





Original Article



Predictors of Decreased Quality of Life in Breast Cancer Survivors Five Years After Diagnosis

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ABSTRACT

Purpose: Due to improved therapy, early diagnosis, and growing incidence rates, the number of long-term breast cancer survivors is increasing. Survivors can still be affected by aftercare, resulting in reduced quality of life (QoL). Thus, in this study, we investigated possible predictors of decreased physical and social functioning in breast cancer survivors.

Methods: In a German multicenter prospective study, we enrolled 759 female patients with breast cancer before surgery (t1), and contacted them again 5 years after surgery (t4). Data on QoL were assessed at t4 using the European Organization for Research and Treatment of Cancer QoL Core Questionnaire (EORTC QLQ-C30) and its breast cancer module EORTC QLQ-BR23. Predictors of decreased physical and social functioning were analyzed using logistic regression with odds ratios as effect estimates and 95% confidence intervals. Thresholds for the clinical importance of detrimental effects on QoL were defined according to Giesinger.

Results: Questionnaires from 759 patients were retrieved at t1. Of these, 456 participated in the study at t4. Poor QoL 5 years after diagnosis was reported by 20%–50% of the participants. Age, mastectomy, chemotherapy, education, employment, cohabitation, psychiatric comorbidities at t1, anxiety, depression, and intensity of physical activity emerged as predictors of decreased physical and social functioning 5 years after diagnosis.

Conclusion: Relief of symptoms and improvement in the QoL should be priorities in aftercare. Detecting patients with a decreased QoL is a rising challenge. Healthcare providers should take special care of patients aged 50–59 years, patients with psychiatric comorbidities and depression, and patients who have undergone mastectomy.

Keywords: Aftercare; Breast Neoplasms; Quality of Life; Survivors

INTRODUCTION

Breast cancer is the most common malignancy in women worldwide. In Germany, approximately 70,000 new cases of breast cancer are diagnosed annually [1]. Breast cancer

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Conflict of Interest

Prof. Singer has received speaker honorarium from Company Lilly and Pfizer. PD Dr. med. Schläiß has received honorarium from Company Roche, Pfizer, AstraZeneca, Novartis and travel expenses from Celgene. Dr. med. Curtaz joined a mentee program from Novartis and Besins Health. The other authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Conceptualization: Flock F, Felberbaum R, Janni W, Schwentner L, Singer S, Wöckel A; Data curation: Felberbaum R, Janni W, Singer S, Wöckel A; Formal analysis: Herbert SL, Löb S, Kiesel M, Schläiß T, Diessner J, Curtaz C, Joukhadar R, Dayan D, Singer S; Investigation: Wöckel A; Methodology: Singer S; Visualization: Herbert SL; Writing - original draft: Herbert SL, Singer S, Wöckel A; Writing - review & editing: Flock F, Felberbaum R, Janni W, Löb S, Kiesel M, Schläiß T, Diessner J, Curtaz C, Joukhadar R, Dayan D, Schwentner L.

accounts for 24% of newly diagnosed malignancies in women aged 40–50 years [2]. Breast cancer is diagnosed earlier than most other malignancies; 40% of the patients are diagnosed before their sixtieth year of life [2]. Due to advances in breast cancer treatment, early diagnosis, and growing incidence rates [3], the 5-year survival rate has increased [4] in Germany from 60% in 1970 [2] to 87% in 2017 [5]. The American Cancer Society defines people who are still living 5 years after diagnosis as long-term survivors [6]. Mortality has decreased, particularly in younger women. For patients aged 40–44 years a decrease of more than 30%, and for those aged 45–49 years a decrease of more than 20% was observed [2]. As a result, there are more long-term breast cancer survivors in general and younger long-term survivors.

Breast cancer care does not end with initial treatments such as surgery and chemotherapy. However, at the time of diagnosis, patients' focus is on survival, and survivors focus on living beyond. Patients' lives in the long term can be affected in different ways [7]; long-term adverse effects as well as psychological and psychosocial complications can affect the quality of life (QoL) of long-term survivors [8]. The QoL can be divided into global, physical, and social aspects; however, these data remain partially inconclusive [9]. Many studies have shown a good QoL for breast cancer survivors [10,11], while others have reported a lower QoL for long-term survivors of physical and psychological disorders [8,12]. Patient needs can change from the time of treatment to survivorship. Acute and long-term adverse effects have also been reported. Severity depends on personal factors such as comorbidities, age or type of therapy [13]. Concerning adjuvant systemic treatment chemotherapy, targeted therapy, and endocrine therapy can cause long-term side effects such as cardiomyopathy, polyneuropathy, cognitive changes, psychosocial problems, early menopause, impact on sexuality, reduced fertility, reduced bone health, weight gain, fatigue, and sleep disorders [14,15]. Physical well-being can also be affected by long-term surgical effects such as lymphedema and body image changes [4]. Amir and Ramati [8] showed a significantly higher rate of long-term psychological effects such as post-traumatic stress disorder and emotional distress. These circumstances necessitate supportive care. Studies have demonstrated the need for support in dealing with emotional and existential problems [16]. Unmet supportive needs can decrease the QoL [17] and compliance [18], thereby underlining the importance of optimized aftercare.

Patients with breast cancer can develop chronic disorders after treatment that can affect their well-being. Survivors with poor QoL must be identified with the goal of offering interventions to improve their QoL. Thus, this study aimed to answer two questions.

1. How high is the QoL of breast cancer survivors in aftercare?
2. What are the predictors of a reduced QoL, 5 years after breast cancer diagnosis?

METHODS**Study design**

Participants were enrolled before surgery (t1) in a prospective multi-center cohort study conducted from 2009 to 2012. Patients were included if they had a primary diagnosis of breast cancer, were female, were able to complete questionnaires, and provide written informed consent. Patients were excluded if they had metastatic disease, recurrent disease, bilateral breast cancer, primary occult disease, or phyllodes tumors. Patients were contacted again 5 years after surgery (t4), and their QoL was ascertained. Enrollment was performed at the University Medical Center in Ulm, Kempten Hospital, Memmingen Hospital and

Esslingen Hospital, all breast cancer centers certified by the German Cancer Society. Ethical approval was obtained from the Ethics Committee of Ulm University (approval number: 325/08). All procedures involving human participants performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Instruments

QoL

QoL was assessed at t4 using the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) [19] and its breast cancer module EORTC QLQ-BR23 [20]. The QLQ-C30 contains five functional scales (physical, social, role, cognitive, and emotional), three symptom scales (fatigue, pain, nausea, and vomiting), global health status, and single items (dyspnea, loss of appetite, insomnia, constipation, and diarrhea).

We used the thresholds for clinical importance (TCIs) from the study by Giesinger et al. [21]. Concerning functional scales, scores below the TCIs indicates a problem. Concerning the symptom scales, scores above the TCI indicates a problem [22].

Demographic data

The highest school-leaving qualification was categorized as education. Patients not born in Germany, those without German citizenship, or those without German nationality were defined as having a migration background.

Clinical data

Clinical data was obtained from medical records by trained data managers.

Anxiety

Anxiety was measured with the 7-item anxiety scale (Generalized Anxiety Disorder 7-item) [23].

Depression

Depression and its severity were assessed at t1 and t4 using the short form of the Patient Health Questionnaire-9 (PHQ-9) [24].

Psychiatric comorbidity

Psychiatric comorbidity was assessed at t1 using the PHQ in its long form, which measures mental health conditions according to the classification system of International Classification of Diseases 10th Revision. The following syndromes were assessed: major depression (F32, F33), other depression (F32.9, F33.9, F34.1), agoraphobia with panic disorder (F40.01), panic syndrome (F41.0), generalized anxiety disorder (F41.1), other anxiety disorders (F41.9), bulimia nervosa (F50.2), binge eating (F50.9), alcohol abuse (F10.1), alcohol dependence (F10.2), and somatoform disorders (F45.0, F45.1, F45.3).

Statistical analysis

As primary endpoints, we defined global QoL and physical and social functioning. We defined role, cognitive and emotional functioning, and fatigue as secondary endpoints. For each endpoint, we used descriptive analyses, including means, medians, minima, maxima, and standard deviations (SDs).

Decreased QoL was defined using TCI, as established by Giesinger et al. [21]. Clinically important problems and symptoms are indicated if the patients' functioning scales are measured below and symptom scales are measured above the TCI.

Possible predictors of decreased QoL were investigated using multiple logistic regression analyses: age (< 40, 41–50, 51–60, 61–70, > 70 years), education (< 10 years vs. ≥ 10 years), employment (yes/no), treatment (ablation/chemotherapy, endocrine), cohabitation (partner at t1/t4/unknown), psychiatric comorbidity at t1 (yes/no/unknown), depression at t1 (none/mild/moderate to severe), anxiety (none/mild/moderate/severe). We reported the odds ratios (ORs) and 95% confidence intervals .

RESULTS

Sample description

A total of 759 patients were enrolled in this study. Approximately 60% (n = 456) of them participated at 5-year follow-up. Of these, 60 patients died, 101 declined participations, one moved to an unknown place and could not be traced, and 141 could not be contacted for logistic reasons. Patients who rejected participation at t4 but participated in the study before were on average 7.8 years older than the patients who participated at t4.

The average age of participants was 64 years (SD, 11 years) at t4. In total, 43% of patients had less than 10 years of education. More than half of the participants were unemployed (**Table 1**).

At baseline, the tumor sizes were T1 in 57%, T2 in 35%, T3 in 5%, T4 in 2%, and 1% were unknown. Lymph nodes were positive in 5% of the patients. None of the patients had distant metastases, which was the exclusion criterion. Approximately 14% of the tumors were estrogen receptor-negative, 22% were progesterone receptor-negative, and 86% were human epidermal growth factor receptor 2-negative. The Nottingham Prognostic Index was 1 in 10%, 2 in 46%, 3 in 33%, and 4 in 11% of the patients.

Breast-conserving surgery was performed in 86% of the patients, and 14% of the patients underwent mastectomy. Concerning systemic therapy, 46% received chemotherapy (mostly 5 fluorouracil, epirubicin, cyclophosphamide, docetaxel; 91% of all who underwent chemotherapy), rarely cyclophosphamide, methotrexate, 5 fluorouracil (n = 2), xeloda (n = 1), or other substances), and 82% received endocrine therapy (Tamoxifen [55% of all with endocrine treatment], Anastrozol [23%], Letrozol [24%], Exemestan [12%], Faslodex [n = 1], and Zoladex [29%]). Herceptin was administered to 12% of the patients. Approximately 81% of the patients lived with a partner at t1. At t4, this percentage was lower (69%). Approximately 20% of patients were affected by psychiatric comorbidities at t1. Depression was observed in 41% of the participants at t1. Anxiety was observed in 40% of the patients, but the majority of these patients with anxiety (72%) only showed mild anxiety (**Table 1**).

QoL 5 years after diagnosis

Poor physical functioning was reported in 40% of the patients, with a median score of 86.7. For social functioning, the median score was 83.3, and 23% of participants had a poor QoL. Role functioning had a median score of 83.3, and 22% of patients had a poor QoL. The median cognitive functioning was 83.3%, and 34% reported a poor QoL. The median

Table 1. Predictors of decreased quality of life among breast cancer survivors 5 years after diagnosis

Characteristics	No.	Physical functioning		Social functioning	
		OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Age (yr)					
< 40	24	Reference		Reference	
40–49	97	1.7 (0.5–6.6)	0.42	0.9 (0.2–4.3)	0.92
50–59	143	3.6 (1.0–13.5)	0.06	2.1 (0.5–9.2)	0.34
60–69	135	2.3 (0.5–9.6)	0.25	0.6 (0.1–3.5)	0.58
70+	57	2.8 (0.6–12.8)	0.19	0.6 (0.1–4.3)	0.60
Education (yr)					
< 10	195	Reference			
≥ 10	256	0.8 (0.5–1.4)	0.51	1.3 (0.7–2.7)	0.42
Unknown	5	0.6 (0.0–19.0)	0.75	8.0 (0.5–129.3)	0.14
Employment					
Not employed (retired, unemployed, in training, homemaker)	262	Reference			
Employed or self-employed	192	0.3 (0.1–0.6)	< 0.01	1.3 (0.6–3.1)	0.53
Treatment					
Ablatio	64	1.9 (0.9–3.9)	0.08	0.6 (0.2–1.4)	0.23
Chemotherapy received	209	1.3 (0.8–2.2)	0.32	0.9 (0.5–1.8)	0.76
Endocrine therapy received	372	0.9 (0.5–1.8)	0.79	0.7 (0.3–1.7)	0.47
Cohabitation					
Has a partner at t1	370	1.1 (0.5–2.6)	0.81	2.5 (0.8–7.9)	0.11
Has a partner at t4	313	0.7 (0.3–1.7)	0.45	0.5 (0.2–1.5)	0.24
Unknown	54	1.1 (0.4–3.1)	0.85	0.7 (0.2–2.7)	0.57
Psychiatric co-morbidity					
Has a psychiatric diagnosis at t1	89	2.0 (0.9–4.8)	0.10	3.5 (1.3–9.3)	0.01
Unknown	6	0.2 (0.0–4.0)	0.31	Omitted	
Depression at t1					
None	248	Reference			
Mild	133	0.8 (0.4–1.4)	0.42	0.6 (0.3–1.4)	0.25
Moderate to severe	53	0.4 (0.2–1.3)	0.14	1.0 (0.3–3.3)	0.97
Unknown	22	2.4 (0.7–8.2)	0.18	2.0 (0.4–9.0)	0.36
Depression at t4					
None	249	Reference			
Mild	124	2.1 (1.1–4.0)	0.02	5.0 (2.0–12.7)	< 0.01
Moderate to severe	82	13.8 (5.1–37.2)	< 0.01	56.1 (18.0–175.1)	< 0.01
Anxiety					
None	271	Reference			
Mild	133	1.0 (0.5–1.8)	0.90	0.9 (0.4–2.0)	0.71
Moderate	38	0.6 (0.2–1.7)	0.31	1.5 (0.5–5.0)	0.49
Severe	13	2.0 (0.3–15.5)	0.49	0.6 (0.1–4.0)	0.63
Physical activity at t4					
Never	31	Reference			
1× per month or less	17	3.7 (0.7–19.8)	0.12	0.7 (0.1–4.9)	0.74
2–4× per month	81	1.0 (0.4–2.8)	1.00	1.3 (0.3–4.6)	0.72
2–4× per week	226	0.3 (0.1–0.8)	0.01	0.7 (0.2–2.4)	0.57
5× per week or more	95	0.3 (0.1–0.8)	0.02	1.2 (0.3–4.7)	0.78
Unknown	6	1.0 (0.1–7.6)	1.00	78.0 (7.1–856.3)	< 0.01

t1 = before surgery; t4 = 5 years after surgery; OR = odds ratio; CI = confidence interval.

score for emotional functioning was 75.0, and 50% of the participants reported a poor QoL. Fatigue had a median score of 33.3, and 39% of the patients reported a poor QoL (**Table 2**).

Predictors of decreased QoL 5 years after diagnosis

Women between 50 and 59 years of age had 3.6 the odds of poor physical functioning compared to women < 40 years of age ($p = 0.06$). For all other age groups, there was no evidence of differences in the likelihood of poor physical functioning (age of 40–49 years, OR, 1.7; 60–69 years, OR, 2.3; age of 70+ years, OR, 2.8).

Table 2. Quality of life among breast cancer patients 5 years after diagnosis

Domains	Mean	SD	Median	Min	Max	% with poor QoL
Physical functioning	82.0	19.9	86.7	6.7	100	40
Social functioning	76.0	28.5	83.3	0	100	23
Role functioning	75.0	29.3	83.3	0	100	22
Cognitive functioning	80.0	23.0	83.3	0	100	34
Emotional functioning	68.1	27.2	75.0	0	100	50
Fatigue	35.6	28.2	33.3	0	100	39

QoL = quality of life; SD = standard deviation.

Education > 10 years had 0.8 the odds, and employment had 0.3 the odds of having poor physical functioning. The effect of employment was significant ($p < 0.01$).

Women who underwent mastectomy had 1.9 the odds of poor physical functioning ($p = 0.08$). By contrast, women receiving chemotherapy or endocrine therapy had 1.3 and 0.9 the odds of poor physical functioning, respectively.

The effect size of cohabitation at t1 was higher (OR, 1.1) than that at t4 (OR, 0.7). Women with a psychiatric diagnosis at t1 had 2.0 the odds of poor physical functioning. The effect size of depression at t1 was small, but was significant at t4, and increased with depression intensity (OR, 2.1 for mild depression and OR, 13.8 for moderate to severe depression). This statistically significant effect was strongest for poor physical functioning ($p = 0.02$, $p < 0.01$). The effect of severe anxiety on reduced physical functioning was greater (OR, 2.0) than that of mild anxiety (OR, 1.0). Weekly physical activity had a weaker effect (OR, 0.3) than monthly activity (OR, 3.7) on poor physical functioning. We observed a significant difference for physical activity done 2–4 times per week ($p = 0.01$), and done 5 times per week and more ($p = 0.02$).

Women aged between 50 and 59 years had 2.1 the odds of poor social functioning. For all the other age groups, there was no evidence of differences in the likelihood of poor social functioning. We observed that education > 10 years and employment/self-employment had 1.3 the odds of poor social functioning. Women living with a partner at t1 had 2.5 the odds of poor social functioning, whereas at t4 they had 0.5 the odds. A stronger negative effect on social functioning was observed for psychological diseases at t1 (OR, 3.5), which was significant ($p = 0.01$). Moderate-to-severe depression at t1 showed a weak effect on poor social functioning (OR, 1.0), and depression at t4 was significant ($p < 0.01$). The effect increased depending on the intensity of depression from mild (OR, 5.0) to moderate/severe (OR, 56.1). Women with moderate anxiety had 1.5 the OR for poor social functioning. Women who engaged in physical activity at t4 had 1.3 the odds of poor social functioning in the case of activity 2–4 times per month, and 1.2 the odds of poor social functioning in the case of activity 5 times per week or more (**Table 1**).

DISCUSSION

In this study, we analyzed the QoL in aftercare, and the predictors of decreased QoL 5 years after the diagnosis of breast cancer. We observed that up to 50% of the survivors had poor QoL 5 years after diagnosis. The amount depends on the QoL category: age, mastectomy, chemotherapy, education, employment, cohabitation, psychiatric comorbidity at t1, anxiety, depression, and various intensities of physical activity were predictors of decreased QoL

in after care. The strength of this effect differs between the physical and social functions. Moderate-to-severe depression at t4 had the strongest negative effect on the QoL.

In particular, the age of 50–59 years was observed to be a predictor of reduced QoL concerning physical functioning. A possible explanation could be that with increasing age, the number of comorbidities also increase. However, this explanation is not consistent with the literature. There are studies including older patients (aged 70 years) which observed better coping with treatment despite increasing comorbidities [25]. However, studies among older patients are scarce and may show a bias concerning undertreatment if the study is not current. In contrast, studies concerning women younger than 50 years showed reduced emotional and social functioning [26] and a poorer QoL compared to that in older patients, which strongly correlated with physiological changes [15].

Muñoz [26] showed that young patients were more concerned about economic issues. Continuing to work after a breast cancer diagnosis may be beneficial to the patients' QoL [27]. In the study by Timperi et al. [27], 54% of the patients were 60 years of age, whereas in our study, only 42% of the participants were of this age. The fact that older patients are coping better than younger patients and the time until retirement is shorter for older women, could explain why our data showed employment/self-employment as a predictor for reduced QoL. The next question was how many hours the patients worked per week and what they were working. In cases of physical impairment and reduced cognitive function caused by cancer treatment, employment may be associated with strenuous physical efforts. Patients reported a higher level of work limitations such as fatigue and depression [28]. For young patients, the long time until retirement may also be associated with mental stress due to exhaustion. Another aspect of studies conducted in the United States must be mentioned. In Germany, social support is extremely high compared with that in the United States. The fact that there is no national health insurance system in the United States may force and motivate patients with breast cancer to become employed [29,30]. So far, many factors have to be considered when survivors return to work, but all-in-all work can provide higher global life satisfaction [31]. Thus, employment should be considered during after care.

Mastectomy negatively impacts physical function. The literature is congruent with our findings [32,33] and offers several explanations. Pain after mastectomy is a clinically significant postsurgical complication. Impairment is estimated to occur in 20%–50% of the patients [34,35]. In addition, it must be remembered that for women, the breast is of emotional importance and is associated with body image. After oncological surgery, body image is more positive for breast conserving surgery compared to mastectomy [36], and the loss of a breast through mastectomy may lead to psychological problems [37].

Chemotherapy has a minor negative effect on physical functioning. This can be explained by the long-term side effects. Neurotoxic anticancer drugs such as taxanes are responsible for chemotherapy-induced peripheral neuropathy. The overall incidence of cancer is approximately 38% [38]. Early menopause is another common long-term adverse effect, particularly in young women. Samuel et al. [39] reported amenorrhea 1 year after chemotherapy in 30% of premenopausal patients. Survivors can be affected by hot flashes, weight gain, night sweats, and many other disorders.

Physical activity only 2–4 times per month and only once a month showed a negative effect on physical functioning. Many studies have shown higher QoL [40] and physical functioning in active women [41].

Psychiatric comorbidity at initial diagnosis was a predictor of reduced social functioning ($p < 0.01$), and depression at t4 was a predictor of decreased physical and social functioning ($p = 0.02$; $p < 0.01$).

Depression is known to have a negative impact on adherence to medication [42]. Psychiatric comorbidities are associated with a decreased QoL, increased mortality, and worse outcomes concerning somatic diseases [43,44]. Duijts et al. [45] showed that the combined effects of behavioral techniques and physical exercise can improve the QoL, especially psychosocial functioning. Thus, patients with psychiatric comorbidities require special attention in aftercare, offering psychological interventions.

The manuscript we published in 2017 investigated predictors of QoL during therapy, whereas the current manuscript investigated predictors of QoL 5 years after diagnosis. In the first analysis, the outcome was a pattern of QoL development, whereas in our second analysis, the outcome was at a single time point and a later time point. Interestingly, some predictors such as age and mental health appeared to be similar, which is consistent with data from other studies.

One limitation of our study is that it would have been interesting if we had analyzed more confounders. Loss of a partner, job, or other life events are possible reasons for mental problems; cancer treatment and side effects are not the only reasons for decreased QoL.

Another aspect that needs to be discussed is the use of clinically important thresholds in terms of age. A Vögelis analysis of the effect of age on QoL using the EORTC QLQ-C30 questionnaire, showed that it significantly influenced some of the QoL domains [46]. The domains of financial problems, sexual functioning, and sexual pleasure show a linear decrease in scores across age groups [46]. Body image scores increase linearly with age [46]. Hjermstad et al. [47] have argued that age must be considered when interpreting data on the QoL. They generated mean values after adjusting for age [47]. Giesinger et al. [21] did not provide any age-specific thresholds. Hence, the use of TCIs implies that age cannot be considered. However, for screening symptoms and functional problems, the use of thresholds is helpful to better understand the clinical relevance of QoL data.

The number of breast cancer survivors has been increasing. Overall survival is no longer the primary endpoint. Survivors can still be affected years after the initial treatment, resulting in a decreased QoL.

Consequently, relief of symptoms and improvement in QoL should be a strong goal in aftercare. A major challenge in aftercare is the detection of patients with decreased well-being. Predictors may help to identify these patients; therefore, an anamnesis should be considered in such cases. However, screening methods can be used, for example, to detect depression, and special support such as psychological interventions can also be offered.

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