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Symptoms of depression and anxiety as predictors of physical functioning in breast cancer patients. A prospective study using path analysis

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ABSTRACT

Background: Although symptoms of depression and anxiety are linked to health-related quality of life (HRQoL), the nature of this relationship remained unclear. We therefore aimed to examine, in a prospective study, both possible directions of impact in this relationship. To avoid conceptual and measurement overlap between depressive and anxiety symptoms, on the one hand, and HRQoL, on the other hand, we focused on the physical functioning component of HRQoL.

Material and methods: We conducted a secondary analysis of a prospective cohort study with 436 female breast cancer patients (mean age 51 years). Both at baseline and after 12 months, we measured symptoms of depression and anxiety with the four-item Patient Health Questionnaire (PHQ-4) and physical functioning with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Using path analysis, we estimated (1) the predictive value of symptoms of depression/anxiety for subsequent physical functioning and (2) the predictive value of physical functioning for subsequent symptoms of depression/anxiety, in the same model.

Results: Baseline symptoms of depression/anxiety predicted 1-year levels of physical functioning (depression: standardized $\beta = -.09$, $p = .024$; anxiety: standardized $\beta = -.10$, $p = .009$), while the reciprocal paths linking baseline physical functioning to subsequent depressive and anxiety symptoms were not significant, adjusting for the baseline scores of all outcome variables.

Conclusions: Depressive and anxiety symptoms were predictors of the physical functioning component of HRQoL. Thus, if this relation is causal, treating breast cancer patients' depressive and anxiety symptoms may have a favorable impact on their self-reported physical functioning.

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Introduction

Many breast cancer patients suffer from elevated symptoms of depression and anxiety as well as impaired health-related quality of life (HRQoL) [1–3]. Although previous studies have demonstrated an association between emotional distress and HRQoL in breast cancer, the direction of this association remained unclear, as most studies were cross-sectional (e.g., [4–7]).

Prospective studies evaluating the relationship between symptoms of depression and anxiety on the one hand and HRQoL on the other hand are scarce in breast cancer and seem to be lacking in other cancers [8–10]. One study found that anxiety symptoms at 1 month after surgery predicted lower general and breast-cancer-specific overall HRQoL levels after 1 year, and symptoms of depression were predictive for both HRQoL measures even after 2 years [8]. In another study, lower levels of baseline anxiety and improvements in depressive symptoms predicted physical HRQoL improvements after 1 year, adjusting for baseline physical HRQoL [9]. Conversely, a study found that self-reported preoperative physical health predicted the trajectory of anxiety after 6

months, adjusting for preoperative anxiety [10]. However, each of these studies examined only one of the two possible directions of the relationship between emotional distress and HRQoL at a time, thus leaving the question of causal priority open.

Although the authors of another previous study considered both directions of impact, they used two separate models, one for the distress–HRQoL and the other for the HRQoL–distress relation, respectively, instead of combining both directions of impact in one model [11]. In their study, symptoms of depression and anxiety predicted various HRQoL dimensions including physical functioning across 6 months, adjusting for baseline HRQoL. Conversely, global, not physical, HRQoL predicted symptoms of depression and anxiety across 6 months.

Together, previous studies were either cross-sectional or, if prospective, tested only one of both possible directions, at a time, of the relationship between symptoms of depression and anxiety and HRQoL. Thus, previous research has left the question open whether the impact in this relationship was bidirectional or else one of both possible directions had priority. Examining this research question would require testing both directions of impact in the same model.

The aim of our study was to examine the direction of the prospective relationship between symptoms of depression and anxiety and HRQoL across a period of 1 year in patients with breast cancer. Using path analysis, we aimed to estimate (1) the predictive value of symptoms of depression and anxiety for subsequent HRQoL and (2) the predictive value of HRQoL for subsequent symptoms of depression and anxiety. In so doing, we aimed to clarify the prognostic power of one variable over the other. We used path analysis because it allows for a simultaneous analysis of the impact of multiple independent variables on multiple dependent variables, thus testing both directions of impact in the same model (cross-lagged panel design). Consequently, a direct comparison of the respective predictive power of symptoms of anxiety and depression on HRQoL and HRQoL on symptoms of anxiety and depression is possible. Our hypothesis was that the relation was bidirectional. Most importantly, we focused on the physical functioning component of HRQoL, to avoid conceptual overlap of emotional and social components of HRQoL with symptoms of depression and anxiety.

Material and methods

This is a secondary analysis of a clinical trial using a sequential cohort design. While attending a 3-week inpatient rehabilitation program, the two cohorts received either of two very similar psychoeducational courses that covered related topics but differed regarding group size (large vs. small), group format (open vs. closed), and, in part, didactic methods used (unstructured vs. structured). As no differences between both conditions emerged regarding outcomes [12], we merged both cohorts.

Study participants

Patient inclusion criteria were a diagnosis of histologically verified breast cancer, female sex and age at study inclusion between 18 and 63 years. Exclusion criteria comprised the presence, at baseline, of severe physical, cognitive and/or verbal impairments that would interfere with a patient's ability to give informed consent. All participants provided written informed consent. The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Center of the University of Würzburg.

Measures

We measured symptoms of depression and anxiety with the four-item version of the Patient Health Questionnaire, PHQ-4 [13]. This self-report questionnaire covers two core symptoms of depression according to the Diagnostic and Statistical Manual of Mental Disorders, Version IV (DSM-IV), that is anhedonia ('Little interest or pleasure in doing things') and depressed mood ('Feeling down, depressed, or hopeless'); and two symptoms of a generalized anxiety disorder according to DSM-IV, namely nervousness ('Feeling nervous, anxious or on edge') and worries ('Not being able to stop or control

worrying'). Response options are 'not at all' (0), 'several days' (1), 'more than half the days' (2), 'nearly every day' (3) during the last 2 weeks. Its reliability and validity has been proven [13]. Higher values indicate more severe symptoms. Both variables were included as continuous variables.

Patients' HRQoL was assessed using the self-reported cancer-specific European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) [14]. This instrument is widely used and has a good reliability and validity. Higher values indicate better HRQoL. The subscale physical functioning was selected since it covers restrictions of functioning related to physical performance thus avoiding conceptual and measurement overlap with the core symptoms of depression and anxiety.

We employed all measures both at the start of inpatient rehabilitation (baseline) and after 12 months. At 12 months, we provided participants questionnaires and prepaid reply envelopes.

Statistical analysis

For examining the depression–HRQoL relationship, we created a structural equation model with two independent variables (PHQ-4 Depressive symptoms at baseline, EORTC QLQ-C30 Physical functioning at baseline) and two dependent variables (PHQ-4 Depressive symptoms at 12 months, EORTC QLQ-C30 Physical functioning at 12 months), representing a cross-lagged path-analytical panel design. In this model, we adjusted for the corresponding baseline scores of the dependent variables as well as the cross-sectional correlations of both independent and dependent variables, respectively. Of particular interest are, however, the cross-lagged prospective paths that address the prospective depression–physical functioning and physical functioning–depression relationships, respectively. A similar model was created examining the relationship between PHQ-4 Anxiety symptoms and EORTC QLQ-C30 physical functioning. We present standardized path coefficients (β weights) that can be compared directly in magnitude. All analyses were done using SPSS statistical software version 23 (IBM, Armonk, NY, USA) and MPlus software (Muthén & Muthén, Los Angeles, CA, USA).

Results

Sample characteristics

Of 965 patients approached, 436 (45.1%) provided data at baseline. As we obtained no data from those not consenting, selection effects cannot be tested. At 12 months, 372 (85.3%) returned questionnaires. Drop-out analysis revealed a higher proportion of patients with basic education levels in drop-outs compared to participants (14.1% vs. 6.5%, $p < .042$).

Mean age was 51 years ($SD = 6.3$). Most patients were married/living with a partner (64%). Ninety-two percent had more than basic education, and 82% were employees (88% of them salaried). Ninety-seven percent had a primary tumor, mostly without metastases (94%), and in remission (94%). The most frequent treatments performed were surgery (99%;

Table 1. Descriptive statistics and zero-order correlations of the model variables.

	<i>n</i>	<i>M</i>	<i>SD</i>	Age	PHQ-4 Depressive symptoms (baseline)	PHQ-4 Anxiety symptoms (baseline)	EORTC QLQ-C30 Physical functioning (baseline)	PHQ-4 Depressive symptoms (12 months)	PHQ-4 Anxiety symptoms (12 months)
PHQ-4 Depressive symptoms (baseline)	436	1.72	1.43	−.01	1				
PHQ-4 Anxiety symptoms (baseline)	436	1.84	1.51	−.03	.73	1			
EORTC QLQ-C30 Physical functioning (baseline)	436	74.92	18.28	−.08	−.46	−.35	1		
PHQ-4 Depressive symptoms (12 months)	372	1.55	1.49	−.01	.58	.54	−.32	1	
PHQ-4 Anxiety symptoms (12 months)	372	1.68	1.55	−.04	.53	.59	−.27	.78	1
EORTC QLQ-C30 Physical functioning (12 months)	372	79.05	18.18	−.09	−.39	−.33	.70	−.47	−.41

All correlations with age non-significant; all intercorrelations among model variables significant at $p < .001$. PHQ-4: Patient Health Questionnaire-4; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

73% breast conserving), radiotherapy (94%) and chemotherapy (78%). Time since diagnosis amounted to 10 months as a median (interquartile range 6–18). Table 1 shows the descriptive statistics as well as the zero-order correlations of the model variables.

Prospective relationship between depressive symptoms and physical functioning

As displayed in Figure 1(a), depressive symptoms at baseline predicted physical functioning at 12 months ($\beta = -.09$, $p < .05$), after adjusting for baseline physical functioning ($\beta = .65$, $p < .001$). However, the relation between baseline physical functioning and depressive symptoms at 12 months was not significant ($\beta = -.07$, $p = .12$), after adjusting for baseline depressive symptoms ($\beta = .55$, $p < .001$). As displayed, the autoregressive paths, that is, the relation between the baseline score and the corresponding 12-month score, were strong. Moreover, the cross-sectional paths between both independent and dependent variables had a medium-to-large size at both baseline ($\beta = -.45$, $p < .001$) and 12 months ($\beta = -.37$, $p < .001$). Compared to this, the cross-lagged paths were rather small in magnitude, though significant for the depression–physical functioning relationship, as shown.

Prospective relationship between anxiety symptoms and physical functioning

The model examining the anxiety–physical functioning relationship shows a similar picture (Figure 1(b)). Again, autoregressive paths as well as cross-sectional paths between the model variables were of considerable strengths. Similar to depression, baseline symptoms of anxiety predicted 12-month physical functioning ($\beta = -.10$, $p = .009$), while the relation between baseline physical functioning and anxiety symptoms at 12 months was not significant ($\beta = -.07$, $p = .096$).

Discussion

This is the first study, to our knowledge, to show that greater symptoms of depression and anxiety, respectively, predicted worse physical functioning across 12 months in breast cancer

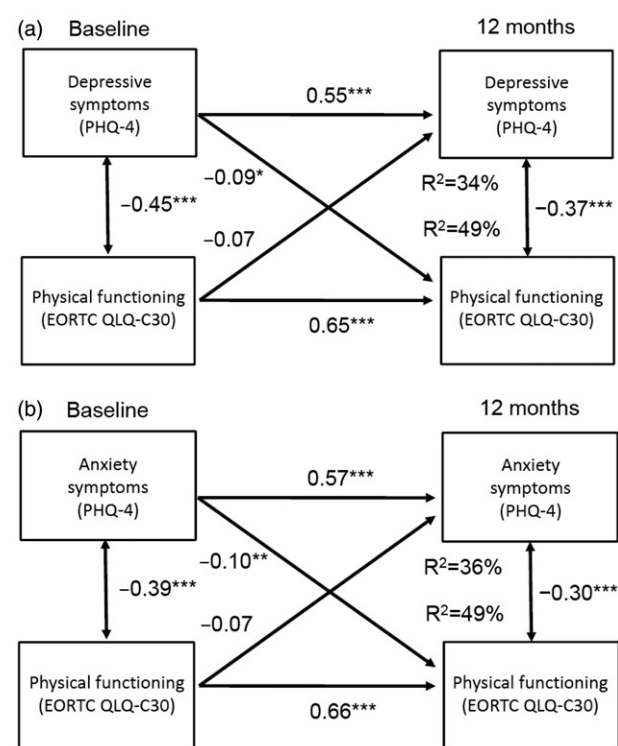


Figure 1. Path analysis models of the depression–physical functioning relationship (a) and the anxiety–physical functioning relationship (b). Note: Figures represent standardized path coefficients. $^*p < .05$, $^{**}p < .01$, $^{***}p < .001$. PHQ-4: Patient Health Questionnaire-4; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

patients, while, at the same time, adjusting for the reciprocal prospective impact of physical functioning on subsequent symptoms of depression and anxiety, respectively. While previous studies demonstrated links of depressive and anxiety symptoms with HRQoL both cross-sectionally [4–7] and prospectively [8–11], we performed a stronger test of this relationship by accounting for both directions of impact within the same model, using path analysis. We also adjusted for the relations between the baseline and follow-up scores of each outcome variable (autoregressive paths), as well as for the concurrent correlations between the variables of interest at both time points. In part due to the multiple

adjustments made, though, the cross-lagged paths representing the prospective relationships between symptoms of depression/anxiety and physical functioning, and, likewise, physical functioning and symptoms of depression/anxiety, were small in magnitude. Nevertheless, symptoms of both depression and anxiety significantly predicted subsequent physical functioning, over and above the predictive value of baseline physical functioning as well as the cross-sectional correlations of the model variables. Thus, greater depressive and anxiety symptoms may not be conceived of as representing mere indicators of reduced physical HRQoL [11], but instead independent predictors of physical HRQoL. This has important implications for assessing and treating emotional distress in breast cancer patients, since patients' emotional distress may contribute to worse physical functioning in the long-term disease trajectory.

As to the issue of causal priority, that is, the question whether the influence of depressive or anxiety symptoms on physical functioning is stronger than the reciprocal influence of physical functioning on depressive or anxiety symptoms, our results are not so clear-cut. Although the depression/anxiety–physical functioning relation proved significant whereas the reciprocal relations did not, the respective path coefficients were of rather similar size, precluding an unambiguous statement on priority [11]. More generally, of course, causality could not be proven within our study as it used an observational design.

Regarding the process underlying the prospective relation between symptoms of depression and anxiety and the physical functioning component of HRQoL, several mechanisms are plausible. Depressed cancer patients are less likely to adhere to treatment recommendations, such as engaging in physical activity [15], thus foregoing an opportunity to improve physical HRQoL [16]. The link between depression and HRQoL may be mediated, however, in part by biased perception and reporting, since depressed patients are more likely to perceive their health status negatively [17]. Clinical trials demonstrating that treatment of depression additionally improved physical functioning lend support to the notion of a causal impact of depression on physical HRQoL [18].

Some limitations should be considered. We investigated a homogeneous sample of breast cancer patients. However, the relationships described in our study may also be relevant for other cancers beyond breast cancer, as well as, even more broadly, other conditions beyond cancer. Thus, the results require confirmation in other cancer and non-cancer samples and male patients. We had a rather high rate of non-response. Moreover, we could not examine selection effects, since no data for non-responders was available. Although we had a rather low dropout rate at 12 months, dropouts reported somewhat lower education levels than did participants. This may reduce generalization. A further limitation was that we used very short instruments measuring depression and anxiety. Furthermore, self-reports were not confirmed by structured interviews. However, good performance of our measures in screening for depressive and anxiety disorders has been established [19,20]. We assessed only the physical functioning component of HRQoL to avoid conceptual and measurement overlap. However, although one

would expect even stronger relations of depressive and anxiety symptoms to the psychosocial components of HRQoL, such relations would be difficult to interpret. Lastly, we cannot exclude residual confounding may contribute to the cross-lagged paths.

In conclusion, depressive and anxiety symptoms were predictive of the physical functioning component of HRQoL after adjusting for the reciprocal impact of physical functioning on depressive and anxiety symptoms. Provided the prospective relationship between symptoms of depression/anxiety and subsequent physical functioning is causal, breast cancer patients' elevated depressive and anxiety symptoms would deserve detection and treatment not only as such, but also as improving them might favorably affect patients' self-reported physical functioning.

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Disclosure statement

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References

- [1] Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. *J Exp Clin Cancer Res*. 2008;27:32.
- [2] Reich M, Lesur A, Perdrizet-Chevallier C. Depression, quality of life and breast cancer: a review of the literature. *Breast Cancer Res Treat*. 2008;110:9–17.
- [3] Howard-Anderson J, Ganz PA, Bower JE, et al. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *J Natl Cancer Inst*. 2012;104:386–405.
- [4] Brunault P, Champagne A-L, Huguet G, et al. Major depressive disorder, personality disorders, and coping strategies are independent risk factors for lower quality of life in non-metastatic breast cancer patients. *Psycho-Oncology*. 2016;25:513–520.
- [5] Faller H, Brähler E, Härter M, et al. Performance status and depressive symptoms as predictors of quality of life in cancer patients. A structural equation modeling analysis. *Psycho-Oncology*. 2015;24:1456–1462.
- [6] Reyes-Gibby CC, Anderson KO, Morrow PK, et al. Depressive symptoms and health-related quality of life in breast cancer survivors. *J Womens Health*. 2012;21:311–318.
- [7] Luutonen S, Sintonen H, Stormi T, et al. Health-related quality of life during adjuvant radiotherapy in breast cancer. *Qual Life Res*. 2014;23:1363–1369.
- [8] Taira N, Shimozuma K, Shiroya T, et al. Associations among baseline variables, treatment-related factors and health-related quality of life 2 years after breast cancer surgery. *Breast Cancer Res Treat*. 2011;128:735–747.
- [9] Hyphantis T, Almyroudi A, Paika V, et al. Anxiety, depression and defense mechanisms associated with treatment decisional preferences and quality of life in non-metastatic breast cancer: a 1-year prospective study. *Psycho-Oncology*. 2013;22:2470–2477.

- [10] Kyranou M, Puntillo K, Dunn LB, et al. Predictors of initial levels and trajectories of anxiety in women before and for 6 months after breast cancer surgery. *Cancer Nurs.* 2014;37:406–417.
- [11] Hutter N, Vogel B, Alexander T, et al. Are depression and anxiety determinants or indicators of quality of life in breast cancer patients? *Psychol Health Med.* 2013;18:412–419.
- [12] Meng K, Richard M, Strahl A, et al. Mittel- und langfristige Effektivität einer Patientenschulung “Curriculum Brustkrebs” in der onkologischen Rehabilitation. [Medium and long-term effectiveness of a patient education program “Curriculum Breast Cancer” within oncological rehabilitation.] 25. Rehabilitationswissenschaftliches Kolloquium vom 29. Februar bis 3. März 2016 in Aachen. DRV-Schriften. 2016;109:193–194.
- [13] Löwe B, Wahl I, Rose M, et al. A 4-item measure of depression and anxiety: validation and standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. *J Affect Disord.* 2010;122:86–95.
- [14] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85:365–376.
- [15] Chipperfield K, Fletcher J, Millar J, et al. Factors associated with adherence to physical activity guidelines in patients with prostate cancer. *Psycho-Oncology.* 2013;22:2478–2486.
- [16] Phillips SM, Awick EA, Conroy DE, et al. Objectively measured physical activity and sedentary behavior and quality of life indicators in survivors of breast cancer. *Cancer.* 2015;121:4044–4052.
- [17] Faller H, Steinbüchel T, Störk S, et al. Impact of depression on quality of life assessment in heart failure. *Int J Cardiol.* 2010;142:133–137.
- [18] Sharpe M, Walker J, Holm Hansen C, et al. SMaRT (Symptom Management Research Trials) Oncology-2 Team. Integrated collaborative care for comorbid major depression in patients with cancer (SMaRT Oncology-2): a multicentre randomised controlled effectiveness trial. *Lancet.* 2014;384:1099–1108.
- [19] Löwe B, Kroenke K, Gräfe K. Detecting and monitoring depression with a two-item questionnaire (PHQ-2). *J Psychosom Res.* 2005;58:163–171.
- [20] Plummer F, Manea L, Trepel D, et al. Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis. *Gen Hosp Psychiatry.* 2016;39:24–31.