control group (p=0.857 for difference between groups at follow-up). After adjusting for baseline depression level, chemotherapy treatment, age, marriage status, education level and having children at home in a multivariate binary logistic regression model, the difference between the groups was still not significant (OR=0.742; 95% CI: 0.162-3.396; p=0.701; Nagelkerke R^2=0.440). When comparing depression levels between baseline and follow-up within the groups, there was an improvement in the control group, but not in the intervention group. However, neither the intervention nor the control group demonstrated improved depression levels between 12 months and follow-up at a mean of 6.5 years from baseline (Figure 3).

Fatigue

The Fatigue symptoms in the intervention and control groups improved significantly over time (Table 2). Even if the improvement in fatigue was larger in the intervention group, the difference in improvement did not attain statistical significance in the univariate analyses (p=0.081 for physical, p=0.119 for mental fatigue and 0.067 for total fatigue). (Table 2).

However, in the multivariate regression model, there was a significant effect of the intervention on physical fatigue (slope=-1.110; 95% CI: -2.022 to -0.198; p=0.017; R^2=0.197), mental fatigue (slope=-0.552; 95% CI: -1.013 to -0.091; p=0.019; R^2=0.228) and total fatigue (slope=-1.638; 95% CI: -2.866 to -0.409; p=0.009; R^2=0.238) after adjustment

baseline fatigue ,chemotherapy treatment, age, marriage status, education level and having children at home. Most of this effect was observed in the stratified group of women treated with chemotherapy.

Health-related quality of life - EORTC QLQ 30 and BR 23

For the EORTC QLQ-C30 instrument, there was a statistically significant improvement from baseline within both the intervention and the control groups, mostly with regards to functioning and the symptom scales. There was also a statistically significant improvement within both the intervention and control groups on the EORTC QLQ-BR23 scales body image, future perspective, systemic therapy and breast symptoms. However, cognitive functioning (p=0.002) and pain (p=0.049) improved significantly only in the intervention group while hair-loss reached statistical significance only in the control group (p=0.034). Comparing the values at baseline with the long term-follow-up, there was a significantly greater improvement in the intervention group with regards to emotional function (p=0.042),cognitive function (p=0.049) fatigue (p= 0.023), body image (p=0.025), future perspective (p=0.019) and breast symptoms (p= 0.029) (Table 3).

After adjusting for baseline HRQLQ levels, chemotherapy treatment, age, marriage status, education level and, having children at home, in a multivariate linear regression model, a statistically significant effect of the intervention were found for cognitive function (p=0.042) body image (p=0.019), and future perspective (p=0.003) but not on global health, role function, emotional function, social function fatigue, systemic therapy and breast symptoms, as measured by EORTC QLQ 30/BR23 (Table 4). The explained variance (R^2) was substantial for cognitive function, body image and future perspective, ranging from 0.271 to 0.372 (Table 4). In the stratified groups, there was a significant effect of the intervention on global health status (p=0.044; R^2=0.338), cognitive function (p= 0.026 R^2=0.261) fatigue

(p=0.003; R^2=0.460), body image (p=0.021; R^2=0.426), future perspective (p=0.015; R^2=0.358) and upset by hair loss (p=0.021; R^2=0.093) in women treated with chemotherapy and on future perspective (p=0.039; R^2=0.302) in those not treated with chemotherapy.

Discussion

This long-term follow-up study of the effects of support intervention on breast-cancer patients demonstrated an improvement in the EORTC QLQ-C30/BR23 domains cognitive function, body image and future perspective for the intervention group compared with the control group, after adjusting for baseline QLQ levels, chemotherapy treatment, age, marriage status, education level and having children at home in a multivariate regression analysis. In the stratified group of women treated with chemotherapy, there was also an effect on global health, upset by hair loss.

The number of women with high anxiety and depression scores was not significantly different between the groups.

There were reduced proportions of high anxiety scores in the intervention group and an increased proportion in controls at 12 months compared with baseline and the difference between the groups were statistically significant (20). In the long-term follow-up there was a decrease in the proportion of high scores compared with baseline in both groups and a slight increase compared with 12 months in the intervention group; however, the difference between the groups were not statistically significant. The proportion of women with high depression scores showed a non-significant decrease at the 12 month follow-up (20) and increase in both groups at the long-term follow-up.The proportion was comparable with a healthy Swedish population.

Thus, there would appear to be a variation over time in anxiety and depression scores. One could speculate that this could be an effect of the intervention in the short run that wears out over time. The participation in the rehabilitation programme might create a sense of security that gradually disappears when the contact with the rehabilitation team ends. On the other hand the results may well be due to chance alone. Since a significant part of the effects on fatigue was achieved in the chemotherapy treated group, a possible explanation might be that the treatment-related fatigue dominated during the first 12 months and therefore possible benefits from the intervention were not possible to detectable. Coping and relaxation strategies might have had a more discernible effect when the treatment-related fatigue faded out.

The improvements in cognitive function, body image and future perspective (EORTC-QLQ30 and BR 23) demonstrated might also be a true effect of the programme, which was directed towards learning coping strategies. There was also an effect on global health, cognitive function fatigue, body image future perspective and upset by hair loss in the stratified group of women treated with chemotherapy were one can speculate that women treated with chemotherapy were so affected by their side-effects in the short-turn follow-up that the intervention could not have any effect on their symptoms.

Long-term follow- up studies on support group intervention are few (28), most studies perform a follow-up during the first year and occasionally after 2 years (14) and the few with long-term follow-ups often have survival as an outcome variable (16, 29)

Helgeson et al (28) showed an effect over time (3.5 years after diagnosis) in the group that received education intervention on quality of life (vitality, bodily pain and physical functioning), measured by SF 36 but no effect of peer discussion. They used interviews over

the telephone and completed their survey with a mailed questionnaire in accordance with SF36.Their follow-up was almost complete, only 2% were lost to follow-up.

Despite the fact that the questionnaires are designed differently, and measure different variables, their results on the quality of life could reflect ours with regard to, cognitive function, fatigue (FQ), body image and future perspective in women threated with chemotherapy.

The lack of an evident positive effect of the rehabilitation programme used in this setting may be due to the content of the programme, duration of the intervention and the selection, or rather non-selection, of patients. It has previously been described that factors that have a great significance for health- related quality of life in particular are age and children at home. Younger women have a greater need for psychosocial intervention (30) and older women of physical intervention (31). A small decline in physical activity or moderate fatigue could be devastating for fragile elderly women. An intervention programme should probably take such differences into account when designing a specific programme for the individual.

Moreover, different calamities occur in the patients' lives and families during the years which may be make it difficult for the patients to discriminate the symptoms associated with breast cancer from other life events.

The strengths of the present study are a homogenous group of patients, women with primary breast cancer and a long-term follow-up with a high response rate (mean time of follow-up 6.5 years). A weakness is that there is a selection of patients who agreed to participate (17), and, in the long- term follow-up slightly, fewer women in the control group wanted to participate. This limits the possibility of drawing general conclusions about breast cancer patients. Another weakness is that we included patients in the study without screening for

possible needs. Many women might not have a need of rehabilitation, while others had a greater need. The needs may also vary in nature, depending on age, treatment and family situation whereby some have more need of psychological or psycho-educational rehabilitation while others may have more physical needs.

When we planned our study, we chose to stratify women by treatment with chemotherapy, since we assumed that women with a more serious disease and heavier treatment would be more anxious and have a greater need of support and may thus have a better effect of the intervention. Our results showed that these women had a better effect on global health and the greatest effect on, cognitive function fatigue and body image than women not treated with chemotherapy. Even if there was a selection of women in the study, in which many women chose not to participate for family reasons and the organization of the arrangement (20), we were able to show that those with the highest needs benefit the most from the intervention. This is in line with earlier studies (32). The review by Fors (33) et al could not find any effect of psycho education on HRQoL however a short term benefit for fatigue was shown, only in their review. Follow-up usually occurred a year and an occasion at two years which prevents a direct comparison with our results. Others who have made systematic reviews of the effects of different types of intervention have found only a few long-term follow-up of the effect which complicates the comparison of our results (19, 34, 35). Most studies that have a long-term follow-up after support intervention have, survival as an outcome measure such as that by Boesen et al (36).

Our results illustrate the difficulties involved in evaluating the effect of support group intervention, especially after breast cancer, where symptoms in women treated for breast cancer are multi-facetted, may persist for a long time and the need of different types of

rehabilitation remains for several years in women affected by breast cancer (37). The questionnaires used today may not be able to capture all the symptoms or needs, particularly existential ones (13) and may be too blunt and may need to be developed and more refined. This was obvious also from our own additional data, recently published elsewhere(13). When persons in the intervention group were asked to spontaneously respond to an open-ended question about "*What did you appreciate most* (about the rehabilitation week)?", the largest group of responses were categorized to be of an existential nature, not particularly well covered by our questionnaires. Other studies show that existential issues are generally rated as important by cancer patients and this dimension comprises issues such as death awareness, meaning, awareness of values in life, need of a positive outlook and need for nature and relationships with fellow persons (38-41). A questionnaire such as FACIT-sp12 at least covers these issues partly , as the first part (8 items) are measuring a sense of meaning and peace, whereas the other part (4 items) focus on the role of faith in illness (39).However, there are aspects not covered by current questionnaires.

When we planned and began our study, focus was on psychosocial intervention, but, over the years, the knowledge and significance of physical activity in rehabilitation has increased (42, 43) and there is a Cochrane report (44) showing that exercise have some benefit in the management of fatigue, both during and after treatment. Further research should be conducted, rehabilitation programmes should be developed according to patient needs and requirements, individually tailored with regards to contents and duration and contain more physical aspects.

Conclusions

This long-term follow–up of a prospective randomised trial of support group intervention in a large homogenous group of women treated for primary breast cancer showed a significant effect of intervention on cognitive function, body image and future perspective (EORTC-QLQ30 and BR 23) and a significant effect on physical, mental and total fatigue in women measured by the Norwegian version of the (FQ), but no significant effect on levels of anxiety, depression (HAD).

Conflict of interest statement

None of the authors have declared any conflict of interest.

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Table 1 Distribution of patients according to surgical intervention, node status, tumour characteristics, menopausal status, post-operative endocrine treatment and civil status at baseline, with values given separately for all patients and including only long-term follow-up patients

	All patients			Long-term follow-up patients		
	Intervention *(n=191)*	**Control** *(n=191)*	**P-value**	**Intervention** *(n=136)*	**Control** *(n=125)*	**P-value**
Age, mean (range)	57.8 (30-84)	58.7 (38-83)	0.360	58.0 (40-79)	59.2 (38-83)	0.276
≤50 år	46	42	0.784	29	26	0.393
51-65 år	106	105		82	69	
≥ 65 år	39	44		24	31	
Surgery						
Mastectomy	42	47	0.545	27	32	0.298
Breast conservation	149	144		108	94	
Sentinel node biopsy	85	80	0.606	67	51	0.138
Axillary clearance	95	103	0.413	61	70	0.094
Neither axillary dissection, nor sentinel node	11	10	0.822	7	6	0.875
Cancer in situ	12	14	0.685	8	8	0.887
Lymph nodes						
Negative	104	107	0.370	83	63	0.274
≤3	53	62		35	48	
4-8	16	8		9	7	
≥9	7	4		1	2	
Lgll not done	11	10		7	6	
Receptors						
ER+	158	158	0.730	113	110	0.676
ER-	21	24		14	11	
ER not known	12	9		8	5	
PR+	109	115	0.800	77	80	0.567
PR-	69	65		49	39	
PR not known	13	11		9	7	
Her2+	15	10	0.585	9	6	0.662
Her2-	82	84		58	60	
Her2 not known	94	97		68	60	
Tumour size						
≤2 cm	109	122	0.174	81	82	0.397
>2 cm	82	69		54	44	
Menopause						
Pre-menopausal	53	42	0.158	34	26	0.143
Post-menopausal	127	143		92	97	
Not known	11	6		9	3	
Chemotherapy†	81	80	0.918	55	59	0.322
Radiotherapy	188	187	1.000‡	133	123	0.675‡
Tamoxifen	123	126	0.747	87	87	0.431
Aromatase inhibitor	52	42	0.235	33	35	0.540
Hormone before cancer diagnosis	24	32	0.247	19	19	0.818
Civil status						
Married, cohabiting	136	151	0.076	98	97	0.415
Single, divorced, widow	55	40		37	29	
Have children living at home	47	43	0.629	31	25	0.540
Education level						
Elementary school	60	59	0.815	48	41	0.699
High school	42	46		33	30	
College/University	77	71		46	50	

† Randomization stratified on this variable.
‡P-value from Fisher's exact test.

Table 2. Mean value of fatigue measured by the Norwegian version of the fatigue scale at baseline and long-term follow-up and change from baseline to long-term follow-up within the groups and comparison between intervention and control groups. P-values are from Wilcoxon's signed rank test for comparison between baseline and long- term follow-up within the intervention and control groups, respectively, and from Mann-Whitney's *U*-test for comparisons between the intervention and control groups.

			Intervention				Control		
Fatigue	Baseline	Follow-up	Change	P-value[a]	Baseline	Follow-up	Change	P-value[a]	P-value[b]
	Mean (SD)	Mean (SD)	Mean (SD)	Within group	Mean (SD)	Mean (SD)	Mean (SD)	Within group	Between groups
Physical	10.6 (4.2)	7.7 (3.2)	-3.0 (4.2)	**<0.001**	10.8 (4.0)	8.9 (4.2)	-2.0 (4.6)	**<0.001**	0.081
Mental	5.4 (2.4)	4.6 (1.8)	-0.9 (2.2)	**<0.001**	5.5 (2.1)	5.2 (2.2)	-0.4 (2.3)	**0.053**	0.119
Total	16.1 (6.1)	12.2 (4.3)	3.9 (5.8)	**<0.001**	16.4 (5.6)	14.0 (5. 9)	2.4 (6.0)	**<0.001**	0.067

[a]P-value for test of difference between baseline and follow-up within intervention and control groups, respectively.

[b]P-value for test of difference in change from baseline to follow-up between intervention and control groups.

Table 3. Health- related quality of life measured by EORTC QLQ 30 and BR 23: Mean scores at baseline and follow-up and mean changes within the groups from baseline to follow-up.and comparison between the intervention and control groups

		Intervention				Control				
		Mean value			p value change within the group	Mean value				
		Baseline (SD)	follow-up (SD)	mean (SD) change		Baseline (SD)	follow-up(SD)	Mean (SD) change	p value change within the group	p value change between the groups
EORTC-QLQ30	Global health status†	68.4(18.7)	75.0(21.7)	6.6(21.3)	**<0.001**	66.4(22.8)	70.4(24.2)	4.0(25.3)	**0.032**	0.459
	Physical function†	79.0(18.6)	78.8(22.1)	-0.2(17.6)	0.684	80.6(19.3)	78.5(21.8)	-2.1(19.6)	0.407	0.463
	Role function†	74.2(30.9)	84.1(26.5)	9.9(31.7)	**0.001**	72.4(33.6)	80.6(27.8)	8.2(36.0)	**0.020**	0.656
	Emotional function†	71.4(21.5)	81.2(21.2)	9.8(19.1)	**<0.001**	72.9(25.0)	77.5(22.7)	4.7(22.4)	**0.031**	**0.042**
	Cognitive function†	78.5(22.0)	84.4(18.5)	5.9(20.0)	**0.002**	81.4(21.6)	81.4(22.0)	0.0(22.2)	0.976	**0.049**
	Social function†	77.3(24.4)	88.3(20.7)	11.0(23.0)	**<0.001**	77.2(26.8)	84.3(25.5)	7.1(27.1)	**0.002**	0.242
	Fatigue‡	37.8(25.1)	24.7(23.8)	-13.0(24.6)	**<0.001**	36.2(24.5)	29.7(25.7)	-6.5(24.5)	**0.003**	**0.023**
	Nausea/Vomiting‡	6.4(15.2)	5.2(14.0)	-1.2(18.5)	0.433	4.5(11.8)	4.2(10.9)	-0.3(15.0)	0.785	0.459
	Pain‡	27.9(28.9)	24.1(28.7)	-3.8(25.7)	**0.049**	25.8(27.8)	26.5(29.3)	0.7(32.4).	0.795	0.410
	Dyspnoea‡	23.0(25.4)	19.1(24.6)	-3.9(28.9)	0.127	25.5(26.6)	23.5(27.6)	-2.0(30.0)	0.490	0.525
	Insomnia‡	39.8(34.0)	33.8(30.2)	-6.0(30.0)	**0.026**	37.2(33.7)	30.0(30.2)	-7.3(34.2)	**0.027**	0.970
	Appetite loss‡	7.8(18.0)	6.2(18.6)	-1.6(20.0)	0.423	8.5(17.0)	8.8(19.7)	0.3(22.4)	0.939	0.788
	Constipation‡	8.6(19.7)	9.9(21.5)	1.3(20.7)	0.429	10.6(23.7)	8.4(19.5)	-2.2(25.2)	0.273	0.202
	Diarrhoea‡	7.6(16.9)	6.2(15.6)	-1.3(21.2)	0.492	7.0(18.4)	8.2(18.4)	1.1(16.3)	0.448	0.315
	Financial problems‡	12.8(21.5)	8.0(20.5)	-4.8(23.8)	**0.031**	15.7(26.8)	7.4(20.6)	-8.3(29.0)	**0.003**	0.745
BR-23	Body image†	71.4(29.7)	86.0(23.9)	14.6(23.8)	**<0.001**	72..0(27.8)	80.3(26.2)	8.3(25.7)	**<0.001**	**0.025**
	Sexual functioning†	24.2(23.9)	22.0(22.4)	-2.2(22.7)	0.201	19.9(23.0)	18.7(22.1)	-1.0(22.0)	0.716	0.745
	Sexual enjoyment†	64.4(25.3)	65.2(28.7)	0.8(33.3)	0.933	67.7(26.5)	66.6(24.3)	-1.1 (25.1)	0.808	0.607
	Future perspective†	52.6(28.7)	70.4(26.4)	17.7(25.9)	**<0.001**	54.0(31.7)	62.4(27.8)	8.5(31.5)	**0.003**	**0.019**
	Systemic therapy‡	21.0(15.5)	15.6(13.1)	-5.4(12.5)	**<0.001**	21.5(17.8)	18.8(16.0)	-2.7(17.0)	**0.027**	0.146
	Breast symptoms‡	33.0(22.9)	10.3(13.6)	-22.6(23.0)	**<0.001**	29.6(23.3)	12.8(16.5)	-16.8(21.8)	**<0.001**	**0.029**
	Arm symptoms‡	15.4(18.4)	14.7(21.3)	-1.0(19.1)	0.581	19.0(23.0)	17.1(23.1)	-2.0(21.7)	0.260	0.573
	Hair loss‡	7.7(23.2)	6.7(20..3)	-1.1(29.6)	0.676	5.2(19.5)	11.0(26.3)	5.7(28.2)	**0.034**	0.236

† Higher is better; ‡ Lower is better.

Table 4. Health- related quality of life measured by EORTC QLQ 30 and BR 23 in a linear regression model; Effect of intervention adjusted for treatment with chemotherapy age, marriage, education and children at home.

	Domain	Slope (95%CI)		p value	R^2
EORTC-QLQ30	Global health status†	2.842	(-2.163-7.847)	0.264	0.489
	Physical function†	0.550	(-3.516-4.615)	0.790	0.206
	Role function†	1.835	(-4.463-8.133)	0.567	0.373
	Emotional function†	3.894	(-0.631-8.420)	0.091	0.272
	Cognitive function†	4.698	(-0.182-9.214)	**0.042**	0.271
	Social function†	3.315	(-1.847-8.477)	0.207	0.330
	Fatigue‡	-5.220	(-10.471-0.031)	0.051	0.059
	Nausea‡/Vomiting	0.961	(-2.216-4.137)	0.552	0.270
	Pain‡	-2.181	(-8.572-4.209	0.502	0.181
	Dyspnoea‡	-2.926	(-9.108-3.256)	0.352	0.310
	Insomnia‡	2.551	(-3.947-9.049)	0.440	0.174
	Appetite loss‡	-2.121	(-6.643-2.401)	0.356	0.203
	Constipation‡	2.438	(-2.320-7.197)	0.314	0.181
	Diarrhoea‡	-1.711	(-5.727-2.304)	0.402	0.112
	Financial problems‡	1.829	(-3.263-6.921)	0.480	0.373
BR-23	Body image†	6.6.233	(1.016-11.430)	**0.019**	0.329
	Sexual functioning†	0.672	(-4.165-5.509)	0.784	0.201
	Sexual enjoyment†	1.472	(-10.331-13.276)	0.804	0.296
	Future perspective†	9.080	(3.089-15.071)	**0.003**	0.372
	Systemic therapy‡	-2.828	(-5.820-0.164)	0.064	0.147
	Breast symptoms‡	-3.207	(-6.861-0.448)	0.085	0.327
	Arm symptoms‡	0.132	(-4.648-4.913)	0.957	0.045
	Hair loss‡	-4.562	(-10.623-1.499)	0.139	0.045

† Higher is better; ‡ Lower is better.

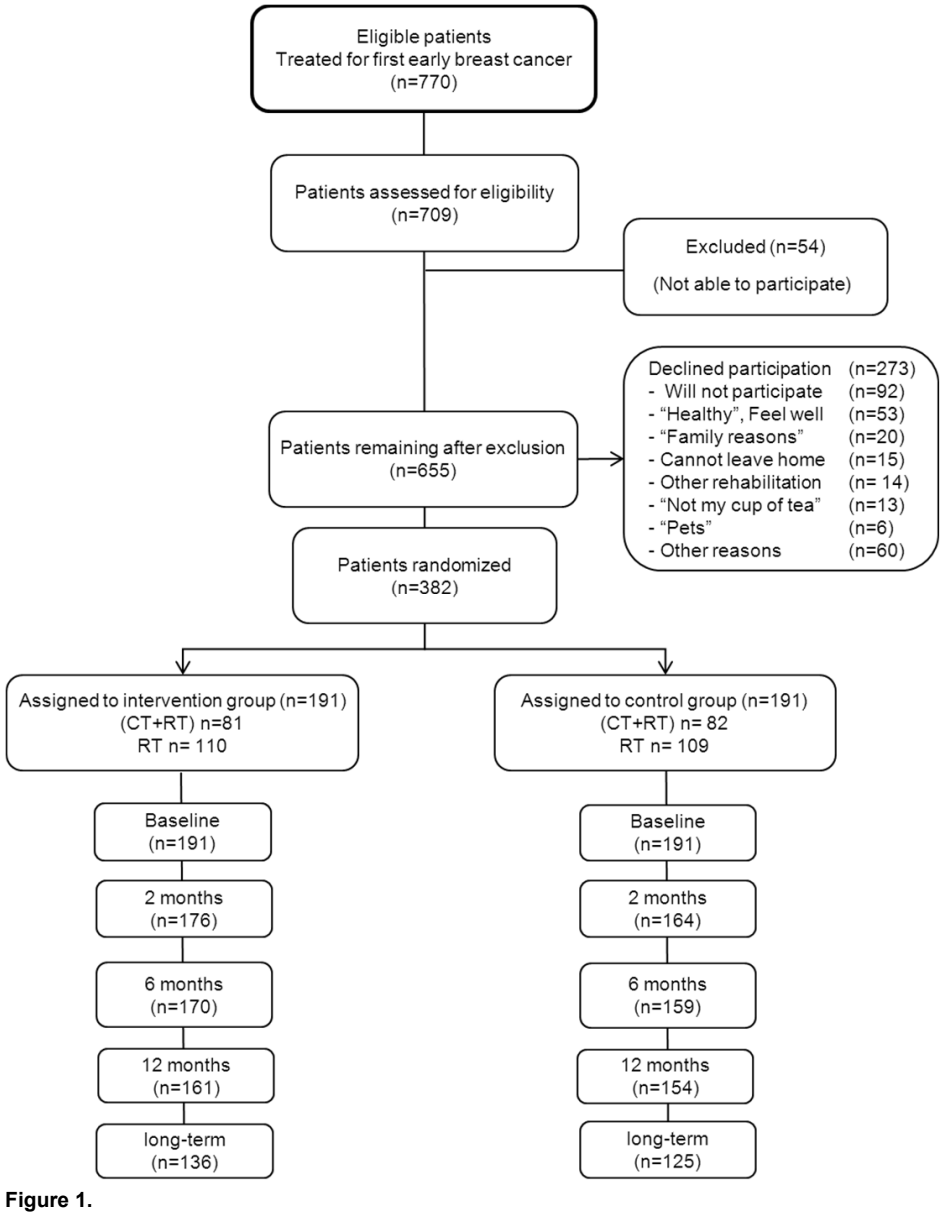

Figure 1.

Flow chart of participants' progress through the randomized trial.
CT=Chemotherapy RT=Radiotherapy

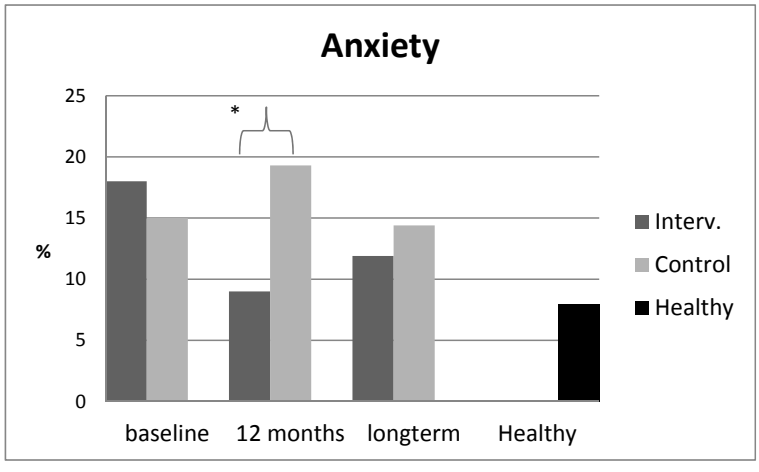

Figure 2.

Anxiety: Proportion of women with high anxiety scores at baseline, 12 months and long-term follow-up. Intervention group and control group compared with a healthy Swedish population with symptoms of anxiety. Intervention group: dark grey bars, control group: light grey bars and healthy: black bars

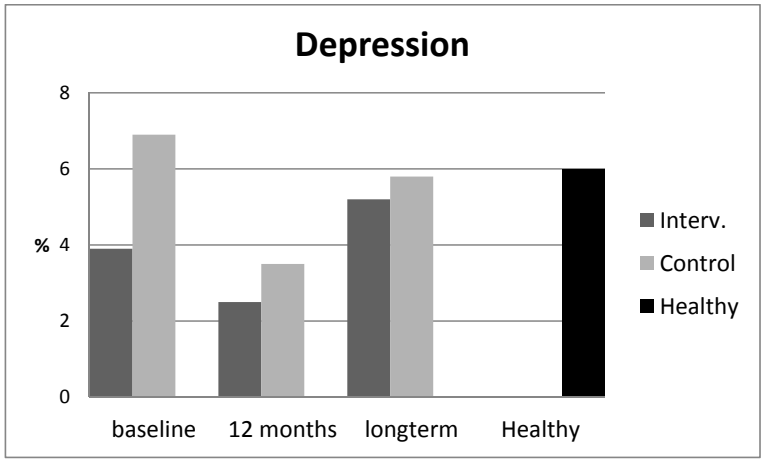

Figure 3

Depression : Proportion of women with high depression scores at baseline, 12 months and long-term follow-up. Intervention group and control group compared with a healthy Swedish population with symptoms of depression. Intervention group ;dark grey bars, control group light; grey bars and healthy; black bars