

Associations among baseline variables, treatment-related factors and health related quality of life two years after breast cancer surgery

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## **Abstract**

Provision of social support and rehabilitation for patients with physical, mental and functional problems after cancer treatment is important for long-term health-related quality of life (HRQOL). Effective use of human and financial healthcare resources requires identification of patients requiring rehabilitation. The objectives of the current study were to clarify the patterns of physical and psychosocial recovery over time, to evaluate the associations among baseline variables, treatment-related factors and HRQOL at 6 months, 1 and 2 years after breast cancer surgery, and to identify the significant factors predicting HRQOL at each point. A multicenter longitudinal study was performed to evaluate physical conditions, anxiety, depression and HRQOL at one month (baseline), 6 months, and 1 and 2 years after surgery in 196 patients (mean age: 53.3 years old) with early breast cancer and no postoperative recurrence. Physical conditions were evaluated using a patient-reported symptom checklist. HRQOL was rated using the Functional Assessment of Cancer Treatment scale-General (FACT-G) and the Breast Cancer subscale (FACT-B). Anxiety and depression were rated using the Hospital Anxiety and Depression Scale (HADS). More than 50% of patients had local problems of "tightness", "arm weakness" and "arm lymphedema", and systemic problems of "reduced energy, fatigue, and general weakness" postoperatively. The HRQOL score significantly improved one year after surgery, and scores for physical, emotional and functional well-being also increased with time, whereas the score for social well-being was highest at baseline and decreased with time. Depression and anxiety significantly improved with time. Concomitant disease, marital status and the presence of a partner, anxiety and depression at baseline, pathological lymph node involvement, and adjuvant intravenous chemotherapy were significant factors predicting FACT-G scores at 6 months and 1 and 2 years after surgery. Depression at baseline was a strong predictor of HRQOL up to 2 years after surgery. These results suggest that physical rehabilitation is required for tightness and lymphedema to improve long-term postoperative physical function. A further study of psychosocial interventions is required to improve depression and social well-being after breast cancer surgery.

**Key words:** Breast cancer; HRQOL; Depression; Anxiety; Chemotherapy

## **Introduction**

Data in the National Statistics of Cancer Registries by Region (1975-2004) indicate that the prevalence of breast cancer in Japan has increased continuously since 1975. More than 50,000 patients are thought to have breast cancer in 2004 and the mammary gland is the most common site of a malignant tumor in women [1]. Based on the Vital Statistics Japan database (Statistics and Information, Department, Ministry of Health, Labour and Welfare), the mortality of breast cancer has also increased, although this is still ranked fifth after lung, stomach, colon and pancreatic cancers. This suggests that breast cancer has a better prognosis than other solid cancers and that many patients overcome breast cancer. Cancer survivors in the United States have reached approximately 12 million and female patients with breast cancer accounted for 23% in 2006 [2].

Treatment for breast cancer has become increasingly complicated and includes surgery, radiotherapy, endocrine therapy, chemotherapy and targeted molecular treatment. These therapies are based on scientific evidence of survival benefits, but may have undesirable acute and chronic physical, functional, mental and social effects. Health-related quality of life (HRQOL) is a multidimensional, multifaceted concept that includes the influence of disease and treatment on the patient's life, with QOL being an important outcome of cancer therapy [3, 4]. The improvement of overall HRQOL after surgery for breast cancer is generally dependent on the time from diagnosis to treatment [5]. However, breast cancer patients after diagnosis have poorer physical functioning in comparison with healthy controls [6- 9], and more frequent malaise [10-12]. Furthermore, breast cancer patients feel more stress and anxiety about the future compared to the general population and have lower mental domain scores [13-15]. These findings suggest that the diagnosis and various treatments of breast cancer will affect the long-term HRQOL.

Cancer survivorship research seeks to identify, examine, prevent and control adverse cancer- and treatment-related outcomes. The most important task is to provide a social support system and rehabilitation for patients with long-term physical, mental and functional problems after cancer treatment,

with the goal of improving long-term HRQOL, on which social support has a great effect [5, 8, 14, 16]. To distribute limited human and financial healthcare resources more effectively, it is important to understand HRQOL of breast cancer patients comprehensively. This includes clarifying patterns of physical and psychosocial recovery over time, identifying social backgrounds, clinicopathological and treatment-related factors that influence long-term HRQOL, and identifying areas and persons requiring support in the future. Factors with significant effects on long-term HRQOL after treatment of breast cancer include age [18- 25], race [9, 25], educational status [19- 21], income [7, 8, 13], marriage [11, 13, 21, 24, 25], recurrence [9, 26], disease period [11, 20], surgical procedure [7, 19, 20], chemotherapy [8, 10, 11, 14, 20, 24], physical activities [27] and culture [25, 28]. In our previous longitudinal prospective study, the factors predicting HRQOL at one year after surgery were mood disturbance, poor body image, lower income and positive axillary nodes one month after surgery [17].

As described above, the improvement of overall HRQOL after surgery for breast cancer is generally dependent on the time from diagnosis to treatment, so evaluation at this point is very important when assessing HRQOL [8, 22, 23]. Social and clinicopathological factors that have significant effects on HRQOL may differ at different time points, and therefore accurate evaluation of HRQOL requires prospective studies. Many previous studies were cross-sectional, while few longitudinal prospective studies have been performed [8, 11, 14, 17-20, 26, 27].

The objectives of the current study were to clarify the patterns of physical and psychosocial recovery over time, to evaluate the associations among baseline variables, treatment-related factors and HRQOL at 6 months, 1 and 2 years after breast cancer surgery, and to identify the significant factors predicting HRQOL at each time point by prospectively determining HRQOL.

## **Patients and Methods**

### **Study design**

The study was designed based on the hypothesis that psychological distress, body image, lower income, and positive axillary nodes one month after surgery for breast cancer are important predictors of postoperative HRQOL in Japanese women. This hypothesis was developed from the results of our earlier study [17]. The current analysis was conducted as a multicenter longitudinal study. The subjects were patients with primary breast cancer who underwent breast surgery and their data of the surgical procedure, area of lymph node dissection, and lymph node metastases were available. All subjects gave written informed consent for participation in the study. The exclusion criteria were lymph node involvement of N2 or more in preoperative UICC TNM classification, preoperative therapy (including chemotherapy, endocrine therapy, radiotherapy), bilateral breast cancer, double cancer, cancer in pregnancy or the lactating period, and male breast cancer. Patients who met the inclusion criteria at less than 6 weeks after surgery for breast cancer were recruited. After registration, physical symptoms, anxiety and depression, and HRQOL (see below) were evaluated at baseline and 6 months and 1 and 2 years after surgery. Patients in whom recurrence was confirmed during the follow-up period discontinued the study. A total of 8 institutions in Japan participated in the study: Kawasaki Medical School Hospital, Shikoku Cancer Center, Showa University Toyosu Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Kurashiki Medical Center, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, National Cancer Center Hospital, and Fukushima Medical University Hospital.

#### Data collection

Information on marital and educational status, occupation, income and family was obtained from a baseline questionnaire. Information on the following clinicopathological and therapeutic factors was obtained from medical records: surgical procedures (mastectomy or breast-conserving surgery (BCS)), clinical stage, pathological stage, radiotherapy, performance status, postoperative chemotherapy and chemotherapeutic agents used, postoperative endocrine therapy and agents used, recurrence, and

concomitant disease.

#### Health-related quality of life instruments

HRQOL was assessed at one (baseline), 6, 12 and 24 months after breast cancer surgery using the Japanese version of the Functional Assessment of Cancer Treatment Scale-General (FACT-G) and the Breast Cancer subscale (FACT-B). The questionnaires were returned by mail. The FACT-G was developed by Cella et al. in 1993 to evaluate HRQOL of patients with chronic disease and has been widely used [29]. The FACT-G version 4 consists of 27 items: 7 in the physical subscale, 7 in the social and family subscale, 6 in the mental subscale, and 7 in the functional subscale. The FACT-B is a breast cancer-specific HRQOL questionnaire consisting of FACT-G and an additional 9 items in the breast subscale [30]. Higher scores indicate better HRQOL. The reliability and validity of the Japanese version of the FACT-G and FACT-B have been verified [31-33].

#### Instrument for psychosocial distress

The Hospital Anxiety and Depression Scale (HADS) was used to detect clinically significant anxiety and depression. The study period was the same as that of the HRQOL survey. The HADS is a 14-item self-rating scale [34-37] on which each item is rated on a scale of 1 to 4. Higher scores indicate a greater tendency for anxiety and depression. The validity and reliability of the Japanese version of HADS have been shown [38].

#### Patient-reported symptom check list

Physical problems related to disease and treatment were evaluated using a patient-reported symptom checklist. In our previous study, we developed a list of symptoms related to disease and treatment and collected these data in a structured interview [17]. In the current study, this list was translated into



Japanese and the patient-reported symptom checklist was developed. The checklist included 2 questions on body image, 11 on local postoperative problems, 2 on activities of daily living, 4 on systemic symptoms including fatigue, and 10 on physical activity, pain, weight and diet, acute post-surgical complications, radiotherapy, chemotherapy and endocrine therapy, recreation and social activities; i.e., 29 questions in total. The questionnaire uses a 5-point Likert scale of 0: not at all, 1: a little bit, 2: somewhat, 3: quite a lot, and 4: very much; in accordance with the FACT.

#### Statistical analysis

Changes in overall HRQOL; in physical, psychological, functional and social well-being domains, and corresponding facets; and in predictors of long-term HRQOL were evaluated in the study. Multiple regression analysis was performed to examine baseline variables that were predictive of HRQOL outcome (FACT-G, Breast Cancer subscale and FACT-B Trial Outcome Index) after 6 months and 1 and 2 years. The FACT-B Trial Outcome Index (TOI) is the sum of scores from the physical and functional well-being and the Breast Cancer subscale. The 23 items have a maximum sum of 92, reflecting a good HRQOL. The following baseline variables (data at one month after surgery) were used as independent predictors: demographic and medical characteristics (age [ $\leq 49$ , 50-69,  $\geq 70$  years old], marital status [married or with a partner / single or without a partner due to divorce or bereavement], children [presence / absence of children], education [junior or high school / university or higher], employment status [full-time or part-time job / housewife or jobless], household income [annual income < 5 million Japanese Yen (JPY) / 5 - 10 million JPY / > 10 million JPY], concomitant disease [history of hypertension, diabetes, hyperlipidemia, or other diseases / no medical history], pathological nodal involvement [pathological lymph node involvement / no involvement], and surgical procedure [BCS / mastectomy]). The income classification used in the analysis was established using almost the same amounts as those in previous studies, based on the exchange rate at that time. Mental depression was included in the analysis model as

a continuous variable using the HADS score for Depression and Anxiety determined at baseline. Body image was evaluated using 2 questions in the symptom checklist ("I am displeased with my change in body shape." and "I hesitate to show my body to others.") and the results were included in the model as an ordinal variable with 5 grades from 0 to 4. It has also recently been shown that adjuvant therapy including radiotherapy, hormone therapy and chemotherapy after surgery for breast cancer has effects on HRQOL. Therefore, postoperative treatment-related factors were added as potential predictive factors. Postoperative radiotherapy [radiation administered to the remaining breast or chest wall / no radiation], chemotherapy [intravenous chemotherapy / chemotherapy with oral 5-FU / no chemotherapy], and endocrine therapy [endocrine therapy / no endocrine therapy] were also added to the analysis model. Multiple regression analysis was conducted by the least squares method using FACT-G, Breast Cancer subscale and FACT-B TOI scores as objective variables and the baseline and treatment-related factors described above. Differences were considered to be significant at the 5% level and the contribution ratio is shown in the parameter estimate. Statistical analysis was performed using JMP version 8.0.2 (SAS Industry Incorporation).

## **Results**

### Demographic and clinical characteristics of the subjects

The subjects were recruited in 8 institutions in Japan from December 1998 to March 2003 and consent for participation in the study was obtained from 196 patients. The demographic and clinical characteristics of the subjects at one month after surgery are shown in Table 1. The mean age of the subjects was 53.3 years old. Most patients were married (70.9%) and about 28% had a college education. About 50% of the subjects underwent BCS, which is consistent with the general population of Japanese breast cancer patients. Sentinel lymph node biopsy was not generally conducted in Japan from 1998 to 2003, so radical dissection of axillary lymph nodes of level I or more was conducted in all patients.

Pathological lymph node involvement was found in 34.7% of the subjects.

Of 97 patients who underwent BCS, 82 (84.5%) underwent radiotherapy for the remaining breast. Post-mastectomy irradiation was conducted in 2 (2%) of 99 patients who underwent mastectomy. Postoperative adjuvant chemotherapy was conducted in 112 of 196 patients. The major regimens were cyclophosphamide, methotrexate and fluorouracil (CMF) in 66 patients (59%), and anthracycline-containing regimens in 19 (17%). Docetaxel monotherapy was administered to 2 patients, and oral 5FU such as uracil and florafur (UFT) was given to 25 patients. Postoperative hormone therapy was administered in 126 patients (64.3%) using tamoxifen in 102 (81%), toremifene in 7, anastrozole in 1, and a combination of tamoxifen and gonadotropin-releasing hormone analogs in 16. During the 2-year follow-up period, there was recurrence in 12 patients (6.1%): in 3, 1 and 8 within 6 months, 1 year and 2 years, respectively. The recurrent organs were the local site and a lymph node close to the lesion in 6 cases; and bone, lung and liver metastases in 2, 1 and 3, respectively. No patient died during the follow-up period.

#### Physical and treatment-related problems

The response rates for the patient-reported symptom checklist were 97.4%, 96.4%, 94.9% and 79.6% at registration, and at 6 months and 1 and 2 years, respectively. Physical and treatment-related problems at 1 month and 1 and 2 years after surgery are shown in Table 2. Most of these problems gradually decreased with time. However, more than 50% of patients complained of at least one of the following problems at 2 years after surgery: “tightness or tenderness in the chest wall” in mastectomy; “tightness, tenderness or discomfort in the breast” in BCS; “arm weakness” in BCS; “arm lymphedema” in BCS; “sensory loss (chest wall, axilla, or arm)”, “tightness, pulling or stretching (arm or axilla)”; “reduced energy, fatigue, general weakness” in mastectomy and BCS; and “intermittent pain or mild pain” in BCS. The percentage and severity of these symptoms remitted with time, but those for “cognitive difficulties”,

“weight gain, including difficulty in losing weight” and “endocrine problems” increased over time and half or more of the subjects complained of these symptoms.

#### Changes in HRQOL scores

The response rates for the questionnaire were 97%, 96%, 93.4% and 86.7% at registration, and at 6 months and 1 and 2 years, respectively. The mean, standard deviation and alpha coefficient of the scores for each domain, TOI, FACT-G and FACT-B at baseline, and 6 months and 1 and 2 years after surgery are shown in Table 3. The scores for physical, emotional and functional well-being increased with time (better HRQOL). The score for functional well-being at 6 months after surgery and emotional well-being at 1 year after surgery were significantly higher than those at baseline. In contrast, the score for social well-being was highest at baseline and then decreased with time and was significantly lower at 6 months and thereafter compared with baseline. The scores for the Breast Cancer subscale did not change significantly. The TOI, FACT-G and FACT-B scores increased with time (improved HRQOL) and showed a significant improvement at 1 and 2 years after surgery compared with baseline. After 2 years, the mean TOI, FACT-G and FACT-B scores were improved by 7.5, 4.8 and 4.9 points, respectively, compared to the baseline scores. Alpha coefficients ranged from 0.71 to 0.9, except for the Breast Cancer subscale (0.51-0.53).

#### Changes in HADS scores

The mean, standard deviation and alpha coefficient of the HADS scores at baseline, and 6 months and 1 and 2 years after surgery are shown in Table 4. In general, HADS depression, anxiety and total scores decreased with time (less depression and anxiety). The scores for HADS depression showed a significant improvement at 1 and 2 years after surgery in comparison with baseline, but the scores for HADS anxiety did not change significantly. The scores for HADS total showed a significant improvement at 2 years after

surgery in comparison with baseline, and the mean HADS score decreased from 10.4 points to 9.1 points.

Alpha coefficients for the HADS scores ranged from 0.73 to 0.89.

Associations among baseline variables, treatment-related factors and HRQOL at 6 months, 1 and 2 years after breast cancer surgery

We next examined the relationship between potential predictor variables and HRQOL outcome at 6 months and 1 and 2 years after surgery, using multiple regression analysis of Breast Cancer subscale, FACT-B TOI and FACT-G scores. The results are shown in Table 5. The variables with a significant effect on the Breast Cancer subscale score were employment status, poor body image, anxiety, depression, age, chemotherapy, endocrine therapy, type of surgery. Poor body image at baseline was a significant predictive factor for the Breast Cancer subscale score, with patients with a poor body image at 1 month after surgery having a low Breast Cancer subscale score (worse HRQOL) at 6 months and 2 years after surgery. HADS anxiety score and age were significant predictive factors for Breast Cancer subscale scores at 6 months and 1 year after surgery. HADS depression and chemotherapy had a particularly important effect and these variables were significant predictors for Breast Cancer subscale scores at 6 months and 1 and 2 years after surgery. Patients with a higher HADS depression score (more depression) and those treated with adjuvant intravenous chemotherapy had a lower Breast Cancer subscale score (worse HRQOL). The variables with a significant effect on the FACT-B TOI score were concomitant disease, children, poor body image, anxiety, depression, age, positive lymph node involvement, chemotherapy, type of surgery. HADS depression and chemotherapy also had a particularly important effect and were significant predictors for FACT-B TOI scores at 6 months and 1 and 2 years after surgery.

Concomitant disease was a significant predictive factor for the FACT-G scores at 6 months and 1 year after surgery, with patients with concomitant hypertension, hyperlipidemia or diabetes having low FACT-G scores (worse HRQOL). The HADS anxiety score at baseline was a significant predictive factor

for the FACT-G scores at 6 months and 1 year after surgery. The HADS depression score at baseline was also a significant predictive factor for the FACT-G scores at 6 months and 1 and 2 years after surgery. The depression score had a particularly important effect and was the strongest parameter in the model.

Pathological lymph node involvement and adjuvant intravenous chemotherapy were significant predictive factors at 6 months and 2 years after surgery, with patients with pathological lymph node involvement having a higher HRQOL score (better HRQOL) and those treated with adjuvant intravenous chemotherapy having a lower HRQOL score (worse HRQOL). Marital status or the presence of a partner at surgery was a significant predictive factor for the FACT-G score at 2 years after surgery, with this score being higher in patients with a partner.

In general, significant factors affecting the Breast Cancer subscale, FACT-B, TOI and FACT-G scores differed at each assessment point, but the HADS depression score at baseline and adjuvant intravenous chemotherapy were consistent significant factors affecting all examined HRQOL scores at almost all assessment points within 2 years after breast cancer surgery.

## **Discussion**

In this study, physical problems related to disease and treatment were evaluated using a patient-reported symptom checklist. Many patients complained of such physical problems even 2 years after surgery. Most physical symptoms remitted with time, but local symptoms such as "tightness, tenderness in the breast or chest wall", "sensory loss (chest wall, axilla, or arm)" and "tightness, pulling or stretching (arm or axilla)" were perceived by more than half of the patients at 2 years after surgery. Furthermore, the systemic symptoms of "reduced energy, fatigue, general weakness" were perceived by more than 60% of the patients at 2 years after surgery. The improvement in most symptoms with time and the persistence of tightness and sensory loss and reduced energy, fatigue and general weakness were consistent with our previous study [17].

The frequency of arm lymphedema increased with time and the incidence at 2 years after surgery was more than 50% in patients who underwent BCS. The symptom of "sensory loss" is thought to be caused by breakage or damage of nerves in surgery and was similar in patients who received mastectomy and BCS. There is no effective treatment to improve long-term sensory loss; therefore, it is necessary to explain to patients prior to surgery that there is a strong risk of sensory loss, and that if sensory loss occurs it is difficult to improve and may remain for a long time. Conservation of the intercostobrachial nerve (ICBN) in axillary lymph node dissection (ALND) improves long-term sensory deficits in the upper arm without influencing survival [39]. The symptoms of tightness and arm lymphedema perceived in the remaining breast, chest wall, arm and axilla are likely to be caused by ALND, postoperative contracture and radiotherapy. A recent prospective cohort study of upper limb dysfunction (ULD) after surgery for breast cancer determined the incidence, time course and risk factors for various ULD subtypes, including pectoralis tightness, lymphedema and lymphostasia, myofascial pain syndrome, rotator cuff disease, adhesive capsulitis, and post-mastectomy pain syndrome [40]. The highest incidences of ULD were due to pectoralis tightness and lymphedema, which is consistent with our results, and development of these symptoms caused long-term rotator cuff disease, indicating that physical rehabilitation is needed in patients with tightness and lymphedema to improve long-term postoperative physical function.

Generalization of the information on local symptoms after breast surgery found in this study is limited because sentinel lymph node biopsy (SLNB) is currently covered by National Health Insurance and is generally conducted in patients with clinical node-negative results, which differs from the conditions at the time the study was conducted. Widespread SLNB has decreased the frequency of ALND, and patients show significantly less treatment-related upper limb morbidity after SLNB compared with ALND [41]. The symptom of "weight gain, including difficulty in losing weight" increased with time, in contrast to general physical symptoms, which was also consistent with our previous study [17]. Negative associations between excessive body weight and breast cancer recurrence and survival have been reported

in pre- and postmenopausal women [42], and the American Cancer Society recommends that patients with cancer maintain normal weight as a potential aid in prognosis [43]. The results of this study showed that breast cancer patients recognized the importance of body weight control, but struggled to control body weight. These results show that it is necessary not only to keep patients informed about body weight control after surgery, but also to build a comprehensive support system for improving lifestyle, including exercise and diet to control body weight.

The results of our previous study showed that the incidence of "cognitive difficulties" decreased with time. In contrast, this incidence increased with time in the current study and more than half of the patients complained of this symptom at 2 years after surgery. However, no objective cognitive function was evaluated in the study and this limits discussion of these results. There has been a recent focus on the effect of adjuvant therapy after surgery for breast cancer on cognitive function, including memory, attention and executive function. However, it remains unclear whether postoperative chemotherapy has an effect on cognitive function since different results have been found. Adjuvant CMF chemotherapy caused late cognitive impairment [44] and subjects treated with high-dose chemotherapy with cyclophosphamide, thiotepa and carboplatin showed a decline in cognitive performance compared with healthy controls [45]; however, it has also been found that postoperative chemotherapy had almost no effect on cognitive function [46]. The tendency seems to be that subjective ratings of memory and concentration decrease after treatment with chemotherapy, and that breast cancer patients treated with chemotherapy also seem to be more likely than controls to perceive themselves as impaired [47]. It is also unclear whether tamoxifen used for postoperative endocrine therapy has an effect on cognitive function [48, 49], and the effect of aromatase inhibitors, the first option for postmenopausal breast cancer, on cognitive function is also an important issue for further study [50, 51].

HRQOL after surgery for breast cancer improved over time based on the increase in mean TOI, FACT-G and FACT-B scores. Physical, emotional and functional well-being significantly improved, but



social well-being significantly decreased. Lu et al. [20] recently examined changes in HRQOL and factors predicting long-term HRQOL in breast cancer patients using an approach similar to that in the current study. HRQOL was evaluated in 2232 Chinese patients with breast cancer who enrolled in the Shanghai Breast Cancer Survival Study at 6 and 36 months after diagnosis. Overall HRQOL and physical, psychological and social well-being improved over time, while several factors showed a decline with time, including negative feelings, social support, interpersonal relationships, financial situation and living environment, with a particularly marked worsening of interpersonal relationships [20]. The FACT-G questions concerning social well-being examine relationships with family, partner and friends; therefore, the decreased social well-being found in the current study is similar to the changes observed by Lu et al. Bloom et al. found that emotional support and the size of a patient's social network, which were included in the domain related to social well-being, significantly decreased at 5 years after surgery in a longitudinal study in breast cancer patients aged 50 years old or less [14]. These results suggest that support for cancer survivors requires maintenance and improvement of social well-being after treatment, and that psychosocial support is necessary for maintenance of good relationships with family, partner and friends. In a long-term follow up study, Ganz et al. found that physical and emotional well-being decreased in comparison with baseline in disease-free breast cancer survivors over a mean period of 6.3 years after early treatment, but that the changes were not significant when the effect of aging was included [8]. Ganz et al. also found that there was no significant change in energy levels or social functioning [8]. A comparison of changes in HRQOL based on differences in race and culture requires further accumulation of HRQOL data over a longer period.

Our results allowed a clear conclusion to be drawn on factors predicting HRQOL after surgery for breast cancer. The HADS score at baseline (1 month after surgery), and especially the depression score, was the strongest significant predictor for HRQOL at 6 months and 1 and 2 years after surgery. Our previous study also showed a significant relationship between mood disturbance at 1 month after surgery

and HRQOL at 1 year after surgery [17]. Thus, depression in the early period after surgery seems to be an extremely important factor determining postoperative long-term HRQOL regardless of race or culture. Therefore, important future issues include analysis of data from screening for depression in the early period after surgery and investigation of the effects of interventions such as mental rehabilitation on depression and overall HRQOL. There are only a few studies evaluating psychosocial interventions as breast cancer rehabilitation programs; however, psychoeducation, cognitive behavioral therapy and social and emotional support may be beneficial for improving QOL [52].

Body image was a significant factor associated with HRQOL in our previous study. It has been suggested that traditionally the breast carries less significance in sexuality and body image in Asian cultures than in Western countries, and that attitudes on changes in body image caused by breast cancer treatment depend on race and social background [20]. The results of this study in Japanese women showed that body image at baseline had no significant effect on the FACT-G, a comprehensive QOL scale. However, body image had significant effects on Breast Cancer subscales and FACT-B TOI, including femininity and physical and functional factors. Therefore, breast cancer in Japanese patients should be treated with consideration of body image.

Income was also a significant factor in our previous study, but was not significant in this study. In our previous study, the income of patients was classified into 3 categories with cut-off values of 30,000 and 60,000 dollars to provide factors for analysis. The dollar-yen exchange rate was approximately 150 yen in 1987 when our previous study began; therefore, the cut-off values were approximately 4.5 and 9 million yen (<http://research.stlouisfed.org/fred2/data/EXJPUS.txt>). These values are close to the cut-off values in this study (5 and 10 million yen). All previous studies that indicated a significant correlation between income and HRQOL were conducted in the United States [7, 8, 13, 17]. The difference in the results in this study may be due to the difference in the health insurance system in Japan.

Pathological lymph node involvement also had an unusual effect, since it was related to high HRQOL

scores at 6 months and 2 years after surgery. This finding requires further analysis, since cancer progression generally correlates with poor HRQOL [11, 20]. Of the treatment-related factors, intravenous systemic chemotherapy after surgery was the strongest significant predictor for HRQOL. We also note that Ganz et al. found that systemic pharmacotherapy after surgery was significantly associated with physical function at 5-10 years after diagnosis [8]. Therefore, it is important for physicians to recognize that postoperative systemic chemotherapy has a long-term effect on HRQOL, even after completion of treatment. Further cancer survivorship studies should be conducted to investigate the kinds of support needed to improve long-term HRQOL in breast cancer patients who are treated with chemotherapy. The results of symptom checklists of therapy-related factors showed that hot flash and other symptoms associated with endocrine therapy showed a time-dependent increase. On the other hand, endocrine therapy itself had less effect on overall HRQOL and even had a positive effect on breast cancer subscales one year after therapy. Adjuvant endocrine therapy reduces the risk of breast cancer recurrence and death. Endocrine therapy is beneficial for patients with hormone receptor-positive breast cancer.

In conclusion, patients with breast cancer have physical symptoms for a long period postoperatively. Our results suggest that physical rehabilitation should be performed in patients with tightness and lymphedema to improve long-term postoperative physical function. Patients should be supported with a comprehensive system for improving lifestyle after surgery, including exercise and diet to control body weight, because they recognized the importance of body weight control, but struggled to control body weight. HRQOL and anxiety/depression generally improved with time after surgery, but depression in the early period after surgery has a major effect on long-term HRQOL, and the score for social well-being decreased with time. Therefore, further studies are required to examine depression with a screening tool and psychosocial support as part of breast cancer rehabilitation.

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Table 1. Demographic and medical characteristics of the sample (N=196)

Characteristics	Number	%	Characteristics	Number	%
Age at baseline, years			Clinical stage at diagnosis		
Mean	53.3		0	11	5.6
Range	24-77		I	72	36.7
Age group at baseline, years			II	102	52.0
<50	75	38.3	III A	9	4.6
50-69	106	54.1	III B	2	1.0
70 and older	15	7.7	Pathological nodal involvement		
Marital status			Negative	128	65.3
Single	22	11.2	Positive	68	34.7
Married	139	70.9	Surgical procedure		
Separated	1	0.5	Breast conserving surgery	95	48.5
Divorced	9	4.6	Modified Radical mastectomy	94	48.0
Widowed	20	10.2	BCS* and reconstruction	2	1.0
Unknown	5	2.6	Mastectomy and reconstruction	5	2.6
Education			Received adjuvant radiotherapy		
High school or less	135	68.9	No	112	57.1
College education	54	27.6	Yes	84	42.9
Unknown	7	3.6	Received adjuvant chemotherapy		
Employment status before diagnosis			No	84	42.9
Not working	107	54.6	Yes	112	57.1
Working	68	34.7	Received adjuvant endocrine therapy		
Unknown	21	10.7	No	70	35.7
Household income (Japanese Yen)			Yes	126	64.3
-5,000,000	67	34.2	Recurrence		
5,000,000- 10,000,000	84	42.9	No	184	93.9
10,000,000-	21	10.7	Yes	12	6.1
Unknown	24	12.2	Concomitant disease		
Concomitant disease			None	121	61.7
None	121	61.7	Hypertension	25	12.8
Hypertension	25	12.8	Hyperlipidemia	4	2.0
Hyperlipidemia	4	2.0	Others	16	8.2
Others	16	8.2	Unknown	30	15.3
Unknown	30	15.3			

\*Breast conserving surgery

Table 2. Physical and treatment-related problems after breast cancer surgery by surgery type

	Mastectomy (N=99)			Breast conserving surgery (N=97)		
	1Month	1Year	2Year	1Month	1Year	2Year
Number of responders	96	93	77	95	93	79
Response rate (%)	97.0	93.9	77.8	97.9	95.9	81.4
Problem	Percentage of responders have any problems <sup>a</sup> (Percentage of responders have severe problems <sup>b</sup> )					
<b>Local post-operative problems</b>						
Difficulty in lifting	83.0 (24.5)	34.4 (2.2)	19.5 (1.3)	88.3 (20.2)	38.5 (3.3)	28.2 (3.8)
Limited arm mobility or frozen shoulder	67.7 (15.1)	32.2 (4.4)	23.3 (0)	73.1 (14.0)	40.0 (6.8)	29.9 (3.9)
Tightness, and/or tenderness in chest wall (mastectomy)	93.3 (33.8)	69.0 (14.3)	<b>58.7</b> (10.7)	-	-	-
Tightness, tenderness or discomfort in breast (BCS)	-	-	-	89.7 (27.6)	80.7 (19.3)	<b>79.7</b> (17.4)
Sensation that breast is still present (mastectomy) (phantom breast syndrome)	45.5 (13.6)	34.1 (7.3)	35.6 (6.8)	-	-	-
Arm weakness	66.7 (9.7)	47.7 (6.7)	39.2 (5.4)	71.6 (18.2)	51.2 (4.9)	<b>56.1</b> (6.8)
Lymphedema of arm	27.2 (1.1)	26.1 (3.4)	33.3 (9.7)	41.2 (7.1)	47.6 (10.7)	<b>52.1</b> (15.1)
Swelling (chest wall, breast, and/or axilla)	60.4 (14.3)	31.1 (5.6)	33.8 (4.1)	71.6 (20.5)	59.0 (7.2)	40.3 (5.6)
Numbness (chest wall, axilla, and/or arm)	61.3 (10.8)	48.8 (11.1)	36.5 (5.4)	75.3 (19.1)	53.6 (6.0)	47.9 (10.0)
Sensory loss (chest wall, axilla, and/or arm)	93.5 (35.9)	87.4 (20.7)	<b>73.0</b> (20.3)	85.9 (30.6)	85.7 (15.5)	<b>83.6</b> (26.0)
Tightness, pulling and/or stretching (arm and/or axilla)	96.8 (50.5)	85.6 (18.9)	<b>59.5</b> (8.1)	91.0 (46.1)	74.1 (12.9)	<b>70.3</b> (16.2)
<b>Activity of daily living</b>						
Difficulty in doing household chores	61.1 (4.2)	27.7 (4.4)	18.2 (1.3)	63.8 (12.8)	33.0 (1.1)	20.8 (2.6)
Difficulty with self-care and grooming	55.8 (4.2)	16.3 (0)	10.4 (0)	62.8 (8.5)	12.1 (1.1)	14.3 (3.9)
<b>Symptoms</b>						
Less energy than before, fatigue, general weakness	82.1 (13.7)	70.3 (14.3)	<b>68.4</b> (14.5)	83.2 (18.9)	71.4 (19.8)	<b>66.7</b> (21.8)
Cognitive difficulties	47.9 (4.3)	57.8 (12.2)	<b>57.1</b> (16.9)	46.8 (7.5)	50.0 (12.2)	<b>52.0</b> (18.2)
Difficulty in sleeping	56.8 (12.6)	38.9 (14.4)	44.2 (9.1)	54.7 (12.6)	52.2 (6.7)	44.2 (16.9)
Fatigue associated with treatments	41.3 (4.3)	8.9 (1.1)	13.2 (2.6)	43.6 (6.4)	18.0 (1.1)	15.6 (3.9)
<b>Physical activities</b>						
Difficulty in doing physical activities	72.9 (18.8)	41.1 (4.4)	33.8 (6.5)	75.8 (18.9)	39.1 (4.3)	30.8 (5.1)
<b>Pain</b>						
Intermittent pain or mild pain	75.0 (17.7)	59.8 (12.0)	41.6 (7.8)	82.1 (20.0)	63.0 (6.5)	<b>56.4</b> (5.1)
<b>Weight and diet</b>						
Weight gain problem, including difficulty in losing weight	38.5 (3.1)	57.6 (13.0)	<b>58.6</b> (18.7)	44.7 (4.3)	70.3 (22.0)	<b>78.2</b> (28.2)
<b>Endocrine problems<sup>c</sup></b>						
Hot flashes from endocrine therapy or chemotherapy	27.0 (0)	41.7 (18.8)	45.2 (19.0)	26.3 (15.8)	57.3 (19.7)	<b>55.9</b> (22.0)
Other side effect from endocrine therapy	23.1 (11.5)	44.9 (18.4)	41.0 (20.5)	42.1 (5.3)	58.7 (12.7)	<b>63.6</b> (16.4)
<b>Recreational and social activities</b>						
Decline in recreational and social activities	80.2 (41.8)	50.5 (15.4)	43.2 (10.8)	69.9 (22.6)	54.4 (11.1)	40.3 (9.1)
Difficulty in planning activities	70.7 (27.1)	34.8 (4.5)	32.4 (2.8)	80.9 (22.3)	40.4 (5.6)	31.6 (6.6)

a: 5-point Likert scale (scale: 0 to 4) and % of the total excluding "0: Not at all"

b: 5-point Likert scale (scale: 0 to 4) and % of the total of "3: Quite a lot" and "4: Very much"

c: Denominator includes only subjects receiving endocrine therapy (N=126)

Percentages that are bolded were reported by >50% of women at two year

Table 3. Change of health-related quality of life score after breast cancer surgery

	Baseline (N=190)			6 months (N=188)				1 year (N=183)				2 years (N=170)			
	Mean	SD	alpha	Mean	SD	alpha	p	Mean	SD	alpha	p	Mean	SD	alpha	p
Quality of life assessment															
Physical well-being	21.0	4.6	0.78	21.6	5.4	0.85	0.221	24.3	3.8	0.78	<.0001	24.7	4.3	0.85	<.0001
Social well-being	20.8	5.2	0.71	18.4	6.3	0.78	<.0001	17.7	6.7	0.83	<.0001	17.5	6.9	0.84	<.0001
Emotional well-being	16.5	5.5	0.86	17.2	5.0	0.84	0.122	18.1	4.4	0.78	0.001	18.0	4.8	0.78	0.004
Functional well-being	17.5	5.7	0.82	19.7	5.3	0.85	<.0001	20.9	5.6	0.88	<.0001	21.0	5.5	0.87	<.0001
Breast cancer subscale	23.2	5.1	0.58	22.6	5.5	0.62	0.283	24.0	4.8	0.54	0.158	23.6	5.2	0.57	0.516
Trial outcome index <sup>a</sup>	62.0	12.1	0.85	64.0	12.9	0.86	0.122	69.2	11.2	0.85	<.0001	69.5	11.2	0.85	<.0001
FACT-G <sup>b</sup>	76.0	15.1	0.88	77.0	15.5	0.89	0.532	81.3	14.2	0.88	0.001	81.3	14.4	0.87	0.001
FACT-B <sup>b</sup>	99.5	18.1	0.89	99.6	19.2	0.90	0.952	105.1	17.2	0.88	0.004	105.0	17.2	0.87	0.006

a: Trial outcome index is the sum of the score from the physical and functional well-being and the breast cancer subscale

b: Functional assessment of cancer treatment scale- general and breast cancer subscale

The difference between the mean at each time point and baseline was analyzed using a paired t-test.

Table 4. Change of HADS score after breast cancer surgery

	Baseline (N=190)			6 months (N=188)				1 year (N=183)				2 years (N=170)			
	Mean	SD	alpha	Mean	SD	alpha	p	Mean	SD	alpha	p	Mean	SD	alpha	p
HADS <sup>a</sup>															
Depression	4.6	3.0	0.73	4.4	3.2	0.79	0.595	3.9	3.0	0.80	0.034	3.7	3.2	0.81	0.013
Anxiety	5.8	3.3	0.80	5.6	3.2	0.78	0.607	5.4	3.2	0.80	0.256	5.4	3.7	0.83	0.244
HADS-Total	10.4	5.7	0.86	10.0	5.9	0.86	0.569	9.3	5.7	0.870	0.079	9.1	6.4	0.89	0.050

a: Hospital anxiety and depression scale

The difference between the mean at each time point and baseline was analyzed using a paired t-test.

Table 5. Predictors of HRQOL (Breast cancer subscale, Trial outcome index and FACT-G score) at 6 months, 1 and 2 years after breast cancer surgery

	6 months			1 year			2 years		
	Parameter estimate	Standard error	P-value	Parameter estimate	Standard error	P-value	Parameter estimate	Standard error	P-value
<b>Breast cancer subscale</b>									
Employment status (housewife or jobless) <sup>a</sup>	0.69	0.38	0.068	<b>1.03</b>	0.38	0.007	0.22	0.42	0.611
Poor body image <sup>a</sup>	<b>-1.71</b>	0.84	0.044	-1.00	0.84	0.234	<b>-2.38</b>	0.94	0.012
Anxiety <sup>b</sup>	<b>-3.18</b>	1.30	0.016	<b>-2.85</b>	1.33	0.035	-1.54	1.54	0.320
Depression <sup>b</sup>	<b>-2.81</b>	1.06	0.009	<b>-2.84</b>	1.06	0.009	<b>-2.81</b>	1.20	0.021
Age ( $\leq 49$ ) <sup>a</sup>	<b>1.91</b>	0.80	0.018	<b>2.42</b>	0.80	0.003	1.45	0.89	0.108
Adjuvant intravenous chemotherapy	<b>-3.81</b>	0.51	<.0001	<b>-1.84</b>	0.51	<.0001	<b>-1.83</b>	0.56	0.002
Adjuvant endocrine therapy	0.68	0.38	0.079	<b>0.81</b>	0.39	0.037	0.18	0.43	0.680
Breast conserving surgery	-1.23	0.67	0.068	-0.12	0.65	0.853	<b>-1.53</b>	0.74	0.040
<b>Trial outcome index</b>									
Concomitant disease <sup>c</sup>	<b>-2.03</b>	0.92	0.030	<b>-2.75</b>	0.90	0.003	-1.12	1.00	0.265
Children (presence) <sup>a</sup>	<b>-1.72</b>	0.85	0.046	-1.30	0.83	0.118	-0.35	0.89	0.690
Poor body image <sup>a</sup>	-0.52	1.94	0.790	-1.13	1.90	0.554	<b>-4.41</b>	1.99	0.029
Anxiety <sup>b</sup>	<b>-6.01</b>	3.03	0.049	-5.81	3.02	0.057	-1.20	3.30	0.718
Depression <sup>b</sup>	<b>-9.53</b>	2.42	<.0001	<b>-9.96</b>	2.39	<.0001	<b>-9.00</b>	2.54	0.001
Positive lymphnode involvement	1.56	0.95	0.103	1.63	0.94	0.087	<b>2.79</b>	1.00	0.006
Adjuvant intravenous chemotherapy	<b>-8.58</b>	1.17	<.0001	<b>-2.46</b>	1.19	0.041	<b>-4.52</b>	1.19	<.0001
Breast conserving surgery	-2.14	1.54	0.167	-0.11	1.46	0.938	<b>-3.38</b>	1.56	0.033
<b>FACT-G</b>									
Concomitant disease <sup>c</sup>	<b>-2.82</b>	1.29	0.031	<b>-3.89</b>	1.21	0.002	-1.80	1.41	0.203
Anxiety <sup>b</sup>	<b>-12.78</b>	4.15	0.003	<b>-9.35</b>	4.02	0.022	-3.54	4.65	0.448
Depression <sup>b</sup>	<b>-8.78</b>	3.32	0.009	<b>-8.76</b>	3.17	0.007	<b>-10.28</b>	3.58	0.005
Positive lymphnode involvement	<b>2.92</b>	1.30	0.027	0.60	1.25	0.635	<b>3.35</b>	1.40	0.019
Adjuvant intravenous chemotherapy	<b>-5.69</b>	1.60	0.001	-0.98	1.59	0.540	<b>-4.78</b>	1.68	0.005
Married or with a partner <sup>a</sup>	2.02	1.35	0.138	1.50	1.30	0.251	<b>3.06</b>	1.53	0.048

Factors found to be statistically significant in a multiple regression model are listed.

Parameter estimates that are bolded were statistically significant

a: Conditions at baseline (one month after surgery)

b: Scores for the Hospital Anxiety and Depression Scale (HADS) at baseline (one month after surgery)

c: Concomitant disease including hypertension, hyperlipidemia and diabetes at baseline (one month after surgery)