Trajectories and predictors of state and trait anxiety in patients receiving chemotherapy for breast and colorectal cancer: results from a longitudinal study

Short title:

Anxiety during chemotherapy for breast and colorectal cancer

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Highlights:

- Anxiety levels were high in patients with breast and colorectal cancer commencing chemotherapy treatment.
- Both state and trait anxiety declined with treatment progression, contradicting the notion of trait stability over time.
- Trait anxiety was the only significant predictor of state anxiety throughout treatment, overshadowing symptom burden effects.
- Psychosocial/behavioural interventions introduced at pre-chemotherapy could help reduce patient anxiety throughout treatment.

Abstract

Purpose

To examine the trajectories and predictors of state and trait anxiety in patients undergoing chemotherapy for breast or colorectal cancer.

Methods

Secondary analysis of data collected as part of a large multi-site longitudinal study. Patients with breast or colorectal cancer completed validated scales assessing their state and trait anxiety levels (State-Trait Anxiety Inventory) and symptom burden (Rotterdam Symptom Checklist) at the beginning of each chemotherapy cycle. Longitudinal mixed model analyses were performed to test changes of trait and state anxiety over time and the predictive value of symptom burden and patients' demographic (age, gender) and clinical characteristics (cancer type, stage, comorbidities, ECOG performance status).

Results

Data from 137 patients with breast (60%) or colorectal cancer (40%) were analysed. Linear time effects were found for both state (χ^2=46.3 [df=3]; p<0.001) and trait anxiety (χ^2=17.708 [df=3]; p=0.001), with anxiety levels being higher at baseline and gradually decreasing over the course of chemotherapy. Symptom burden (β=0.21; SD=0.06; p=0.001) predicted state anxiety throughout treatment, but this effect disappeared when accounting for trait anxiety scores before the start of chemotherapy (β=0.85; SD=0.05; p<0.001). Patients' baseline trait anxiety was the only significant predictor of anxiety throughout treatment.

Conclusions

Changes in the generally stable characteristic of trait anxiety indicate the profoundly life-altering nature of chemotherapy. The time point before the start of chemotherapy was identified as the most anxiety-provoking, calling for interventions to be delivered as early as possible in the treatment trajectory. Patients with high trait anxiety and symptom burden may benefit from additional support.

Introduction

Anxiety in patients with cancer is a topic of great importance: previous research shows that this particular emotion is not only extremely common in this patient group (Burgess et al., 2005; Lewis et al., 2014), but it also has far-reaching effects on symptom experiences during treatment (Lockefeer and Vries, 2013; Saevarsdottir et al., 2010; Whitford and Olver, 2012), treatment compliance (Greer et al., 2008), patient outcomes such as experienced side-effects (Van Esch et al., 2011), and even survivorship (García-Torres and Alós, 2014). A useful theoretical framework for researching anxiety throughout the course of cancer treatment is Spielberger's anxiety model (Spielberger, 1989; Spielberger et al., 1983), which differentiates between state and trait anxiety.

State anxiety represents a transitory emotional state as a reaction to a particular stressor, e.g. being diagnosed with cancer, and fluctuates over time. Trait anxiety, on the other hand, is a stable susceptibility or proneness to experience anxiety and is regarded as a vulnerability factor for adverse reactions to stress. This distinction has been empirically tested and is consistently supported by research with various populations, ranging from psychiatric, psychosomatic, and medical patient groups to the general population (Spielberger and Reheiser, 2009). Considering this model when investigating the experiences of patients with cancer can help discern the influence of patients' anxiety predisposition and anxiety as a reaction to a stressful life event.

In the cancer care context, high trait anxiety is often accompanied by poor health status as well as negative self-perceptions and expectations for the future (Van Esch et al., 2011). It can also act as a precursor for developing symptoms of depression and fatigue (Lockefeer and Vries, 2013). Of significance is that no study to date has investigated if trait anxiety remains stable when undergoing treatment for cancer, as predicted by Spielberger's theory (Spielberger, 1989; Spielberger et al., 1983).

Unlike trait anxiety, trajectories of state anxiety in patients with cancer have been explored in few longitudinal studies. Lewis et al. (2014) repeatedly assessed anxiety levels of 213 patients with non-metastatic breast cancer undergoing radiotherapy. Within this patient

group, initially high anxiety rapidly declined with the start of treatment, suggesting habituation effects. In women scheduled to receive chemotherapy for breast cancer, the time point before the first treatment cycle was also identified as being the most anxiety-provoking (Jacobsen et al., 1993). Baseline trait anxiety levels and chemotherapy toxicity contributed significantly to higher levels of state anxiety during treatment. This research provides preliminary insight into the development of patients' state anxiety over time, but in qualification, it must be added that state anxiety in both studies was only measured with a single-item visual analogue scale instead of a validated state anxiety questionnaire based on Spielberger's conceptualization (Spielberger et al., 1983).

Burgess et al. (2010) stress the importance of providing psychological support for patients with cancer as anxiety stays elevated even after chemotherapy cessation/completion. This however requires a thorough understanding of underlying processes and pre-cursors of higher levels of anxiety. Further, untangling the influence of situational factors (e.g. diagnosis, treatment commencement, symptom burden) and underlying characteristics of a person (e.g. general anxiety predisposition, symptom experience), can help to identify critical time points and patient groups most in need for interventions.

The current analysis aimed to enhance our understanding of the trajectories and predictors of both state and trait anxiety in patients with cancer undergoing chemotherapy for breast or colorectal cancer, addressing the following research questions:

a) How do state and trait anxiety levels change over the course of treatment?
b) Do any demographic (age, gender) or clinical characteristics (cancer type, staging, comorbidity, performance status, symptom burden) predict initial levels and/or the trajectories of state and trait anxiety over the course of treatment?
c) Does baseline trait anxiety affect state anxiety over the course of treatment?

Testing those questions for the specified patient groups is particularly interesting due to a number of reasons. Firstly, breast and colorectal cancer are two of the most commonly diagnosed forms of cancer (Westlake & Cooper, 2008; Torre et al., 2015). Breast cancer is the most prevalent type of cancer in females, with an estimated incidence rate of 44,400 in the UK alone (Westlake & Cooper, 2008) and 1.7 million cases per year worldwide (Torre et al., 2015). Colorectal cancer is the third most common cancer in males and the second in females, with a

yearly incidence rate of 36,200 in the UK (Westlake & Cooper, 2008) and 1.4 million worldwide (Torre et al., 2015).

Considering the experience of both patient groups is useful as previous longitudinal research predominantly focused on anxiety in female breast cancer patients (e.g. Burgess et al., 2005; Jacobsen, Bovbjerg, & Redd, 1993; Lewis et al., 2014; Lim, Kamala Devi, & Ang, 2011; Van Esch et al., 2011). On the one hand, this is reasonable as women typically report more anxiety problems (McLean & Anderson, 2009), but additionally accounting for male patients in this study allows testing of such gender effects. Beyond this, cancer experiences differ for different types of cancer and therefore it is advisable to research different patient groups (LeMasters, Madhavan, Sambamoorthi, & Kurian, 2013). Finally, considering in particular patients undergoing chemotherapy for an exploration of trait and state anxiety suggested itself as this treatment causes higher anxiety levels than other treatment types (Lim et al., 2011), possibly due to its often distressing and potentially life threatening side effects (Du, Osborne, & Goodwin, 2008).

Methods

Participants and procedures

Data presented in this article derived from the first phase of a wide-scale, before-and-after intervention study that was conducted at four health boards across the UK. The overall aim of the study was to examine the feasibility and acceptability of the use of the Advanced Symptom Management System (ASyMS), a mobile phone-based, real-time, remote patient-monitoring system to assist with the assessment and management of chemotherapy-related toxicity (Kearney et al., 2009).

The 'Before Phase', which was the basis for the secondary data analysis reported in this article, focused on the baseline investigation of patients' experiences of chemotherapy before the introduction of the intervention. It involved the longitudinal assessment of patients receiving standard care, whereas the 'After Phase' collected the same self-reported data from a separate group of patients using the ASyMS system while undergoing chemotherapy. A publication with respect to the primary analysis is currently in preparation and results concerning the intervention are available from the authors. Research Governance and ethical approval were obtained for all

parts of this research (East of Scotland Research Ethics Service: REC Reference No 10/S0501/55). Data was collected for this phase from August 2011 to July 2013.

Health care professionals at each site approached patients diagnosed with non-metastatic breast or colorectal cancer receiving adjuvant chemotherapy treatment aged 18 years or over. Written informed consent was obtained from all interested patients. Demographic and clinical information was collected for study participants, who also completed a battery of self-report questionnaires (see measures) at baseline and with each chemotherapy cycle in a repeated-measures format for a total six consecutive assessments.

Measures

Demographic and clinical characteristics data were assessed at baseline. Participants provided basic demographic information regarding their age and gender. The following clinical characteristics were obtained reviewing participants' medical case notes: cancer type and stage, type of treatment, chemotherapy cycle length, comorbidities and physical functioning (ECOG performance status).

Anxiety was assessed using the 40-item State-Trait Anxiety Inventory (STAI), a widely used measurement of state and trait anxiety (Spielberger, 1989; Spielberger et al., 1983). Each subscale consists of 20 items that are rated on a 4-point scale. The total score range for each subscale is 20 to 80, higher scores indicating higher anxiety. The STAI has been extensively researched in various populations and findings confirm its validity and internal consistency. Furthermore, the STAI has been widely used in cancer research (Jacobsen et al., 1993; Lim et al., 2011; Taoka et al., 2014) and was recommended by an expert panel (including clinicians and cancer survivors) for the assessment of anxiety in patients with cancer (Howell et al., 2013). The internal consistency of the STAI in this study was good (Cronbach's alpha throughout treatment for state anxiety ranging from 0.94-0.97; for trait anxiety from 0.92-0.96).

Symptom burden was determined via the Rotterdam Symptom Checklist (RSCL), which assesses 30 symptoms reported by patients with cancer (Olschewski et al., 1996). Participants rated on a 4-point scale how much physical (e.g. tiredness, nausea) and psychological symptoms (e.g. irritability, nervousness) bothered them in the past three days, with higher scores suggesting higher symptom levels. Additionally, the scale comprises eight ratings concerning participants'

activity level and overall quality of life, where lower scores indicate higher impairment. The RSCL exhibits good psychometric properties as verified across patient populations (de Haes et al., 1990). The internal consistency of the RSCL symptom subscale in this study was good (Cronbach's alpha ranging from 0.83-0.88).

Analyses

Descriptive statistics for baseline characteristics and the outcome measures at each time-point were calculated. Furthermore, the development of trait and state anxiety was plotted over the course of chemotherapy treatment. Repeated measurements of anxiety and symptom severity at different time points resulted in a nested data set, calling for an analysis approach that accounts for this higher level clustering of individuals' ratings by time to avoid type I errors and biased parameter estimations (Peugh, 2010; Shek and Ma, 2011). Therefore, longitudinal mixed model analyses were used to answer our three research questions as stated above.

Models that accounted for linear and quadratic time effects were calculated and -2 log likelihood tests were employed to identify which model was a better fit to the data. For the final conditional models, inter-individual differences were considered modelling the individual change parameters (intercept and slope) of anxiety (outcome) as a function of the potential predictors: age, gender, cancer type, disease stage, ECOG performance status and comorbidities. Significant estimates imply that the change in anxiety over time fluctuates depending on these variables. The research questions informed the inclusion of predictor variables.

To compare participants with lower and higher trait anxiety as measured at baseline with the STAI, a median split was performed as no published cut-off scores are available for the current sample population. An alpha level of <0.05 was applied for statistical significance tests. All analyses were performed in SPSS version 20 (IBM, Chicago, IL) based on restricted maximum likelihood estimation.

Results

Participants' demographic and clinical characteristics

A total of 140 patients diagnosed with breast or colorectal cancer participated in the study. Analysable data were available for 137 participants (breast cancer: 60%; colorectal cancer: 40%) as three participants did not provide information on anxiety. Participants' age ranged from 30 to 76, with a mean age of 56 years (SD=10.41). Baseline characteristics of all participants are summarised in Table 1. Participants were, on average, in their mid-fifties, diagnosed with stage two or three cancer and suffering from at least one comorbidity.

Mainly female participants (98%; n=79) were recruited for the breast cancer group, whereas the male-female proportion was well-balanced for patients with colorectal cancer. Comparing the two sub-groups, patients with colorectal cancer were typically older (Z=-4.24; p<0.001), suffered from more comorbid illnesses (χ^2=12.97; p=0.002), their cancer stage was more advanced (χ^2=22.58; p<0.001) and their performance status was rated lower than their counterparts with breast cancer (χ^2=11.99; p=0.002). However, there was no group difference with regard to symptom burden as reflected by baseline RSCL scores (Z=-0.95; p=0.344).

Prevalence of state and trait anxiety

Pre-chemotherapy anxiety scores are summarized in Table 1. There was no significant difference among trait (Z=-0.86; p=0.392) or state anxiety (Z=-1.47; p=0.141) for patients with colorectal and breast cancer. The median split (Mdn=34) allocated 70 (53.4%) participants to a lower trait anxiety group (STAI trait≤34) and 61 (46.6%) to a higher trait anxiety group (STAI trait>34), allowing to compare participants with lower and higher trait anxiety in the following analyses.

Changes of state and trait anxiety over time

Table 2 provides a summary of those changes over time, reporting means and standard deviations of changes for each chemotherapy cycle compared to baseline. Mixed analyses (Table 3) revealed that including linear time effects significantly improved the model's fit for the current sample compared to a means only models for both, state (χ^2=46.3 [df=3]; p<0.001) and trait anxiety (χ^2=17.708 [df=3]; p=0.001). Modelling squared time effects did not result in

models with a better fit to the data than the presented linear models, evidence by an increase of the -2 log likelihood estimates.

Taking into account negative time coefficients for state (β= -0.84; SD=0.20; p<0.001) and trait anxiety (β= -0.33; SD=0.12; p=0.008), this means that both types of anxiety gradually decreased over the course of chemotherapy in a linear manner. Changes in state anxiety were more pronounced than changes in trait anxiety, even though both shifted significantly (Figure 1). Variance component analysis suggested that after accounting for time effects, enough individual variance was left to explore the influence of other potential predictor variables on state anxiety levels throughout treatment and on baseline trait anxiety scores (Table 3).

Predictors of anxiety levels over time

Symptom burden as measured with the RSCL increased with chemotherapy progression and symptom scores reached a peak at the final assessment time point (Table 2). Accounting for participants' gender, cancer type, age, cancer stage, comorbidities, ECOG status and RSCL symptom scores significantly improved the models' fit (χ^2=262.974 [df=13]; p<0.001), but only the symptom scores were associated with state anxiety. The higher the participants' symptom burden during treatment, the higher their state anxiety levels (β=0.21; SD=0.06; p=0.001).

Similar results were obtained for trait anxiety: accounting for listed predictor variables resulted in a model with a better fit (χ^2=211.435 [df=13]; p<0.001) compared to the unconditional model and experienced symptom burden as measured with the RSCL was associated with baseline trait anxiety ratings (β=0.18; SD=0.05; p<0.001). Participants, who at baseline indicated suffering from more symptoms (e.g. carry-over from previous treatments such as surgery) also rated their trait anxiety higher at this point compared to those without similar complaints.

Baseline trait anxiety as predictor of state anxiety during chemotherapy treatment

Modelling state anxiety during chemotherapy based on group membership according to the median split while adjusting for participant characteristics (age, gender, cancer type, stage, comorbidities, ECOG performance status) and experienced symptoms (RSCL scores) highlighted

the importance of baseline trait anxiety for the trajectory of state anxiety. None of the participant characteristics predicted state anxiety scores over treatment in the current sample except initial trait anxiety ratings ($\beta=0.85$; SD=0.05; $p<0.001$). Even the previously described effect of experienced symptom burden as measured with the RSCL disappeared ($\beta=0.05$; SD=0.05; $p=0.274$). Baseline trait anxiety therefore mediated any effects of experienced symptoms on patients' state anxiety throughout treatment. Participants from the higher trait anxiety group experienced higher levels of state anxiety throughout chemotherapy treatment compared to participants with initial low trait anxiety scores.

Discussion

The present study found linear time effects on anxiety in patients undergoing chemotherapy for breast and colorectal cancer: patients started out with high anxiety, which declined with treatment progression. This trajectory applied to both state and trait anxiety. Symptom burden was the only variable with a statistically significant effect on initial trait anxiety levels. Symptom burden was also identified as a significant predictor for state anxiety throughout chemotherapy, but this effect was cancelled out when accounting for baseline trait anxiety. The latter significantly predicted patients' state anxiety levels throughout treatment.

The described trend, i.e. a decline of anxiety levels when undergoing chemotherapy, could be due to the high overall performance status of the current patient sample (71% ECOG Performance Status Grad 0). This clinical characteristic has been shown to be associated with low anxiety (Bodurka-Bevers et al., 2000), possibly because such patients do not develop as many side-effects as patients with lower performance status. Another explanation for the observed developments might be adaption: after the initial fear of unfamiliar treatment procedures, patients became more acquainted with chemotherapy, reducing anxieties. This argument is backed up by the observation that receiving relevant information seems important in facilitating patients' adaptation (Ream and Richardson, 1996).

Lien et al. (2009) found similar adaption processes as evident in the current sample in patients treated with surgery for cancer. They highlighted social support as an important driver for adjustment and anxiety attenuation. Negative correlations have been reported between patients' self-efficacy and anxiety ratings when undergoing radiotherapy (Cohen, 2014),

suggesting that gaining expertise and confidence in their coping abilities could reduce patients' worries over the course of treatment. Those factors might also play a role in chemotherapy treatment and may have contributed to the observed downtrend in anxiety ratings.

For state anxiety, the trajectory and predictors investigated in the current study mirror findings from previous research. Jacobsen et al. (1993) reported that anxiety in women receiving chemotherapy for breast cancer was highest before their first cycle and that trait anxiety and side-effects predicted anxiety later on. A cross-sectional survey of men with prostate cancer undergoing radical treatment found high correlations of state and trait anxiety and a decline in state anxiety over time (Taoka et al., 2014). Though age is regularly ascribed as an effect on anxiety during cancer treatment (Cohen, 2014; Jacobsen et al., 1993), this was not the case in the current sample although a wide age range was covered. We found that rather physical symptoms experienced while undergoing chemotherapy influence a persons' general vulnerability to react anxiously (state anxiety), explaining why interventions that address chemotherapy side-effects are also effective in reducing anxiety (Vasterling et al., 1993; Yoo et al., 2005). However, when symptom burden and trait anxiety were regressed together on state anxiety levels, the situational anxiogenic effects of symptom burden disappeared. This finding raises the hypothesis that personality traits may be stronger influential variables of stress response than situational factors, such as chemotherapy symptom burden (Du, Osborne, & Goodwin, 2008).

In addition, the significant correlation of trait anxiety with perceived symptom burden at baseline could also be interpreted as patient 'proneness' to over-reporting/experiencing long-standing physical symptoms, which may be true for certain personality types (Shun et al., 2014; Zhang et al., 2016). It is intriguing to hypothesize that the link between personality-driven trait anxiety levels and situational anxiety levels during chemotherapy may be mediated by worry about anticipated physical symptoms and the associated burden, or anxiety somatization that is manifested through certain symptoms (e.g., poor sleep or fatigue).

An unexpected finding of the current study was the decline of trait anxiety in patients over the course of treatment. This dissents the theoretical background, Spielberger's anxiety model, which considers trait anxiety to be a stable personality characteristic, not likely to change over time (Spielberger and Reheiser, 2009; Spielberger, 1989; Spielberger et al., 1983). Research evidence facilitating the interpretation of this change in trait anxiety comes from qualitative

studies exploring the experience and sense-making of patients with cancer. In a longitudinal interview study of 12 women with breast cancer (McCann et al., 2010), their illness emerged as a life-altering experience: presenting as biographical disruption, patients had to renegotiate their identity to make the transition into a future of living with cancer. Similar profound adaptation processes have been shown in other studies of patients with prostate (Navon and Morag, 2004) and terminal cancer (Reeve et al., 2010). It seems likely that such far-reaching changes in a person's life can affect personality traits like a person's vulnerability to experience anxiety, too.

An alternative field of research to considering when trying to explain the observed changes in trait anxiety over time is resilience research. Current evidence suggests that resilience as a baseline characteristic or trait may facilitate coping with cancer, but could also be an outcome of a successful adaptation to the 'trauma' of being diagnosed with and treated for cancer (Jacelon, 1997; Molina et al., 2014). As resilience is attended by positive emotional experiences and might be a more common reaction to traumatic experiences than generally believed (Bonanno, 2004), a decline in a persons' vulnerability to experience anxiety over the course of cancer treatment is logically consistent.

Clinical implications

Our findings offer valuable evidence on how to best support patients undergoing chemotherapy, providing means of identifying those at greatest risk of experiencing anxiety and targeting interventions accordingly. Anxiety should be assessed before the first chemotherapy cycle as this is the most anxiety-provoking moment throughout a patient's journey. Addressing fears at this stage seems the most promising time point to initiate change processes that should show positive effects later during treatment. Ensuring good preparation prior to the start of chemotherapy (Burish et al., 1991) and that patients get the support they need, including help with anxiety issues (Traeger et al., 2012), is essential. Psychosocial interventions, for example supportive counselling, coping or relaxation trainings, seem more suitable to manage fears in the long term than pharmacological treatments with less sustainable effects (Traeger et al., 2012).

Patients with high trait anxiety are particularly likely to require additional, personality-tailored support, as they tend to continue feeling more anxious throughout treatment. In line with Van Esch et al. (2011), screening for trait anxiety and, if necessary, psychological interventions are advisable prior to treatment to improve patients' experiences, potentially reducing side-

effects. To encourage patients' tendency to adapt to their treatment and to feel less anxious over time, health care providers should take on a strengths-based perspective on human functioning and consider adjuvant psycho-social factors, for example building on existing social support (Lien et al., 2009), to foster resilience (Molina et al., 2014).

Limitations and future research

The current research was a secondary data analysis; hence, more focused research is needed to answer the proposed research questions. While presenting an economic approach that granted access to a large patient sample, not all variables that potentially influence state and trait anxiety were measured. Future studies should advance the current findings, researching the role of factors such as patients' type of personality, coping strategies and social support on anxiety, as well as the link between trait anxiety, symptom burden and state anxiety. It would be of particular interest to focus on variables that, similarly to anxiety, potentially change over the course of treatment like self-efficacy and resilience.

We also acknowledge the possibility that certain physical symptoms may generate greater anxiety than others. Yet the objective in this study was to consider multi-symptoms instead of single-symptom burden. Previous research has shown that multiple symptoms (some of them in clusters) may be experienced by the majority of patients receiving chemotherapy (Thomas et al., 2014; Skerman et al., 2012), and it was this cumulative effect of multiple symptoms on anxiety levels that we wished to investigate here. Investigation of the links between single chemotherapy-related symptoms and state/trait anxiety levels is nevertheless warranted.

To the authors' knowledge, no other study has researched trait anxiety in patients undergoing chemotherapy in a longitudinal manner, which is a major advantage of the current research. However, the data was collected from a convenience sample and is therefore not representative of all patients with breast or colorectal cancer. It should be the aim of future research to test our findings within larger samples and other patient groups and to clarify the mechanism behind observed changes in this personality-like trait. It would be worth exploring if similar findings can be demonstrated for patients receiving a different form of cancer treatment. Investigating anxiety during chemotherapy in a first instance suggests itself insofar as this treatment causes higher anxiety levels than other treatment types (Lim et al., 2011). Similarly, researching different tumour groups is advisable as patients' experiences differ for different

types of cancer (LeMasters et al., 2013), but results concerning patients with breast and colorectal cancer are particularly important considering their high incidence rates (Westlake and Cooper, 2008). Finally, interventions based on aforementioned suggestions should be verified in the future to optimise patient care. In particular, testing the effect of psychosocial interventions at the time point of diagnosis on subsequent anxiety seems like a worthwhile endeavour. This could strengthen the evidence base for anxiety treatment in cancer patients as called for by Traeger et al. (2012).

Conclusions

The current study highlights the time point before the start of chemotherapy as extremely anxiety provoking. Patient support at this stage might foster an improvement in patients' experiences of anxiety throughout treatment, in particularly for patients with high trait anxiety. Ensuring patients receive this kind of support could not only help reduce state anxiety throughout chemotherapy, but could also lower their vulnerability to react anxiously in the future, promoting resilience as result of their illness.

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Tables and figures

Table 1. Characteristics of the total group (*N*=140) and separately for the BC group (*N*=74) and the CRC group (*N*=52) at baseline.

Characteristics	Total group	BC group	CRC group
Age (years)[a]	55.96±10.4	52.81±10.13	60.58±9.14
Gender: male/ female[b]	29 (21.2)/ 108 (78.8)	2 (2.5) / 79 (97.5)	26 (47.3)/ 29 (52.7)
Disease stage TNM UICC: I/ II/ III/ IV[b]	11 (8.9)/ 58 (46.8)/ 51 (41.1)/ 4 (3.2)	8 (11.1)/ 47 (65.3)/ 17 (23.6)/ 0	3 (5.8)/ 11 (21.1)/ 34 (65.4)/ 4 (7.7)
Number of co-morbid illnesses: 0/ 1/ ≥2[b]	50 (36.5)/ 39 (28.5)/ 48 (35.0)	38 (46.9)/ 23 (28.4)/ 20 (24.7)	11 (20.0)/ 16 (29.1)/ 28 (50.9)
ECOG status: 0/ 1/ 2	92 (71.3)/ 35 (27.1)/ 2 (1.6)	62 (82.7)/ 12 (16.0)/ 1 (1.3)	29 (54.7)/ 23 (43.4)/ 1 (1.9)
RSCL-Symptom score[a]	31.63± 6.07	31.31±6.10	32.18±6.06
STAI-State score[a]	35.86±12.35	37.26±12.700	34.00±11.71
STAI-Trait score[a]	34.75±10.21	35.42±10.38	34.00±9.96

BC=breast cancer; CRC=colorectal cancer; TNM UICC=Tumour Node Metastasis Union International Contra la Cancrum; ECOG= Eastern Cooperative Oncology Group; RSCL=Rotterdam Symptom Checklist; STAI=State–Trait Anxiety Inventory.
[a]mean±SD. [b]n (%).

Table 2. Changes in state**/trait anxiety and symptom burden** at each time point compared to baseline (mean±SD).

	CTx1	CTx2	CTx3	CTx4	CTx5	CTx6
STAI-State score	35.86±12.35	-3.08±9.63	-2.33±11.16	-3.86±11.49	-3.97±11.06	-4.66±11.09
STAI-Trait score	34.75±10.21	-0.58±7.48	0.15±7.24	-0.47±7.75	-2.08±6.44	-1.69±6.04
RSCL Symptom burden score	31.63± 6.07	0.83±7.14	0.82±7.46	1.97±8.66	2.06±6.32	3.00±7.28

CTx – Chemotherapy cycle; STAI=State–Trait Anxiety Inventory.

Table 3. Mixed model results for the longitudinal relationship between baseline characteristics (predictor variables) and state anxiety/ trait anxiety as (dependent variables) as measured with the STAI.

Variables	Coefficient (SE)		
	Means only model	Unconditional model	Conditional model
State Anxiety			
Fixed effects			
Intercept	33.23 (0.92)**	34.91 (0.94)**	19.83 (10.12)
Time (linear rate of change)		-0.84 (0.20)**	1.02 (2.09)
Time invariant covariates - baseline			
Gender			4.59 (2.87)
Cancer type			.943 (2.49)
Age			-0.02 (0.11)
Cancer stage			-2.91 (4.13)
Comorbidities			-0.25 (1.29)
ECOG status baseline			0.12 (2.26)
Time invariant covariates - change			
Time x Gender			-0.69 (0.61)
Time x Cancer type			-0.24 (0.54)
Time x Age			-0.01 (0.02)
Time x Cancer stage			-1.31 (0.04)
Time x Comorbidities			-0.02 (0.28)
Time x ECOG status baseline			0.60 (0.50)
Time variant covariates			
RSCL-Symptom score			0.21 (0.06)**
Variance components			
In intercept	104.17 (14.00)**	99.46 (14.73)**	93.23 (15.09)**
In linear rate		1.94 (0.61)**	2.08 (0.68)**
Goodness-of-fit deviance Model comparison (χ^2 [df])		46.3 [3]**	262.974 [13]**
Trait Anxiety			
Fixed effects			
Intercept	34.10 (0.88)**	34.79 (0.85)**	27.34 (8.96)*
Time (linear rate of change)		-0.33 (0.12)*	1.18 (1.17)
Time invariant covariates - baseline			
Gender			1.20 (2.56)
Cancer type			-0.71 (2.22)
Age			-0.01 (0.10)
Cancer stage			-3.07 (3.66)
Comorbidities			0.70 (1.15)
ECOG status baseline			1.21 (2.01)
Time variant covariates			
RSCL-Symptom score			0.18 (0.05)**
Variance components			
In intercept	98.81 (12.70)**	86.04 (11.92)**	79.18 (11.95)**
In linear rate		0.32 (0.23)	0.05 (0.21)
Goodness-of-fit deviance Model comparison (χ^2 [df])		17.708 [3]**	211.435 [13]**

STAI=State-Trait Anxiety Inventory; SE=Standard Error; CI – Confidence interval; ECOG – Eastern Cooperative Oncology Group; RSCL=Rotterdam Symptom Checklist. *$p \leq 0.001$; **$p < 0.05$.

Figure 1. Course of state and trait anxiety over the course of chemotherapy
(Error bars: 95% CI; STAI=State–Trait Anxiety Inventory).

Figure 1