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For Robin, who made every low seem less low
and celebrated every success more than I did.

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List of Abbreviations

3P	Model comprising Predisposing, Precipitating, and Perpetuating Factors of Cancer-related Fatigue
ACSM	American College of Sports Medicine
ATP	Adenosine Triphosphate Production
BFI	Brief Fatigue Inventory
CAPO	Canadian Association of Psychosocial Oncology
CAT	Computer Adaptive Testing
CBT	Cognitive Behavioral Therapy
CESD-R	Center for Epidemiologic Studies Depression Scale - Revised
CI	Confidence Interval
CogniFit Study	'Cognitive Function in Patients with Breast or Gynecological Tumors' Study
CONSORT	Consolidated Statement of Reporting Trials
CRF	Cancer-related Fatigue
CTQ	Childhood Trauma Questionnaire
EORTC QLQ-C30 (C30)	European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire
EORTC QLQ-FA12 (FA12)	European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire, Fatigue Module
ePRO(M)s	Electronic Patient-reported Outcomes (Measures)
ESMO	European Society for Medical Oncology
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FACT-cog	Functional Assessment of Cancer Therapy – Cognitive Function
FDA	Food and Drug Administration
FiX Study	'Fatigue in Germany – Examination of prevalence, severity, and state of screening and treatment' Study
HCP	Health Care Professional
HRQoL	Health-related Quality of Life
IL	Interleukin
MBSR	Mindfulness Based Stress Reduction
MID	Minimally Important Difference
ME/CFS	Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome
NCCN	National Comprehensive Cancer Network
NCT	National Center for Tumor Diseases
NCI	National Cancer Institute
NRS	Numeric Rating Scale
OR	Odds Ratio
PHQ-4	Patient Health Questionnaire – 4 items
PSQI	Pittsburg Sleep Quality Index
PTG	Post-traumatic Growth
PTGI	Post-traumatic Growth Inventory
PRO(s)	Patient-reported Outcome(s)
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PROM(s)	Patient-reported Outcome Measure(s)
PROMIS	Patient-Reported Outcome Measurement Information System
QoL	Quality of Life
SF-36	Short Form Health Survey 36
STAI	State Trait Anxiety Inventory
TCI	Threshold of Clinical Importance
TCM	Traditional Chinese Medicine
US	United States (of America)
VAS	Visual Analogue Scale

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1 Introduction

1.1 Patient-reported outcomes in cancer patients

1.1.1 Use and benefits

Cancer is one of the most prevalent chronic diseases globally, representing a significant societal, public health, and economic challenge in the 21st century (Bray et al. 2024). Due to an overall ageing population, continuously improved treatment modalities, and earlier detection of cancer, the number of people living with and beyond cancer is constantly increasing (Emery et al. 2022; Siegel et al. 2022). In Germany, the number of these cancer survivors is estimated to comprise around five million people currently (Arndt et al. 2021). According to recent data from the United States (US), there were approximately 18.1 million cancer survivors in 2022, a number that is expected to rise to 26 million people by 2040 (Tonorezos et al. 2024). Consequently, the number of patients and survivors with multiple symptoms and side effects, both related and unrelated to their cancer, is expected to increase. This will reinforce the need for a more routine and integrated approach to the management of symptoms and side effects, not only during cancer treatment, but also in the subsequent survivorship phase (Henson et al. 2020). Traditional clinical outcomes in oncology, such as tumor response, mortality and morbidity, cancer-free and overall survival, have long been the main and only criteria used in cancer care to assess the effectiveness of treatment (Graupner et al. 2021; Wintner et al. 2012). As a considerable number of cancer patients and survivors experience adverse effects resulting from the disease itself, its treatment, and related complications, the monitoring of these often-invisible sequelae has become crucial. Patient-reported outcomes (PROs) are defined as statements of function or feeling about a health condition, reported directly by the patient and without interpretation by others (Food and Drug Administration; Patrick et al. 2007). They are valuable indicators of patient well-being and treatment effectiveness, providing additional and important information for the understanding of the patient's health status (Howell et al. 2015; LeBlanc and Abernethy 2017). Among others, the US National Cancer Institute (NCI) has identified the promotion of PROs in oncology as one of its major goals (Clauser et al. 2007). In this sense, the focus has increasingly shifted from a 'disease-centered care *for* the patient' to a more 'patient-centered care *with* the patient' (Bellino and La Salvia 2024), with PROs now playing a key role in cancer management and being assessed in an ever-increasing proportion of clinical trials (Mercieca-Bebber et al. 2018a; Mercieca-Bebber et al. 2018b; Øvretveit et al. 2017).

PROs represent a spectrum of patient-reported data, ranging from specific disease symptoms or side effects to more abstract and broader constructs (Mercieca-Bebber et al. 2018a). Figure 1 displays a representation of some of the most important oncological PROs along the spectrum. This includes for example commonly reported cancer sequelae such as pain, depressive symptoms, anxiety, or cancer-related fatigue (CRF), but also quality of life (QoL), which counts as one of the most frequently assessed PROs in clinical trials (Ramsey et al. 2021; Reeve et al. 2014). Importantly, Figure 1 does not claim to be a comprehensive representation and does not imply fixed causal relationships between the variables. Instead, it focuses on the different types of PROs and offers one potential classification along the spectrum of ‘concrete symptoms’ to ‘abstract constructs’. However, it can be argued that social and psychological mechanisms, such as cognitive processes, internal and external resources, and coping strategies contribute to the differentiation displayed, as they are operating mechanisms relevant to the level of appraised burdens or well-being (Costa et al. 2016). More specifically, patients with similar symptoms might respond very differently in terms of how they feel affected by them, which in turn can lead to differences in the subjective evaluation of their QoL (Costa et al. 2016). It is also undeniable that physical or psychological complaints are usually caused by the underlying symptoms experienced. Therefore, both the symptoms themselves and the manner in which they are perceived may have an influence on broader PRO constructs, such as QoL or overall well-being.

Studies have consistently demonstrated that health care professionals (HCPs) tend to underestimate the severity of patients' symptoms during cancer treatment, or fail to recognize their symptoms altogether (Balitsky et al. 2024). At the same time, patients often do not disclose their symptoms, partly due to time constraints during medical consultations (Laugsand et al. 2010; Oechsle et al. 2013; Xiao et al. 2013). Further, patients may be concerned that their symptoms could indicate an inevitable consequence of the disease or a potential disease progression (Bergerot et al. 2022). This can contribute to a sense of uncertainty, increased fear of cancer progression, decreased treatment adherence, and poorer symptom control (Bergerot et al. 2022; Graupner et al. 2021; Mayer et al. 2017; Wintner et al. 2012). Given the significance of these aspects and the discrepancy between symptoms reported by patients and symptoms detected by HCPs, it is essential to proactively integrate PRO assessment into clinical practice (Graupner et al. 2021; Milzer et al. 2024; Minton et al. 2013). There are substantial positive effects of routinely assessing PROs in cancer care. Among other aspects, the use of PROs can lead to a better patient-clinician communication, earlier detection and monitoring of cancer-related problems and symptoms, or improved patient satisfaction through refined clinical decision-making processes (Campbell et al. 2022; Chen et al. 2013; Howell et al. 2015). In particular, the process of shared decision making, involving the patient's

perspective on treatment options, has become increasingly important in recent years (Covvey et al. 2019; Kane et al. 2014). Active inclusion of PROs further has been found to result in improved health-related QoL (HRQoL), in part due to better symptom control, and better patient adherence compared to controls that were not routinely assessed with PROs (Graupner et al. 2021). Moreover, systematic reviews of clinical trials revealed that in the majority of cases, PROs were associated with, and potentially indicative of, patient survival (Balitsky et al. 2024; Gotay et al. 2008).

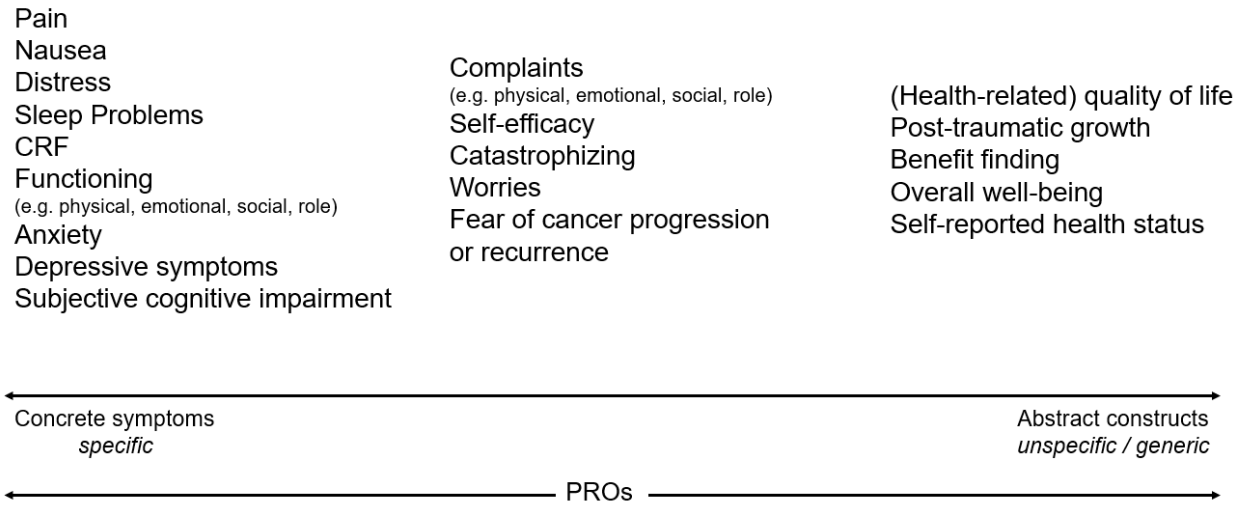


Figure 1. Conceptual abstraction model of PROs in oncological settings

Note. Model based on Wintner et al. (2012) and Wahl et al. (2010); modified and supplemented. CRF = cancer-related fatigue.

1.1.2 Assessment

Depending on the specificity of the symptom, PRO measures (PROMs), the tools used to measure PROs (Weldring and Smith 2013), can be either generic or cancer-specific. Both contribute important aspects to a better understanding and improvement of patient care at different levels of the health care system (Churruca et al. 2021). As identified by a recent review, more than 315 tools to assess PROs exist, indicating a broad variety of PROMs (Churruca et al. 2021). Examples for generic and widely used instruments are the Patient Reported Outcome Measurement Information System (PROMIS; Ader 2007) or the Short Form health survey (SF-36; Lehmann et al. 2021; Ware and Sherbourne 1992; Wintner et al. 2012). One of the most widely used, cancer-specific questionnaires is the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30 (C30); Fayers and Bottomley 2002), which assesses a range of common symptoms, functioning across different domains, and QoL of patients. In addition, a variety of item banks or inventories are available for use in conjunction with existing questionnaires, enabling

multidimensional assessments (Lehmann et al. 2021). Among those are the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE; Trask et al. 2018) library, the PROMIS, and the EORTC Item Library (Bell et al. 2019).

In order to minimize potential sources of confounding, care should be taken when collecting PROs to ensure that psychometrically valid questionnaires and items are used wherever possible (Bellino and La Salvia 2024; Frost et al. 2007). Further, HCPs are required to have a certain knowledge of how to interpret PRO data (Nguyen et al. 2021). As statistically significant results do not necessarily indicate a clinically relevant change in the variables assessed, efforts have been made to calculate thresholds of clinical importance (TCI; Giesinger et al. 2020) and minimally important differences (MID; Musoro et al. 2020) to facilitate data interpretation in research as well as in clinical routine. Although most PROMs are still administered using static and multi-item instruments and are often scored in a paper-pencil format, electronic PROs (ePROs) and computer adaptive testing (CAT), based on psychometric methods such as item response theory (Morris et al. 2017; Petersen et al. 2010), have become increasingly popular in recent years (Eid et al. 2017). The European Society for Medical Oncology (ESMO) clinical practice guideline recommends the use of an ePRO system or device in all patients undergoing active cancer treatment (Di Maio et al. 2022). Alternatives to ePRO collection should be provided to avoid excluding patients who have difficulty accessing electronic measurement systems (Di Maio et al. 2022). These developments and the progress made in PRO research may help to overcome barriers, such as time constraints at the patient and HCP level, that currently prevent routine implementation of PRO assessment into existing clinical workflows (Nguyen et al. 2021).

With the aim of covering different aspects of the presented PRO spectrum (see Figure 1), and to meet the need for a deeper understanding of the associations of the constructs of interest, this dissertation will focus on post-traumatic growth (PTG), often referred to as positive psychological change after a traumatic (cancer) event, and CRF, as one of the most common and distressing side effects of cancer and its treatment. Prior to the presentation of the specific research questions, the following introductory sections will provide a comprehensive overview of both constructs within the context of current PRO research.

1.2 Post-traumatic growth

1.2.1 Definition and theoretical framework

People with cancer are frequently forced to adjust their personal life circumstances to the cancer diagnosis and its consequences. This process can be accompanied by various

negative side effects, but may also result in positive long-term consequences. In regard to the latter, adaptive psychological consequences of cancer and its treatment have been demonstrated to exist. Although they have received increasing attention in the last years, they are often still overlooked in cancer research (Costa et al. 2016). PTG is an abstract construct that refers to the positive psychological outcomes of dealing with a challenging event and the ability to fight adversity (Sumalla et al. 2009; Tedeschi and Calhoun 1996). Originally, PTG was not tailored to the field of oncology, but has been observed in people who have experienced traumatic events, such as terrorist attacks (Fausor et al. 2022), natural disasters (Bernstein and Pfefferbaum 2018), or deployment in war zones (Kang et al. 2024). The experience of PTG can encompass heightened ‘appreciation of life’, enhanced ‘relationships to others’, an elevated perception of ‘personal strengths’ and ‘new possibilities’, as well as a ‘spiritual change’ (Tedeschi and Calhoun 1996; Tedeschi and Calhoun 2004). Some researchers have argued that PTG implies that fundamental beliefs about the self, relationships, and the world that lie beyond the causative (cancer) experience, can be positively altered (Dell'Osso et al. 2022). Others argued that PTG is an illusory phenomenon that helps to cognitively avoid the threat posed by the event, rather than a substantial change in identity (Sumalla et al. 2009). As this leads to the suggestion that there are different interpretations and approaches to PTG (Sumalla et al. 2009), this dissertation adopts the theoretical framework of Tedeschi and Calhoun as its foundation (1996; 2004). Here, PTG is proposed to develop over time (Tedeschi and Calhoun, 2006), and as a consequence of (1) facing an event that is appraised as traumatic or at least threatening, and (2) intentionally engaging with the stressor through cognitive processing and restructuring to cope with the distress (Liu et al. 2020). The hypothesized development process of PTG is depicted in Figure 2. Importantly, PTG does not imply that people no longer suffer from the distress caused by the trauma, but rather recognizes that distress and positive development, expressed in positive and negative psychological responses to the adverse event, can coexist. Moreover, PTG can be seen as a consequence of the individual's efforts to adapt and cope with a traumatic event, rather than as a direct result of the event itself (Tedeschi and Calhoun 2004).

Distinctions between PTG and some related psychological concepts should be made. For example, the concepts of resilience, benefit finding, or hardiness all reflect, to some extent, personal tendencies to cope well with adverse events (Tedeschi and Calhoun 2004). Resilience can be broadly defined as the ability to make use of available resources, both external and internal, to respond to challenging circumstances (Pooley and Cohen 2010). Benefit finding describes the process by which a person reassigns a positive value to challenges in form of a cognitive adaption (Liu et al. 2023; Tennen and Affleck 2002). Hardiness refers to a personality trait that enables people to adapt easily to unexpected changes. It further

describes these persons as able to feel a sense of purpose in their daily lives and personal control over what happens (Kobasa et al. 1982). In contrast to PTG, adverse events are not a prerequisite for the development or perception of the concepts described here. Furthermore, PTG can lead to changes in functioning and thus to transformation processes that go beyond the adaptive processes described in the other constructs presented (Tedeschi and Calhoun 2004).

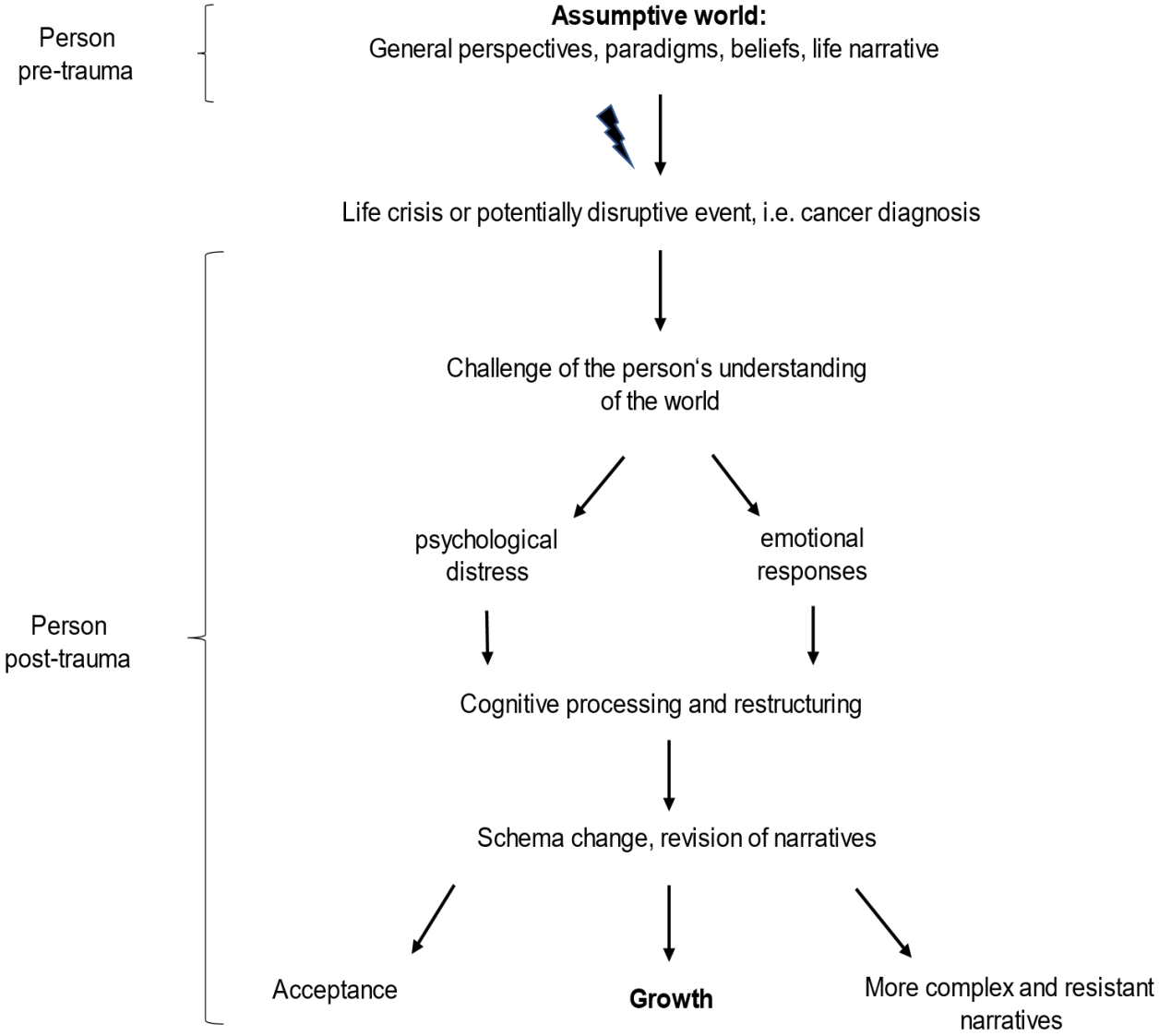


Figure 2. The process of PTG development

Note. Figure adapted and modified from Tedeschi and Calhoun (1996).

1.2.2 Relevance in cancer patients

In cancer patients, reported prevalence rates of PTG differ substantially, depending on the study population and the timepoint of PTG assessment. A recent study from Germany analyzed prevalence rates for moderate to high PTG in long-term cancer survivors (5 – 16 years after diagnosis), with 24% of breast cancer patients reporting PTG compared to 16% of prostate cancer patients (Liu et al. 2021). In colorectal cancer survivors five years after diagnosis, another study found a prevalence rate of 46% of moderate to high PTG, while almost all patients reported PTG to at least some degree (Jansen et al. 2011). In a study of stomach cancer patients, at least 53% of patients reported moderate to high PTG after their cancer experience (Sim et al. 2015). In a similar vein, a study of young adults with cancer revealed a prevalence ranging from 58% to 64% (Husson et al. 2017). The domain of 'spiritual change' was often the least pronounced one, whereas most positive changes were mainly noted in 'appreciation of life' (Husson et al. 2017; Jansen et al. 2011; Sim et al. 2015). It should be noted that moderate to high levels of PTG in the studies described here do not reflect established categories derived from existing cut-offs. Instead, these categories were introduced on the basis of the total response score, which indicate above-average scores on most of the items provided (Bernard et al. 2022).

PTG, disease-related characteristics, and patient demographics

Contradictory to the theoretical assumptions of Tedeschi and Calhoun (1996; 2004), some findings suggest that there is no association of time since diagnosis and PTG (Casellas-Grau et al. 2017). Another study found higher PTG scores corresponding with longer time since diagnosis in breast cancer and female colorectal patients, but an inverse pattern in male colorectal patients (Liu et al. 2021). While most studies found no association between PTG and type of cancer treatment (Baník and Gajdošová 2014; Casellas-Grau et al. 2017), some reported higher PTG levels when patients received chemotherapy (Jansen et al. 2011; Lelorain et al. 2010). Others found lower PTG levels when patients received radiotherapy compared with other types of treatment (Mols et al. 2009). Results regarding PTG and cancer stage were found to be equally inconclusive (Casellas-Grau et al. 2017; Liu et al. 2021), but also have not yet been sufficiently investigated (Marziliano et al. 2020). In terms of cancer type, breast cancer patients appear to be the most studied cancer population regarding PTG and were found to have higher PTG scores than colorectal or prostate cancer patients (Liu et al. 2021; Wang et al. 2023c). This, together with the different prevalence rates described above, suggests that some of the cancer characteristics are contributing to the perceived positive changes, although the picture is not yet clear.

Regarding demographic variables, higher PTG levels were consistently associated with younger age (Boyle et al. 2017; Widows et al. 2005; Wu et al. 2019). One potential explanation for this may be that younger patients tend to perceive a cancer diagnosis as a more significant threat to their life plans compared to older patients. In accordance with the theoretical PTG framework, a heightened level of threat may facilitate enhanced growth (Mystakidou et al. 2008; Tanyi et al. 2020). Although there are some conflicting results regarding sex and PTG, studies indicate that women tend to report more, or higher levels of, PTG than men (Jaarsma et al. 2006; Liu et al. 2021; Zwahlen et al. 2010). Few studies analyzed the association between education or socioeconomic status and PTG, but trends have been found for highly educated cancer survivors to report more PTG than others (Jansen et al. 2011). Consistent with this, high income, as opposed to low income, was associated with higher PTG levels in a sample of oral cavity cancer patients (Ho et al. 2011). Studies testing the effect of specific knowledge on the development of PTG are scarce. However, there have been hints that health literacy may enhance coping via cognitive restructuring and therefore could facilitate PTG (Cafaro et al. 2019; Roohi et al. 2020).

1.2.3 Post-traumatic growth and associations with other patient-reported outcomes

Anxiety and depressive symptoms, often collectively referred to as emotional or psychological distress, are common side effects of cancer (Linden et al. 2012; Mitchell et al. 2011). Although the associations of anxiety and depressive symptoms with PTG have been studied to some extent, the results have been mixed. A considerable amount of the studies found no significant association between PTG and anxiety (Casellas-Grau et al. 2017; Cormio et al. 2017; Leong Abdullah et al. 2015). Besides, one study reported an overall explained variance of 42.7% in PTG of a mixed cancer population when considering depressive symptoms, anxiety, perceived threat, and positive cognitive processing as predictors in a hierarchical regression model (Caspari et al. 2017). A few studies found either no or rather weak and negative associations between depressive symptoms and PTG (Gunst et al. 2016; Leong Abdullah et al. 2015; Shand et al. 2015). A study by Tomich and Helgeson (2012) identified a quadratic relationship between PTG and depressive symptoms, suggesting that individuals with either high or low levels of PTG tend to report fewer depressive symptoms than those with moderate PTG levels. In a study of Jansen and colleagues (2011), the prevalence of high to moderate PTG levels decreased when showing higher depressive symptom scores. Taken together, the experience of PTG appears to be weakly related to anxiety and depressive symptoms, whereas in other studies no relationship was found.

According to theoretical assumptions, higher PTG would be expected in patients who report high levels of optimism, openness to experience, social support, and an adaptive and engaging coping and thought style (Harding et al. 2014; Tedeschi and Calhoun 1996; Tedeschi and Calhoun 2004). A review by Kolokotroni and colleagues (2014) supported these assumptions, indicating that optimism and an optimistic explanatory style regarding the disease positively influenced the amount of PTG. Together with optimism, hope has been found to predict PTG in a sample of head and neck cancer patients, accounting for 25% of variance in PTG as an outcome variable (Harding et al. 2014; Ho et al. 2011). Furthermore, the level of perceived social support, as manifested in family or marital relationships, appeared to be positively associated with PTG. This suggests that individuals in committed partnerships or marriages tend to exhibit higher PTG levels compared to those without partners (Cormio et al. 2017; Kolokotroni et al. 2014; Tanyi et al. 2020). Moreover, some studies have indicated that social support may even predict subsequent higher PTG, thereby underscoring its importance in the development of PTG (McDonough et al. 2014; Morris and Shakespeare-Finch 2011). In terms of coping and thought style, study findings largely support theoretical assumptions in the sense that active cognitive engagement may facilitate PTG. Conversely, rumination and cognitive avoidance have not been found to be associated with PTG (Scrignaro et al. 2011; Sierra-Murguía et al. 2024).

General QoL or HRQoL are probably the most studied PROs in the cancer-related PTG literature, but the nature of the relationship between these constructs remains largely unclear (Liu et al. 2020). There have been various studies suggesting positive, negative, or no associations between PTG and (HR)QoL, as well as linear and curvilinear associations between the constructs (Tomich and Helgeson 2012). Summarizing the results of the analyzed studies in a systematic review, Liu and colleagues (2020) found mostly positive associations between PTG and HRQoL. Another systematic review found highly variable results between studies, with almost half of the studies reporting positive linear associations between the constructs and the other half reporting no associations (Casellas-Grau et al. 2017). If associations were found, correlations between the constructs were usually weak (Jansen et al. 2011; Sharp et al. 2018). A longitudinal study of breast cancer patients found a positive curvilinear association, indicating that women with high or low growth had a higher QoL than those with moderate growth. When this sample was tested for linear associations, no prediction of PTG on QoL was found (Wang et al. 2023a). In an earlier study of another breast cancer sample, results showed a U-shaped association between PTG and general QoL (Lechner et al, 2006). Similar results were yielded in a group of lung and colorectal cancer patients (Tomich and Helgeson 2012). However, in the latter study, this association was only significant in cross-sectional, but not in longitudinal analyses. There may be potential influencing, for example

moderating or mediating, effects on this relationship, such as the level of depression (Li et al. 2019). However, research on these potential influencing factors is still scarce. Taking together different study results, it seems that the nature of the relationship between PTG and (HR)QoL remains inconclusive, especially when examining it as a long-term outcome in cancer survivors. One reason for this is that the results are mainly based on cross-sectional analyses in breast cancer patients (Casellas-Grau et al. 2017). This is particularly limiting, as PTG is assumed to develop longitudinally and over time (Tedeschi and Calhoun 2004). Moreover, variations in QoL measurement tools and weak study designs might contribute to the observed differences as well (Liu et al. 2020). Beside the aforementioned medical, demographic, and psychosocial factors, research into the biological factors underlying PTG is limited. Existing studies have provided only weak correlative evidence of a negative association between hypothesized inflammatory processes and PTG levels (Sierra-Murguía et al. 2024).

1.2.4 Assessment

The PTG Inventory (PTGI; Tedeschi and Calhoun 1996) was developed to measure the individual level of PTG and consists of 21 items divided into five subscales. These comprise ‘appreciation of life’ (three items), ‘relationships with others’ (seven items), ‘personal strengths’ (four items), ‘new possibilities’ (five items), as well as ‘spiritual change’ (two items; Tedeschi and Calhoun 1996). Each item is answered on a six-point Likert Scale ranging from 0 (‘I did not experience this change’) to 5 (‘I experience this change to a very great degree’) with higher scores indicating higher growth, respectively. Consequently, the total score ranges from 0 – 105 points. The PTGI has been assessed in several study populations and has been translated to different languages (Lenz et al. 2021). In the oncologic research field, the five factor structure of PTG was tested and confirmed, indicating a very good fit index (Brunet et al. 2010). When assessed in cancer patients, the PTGI showed good internal consistency in all subscales, acceptable to good reliability, and good validity values of the questionnaire. These metrics allow the questionnaire to be used in cancer patient populations (Mystakidou et al. 2008). As indicated by a recent meta-analysis, most studies used the PTGI in cross-sectional study designs (Marziliano et al. 2020).

1.2.5 Research gaps

In reviewing the existing literature on PTG and its associations in cancer patient populations, it appears that the growing interest in the positive psychological change after cancer has not led to a full understanding of its facilitating factors and associations with other PROs. In

particular, research into PTG is limited in terms of its ability to reveal mechanisms through which PTG develops, or whether any elements of the experience of PTG are unique to the context of cancer (Menger et al. 2021). Cross-sectional study designs are one reason for the largely inconclusive results, in part because they have no or only limited explanatory power when analyzing potential determinants of PTG. This has, for example, contributed to the conflicting results to date regarding the association between PTG and emotional distress (Casellas-Grau et al. 2017). Further, some important, as frequently reported, side effects in cancer patients have not been investigated regarding their relation to PTG. Beside one study that tested a psychoeducational intervention for pain in cancer patients and revealed higher PTG to be associated with lower pain levels in the intervention group compared to the control group, studies analyzing the relationship of PTG and pain barely exist (Arefian and Asgari-Mobarakeh 2024). However, as this study suggested possible links between these two variables, further investigation of this relationship seems promising. Additionally, there have been indications that health literacy may play a role in the development of PTG (Roohi et al. 2020), but more studies are necessary to investigate this association (Arefian and Asgari-Mobarakeh 2024; Cafaro et al. 2019). Moreover, there exists virtually no literature on the relationship between PTG and CRF, apart from one study that assessed CRF, HRQoL, and PTG simultaneously (Tanyi et al. 2014). In addition, the inconclusive association between HRQoL and PTG requires further research, using data of more diverse study samples regarding their cancer entity (Menger et al. 2021). In light of these research gaps, particularly concerning the yet unknown contribution of cancer-related factors to PTG, and the inconclusive nature of the association between PTG and HRQoL, resulting research questions will be outlined (see section 1.4) and addressed in this dissertation (see Manuscript I and Manuscript II).

1.3 Cancer-related fatigue

1.3.1 Definition and prevalence

CRF is a debilitating symptom experienced by many people with cancer. It is defined as an overwhelming, persistent sense of physical, emotional, or cognitive exhaustion and can have a profound impact on patients' QoL, functional status, and overall well-being (Minton et al. 2013; Ruiz-Casado et al. 2021). It has been demonstrated that rest or sleep do not provide sufficient relief from CRF, which marks a contrast to ‘normal’ exhaustion or tiredness (Fabi et al. 2020). It is important to differentiate CRF from other conditions, such as the myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and fatigue following a coronavirus infection. In these conditions, the underlying causes are linked to the infection (Krishna et al.

2023), and physical activity frequently results in a worsening of symptoms, a phenomenon also known as ‘post-exertional malaise’ (Nehme et al. 2023). Conversely, physical activity is regarded as one of the most beneficial interventions for CRF (Fabi et al. 2020; Zhang et al. 2023). It is important to note that fatigue can also appear in the general population, including individuals without any known underlying medical condition or infection (Yoon et al. 2023). Similar to CRF, it is characterized by sustained elevated levels of tiredness, lack of energy, or concentration problems, which are not alleviated by periods of rest or sleep (Yoon et al. 2023). This indicates that fatigue can not only be a symptom or side effect of an underlying disease, such as CRF in cancer patients, but rather a complex problem in its own right (Knoop et al. 2021; Nijrolder et al. 2009). There is some evidence to suggest that it may act as a predictor for the development of cancer or other diseases in the general population (Knoop et al. 2021). Consequently, it has been assumed that CRF also occurs prior to the initiation of cancer treatment. Nevertheless, the number of studies examining CRF in this specific phase of the cancer trajectory is limited, although it is widely acknowledged that the perceived symptom burden in cancer patients is usually already significantly more severe at this stage than in the general population (Cella et al. 2002; Hinz et al. 2020). The few existing studies indicate that the prevalence of pretreatment CRF ranges broadly between 14% and 28% (Goedendorp et al., 2008). The estimated severity-based prevalence rate of pretreatment CRF was found to be 15.9% in a meta-analysis (Kang et al. 2023), but was shown to be higher (ranging between 24.3% and 26.7%) in some study populations, e.g. in breast cancer patients (Di Meglio et al. 2022). These numbers are particularly alarming, as CRF at the onset of the cancer trajectory has been shown to be a strong and persistent predictor of later CRF (Di Meglio et al. 2022).

Throughout the entire process of dealing with cancer, until the phase of long-term survivorship, CRF is one of the most frequently reported symptoms (Di Meglio et al. 2022; Ma et al. 2020). The prevalence of CRF during therapy varies depending on the type of cancer, its treatment, and measures used to assess CRF, with rates ranging from 14% to 100%. An overall (pooled) prevalence of 49%-52% during therapy is estimated (Al Maqbali et al. 2021; Ma et al. 2020). One in three cancer survivors continues to experience CRF up to six years after treatment (Jones et al. 2016), while some patients report higher levels of CRF than healthy controls even 15 years after diagnosis (Gernier et al. 2020). A recent meta-analysis conducted by Kang and colleagues (2023) found that 33.8% of patients reported severe CRF during the course of treatment, and 24.1% indicated severe CRF after treatment. These data highlight the frequency and severity of CRF in cancer patients and survivors and point to the need for a deeper understanding of its etiology, its course, and its associations with psychosocial and sociodemographic factors. The following three sections will provide an overview of the current state of research in these areas and will outline the recommended management and treatment

options based on the international guidelines of various stakeholders, such as the ESMO, the National Cancer Comprehensive Network (NCCN) and the Canadian Association of Psychosocial Oncology (CAPO; Fabi et al. 2020; Howell et al. 2013; National Comprehensive Cancer Network 2023).

1.3.2 Etiology and determinants

The development of CRF is complex, multicausal, and remains incompletely understood (Bower 2019; Savina and Zaydiner 2019). Consequently, the explanatory models for the origins, the development, and maintenance of CRF are based on various hypothesized processes and are not universally valid (Bower 2014; Bower 2019). An attempt to classify the different factors into a comprehensive framework is the '3P-Model' described by Bower (2019) as well as Sleight and colleagues (2022), which includes predisposing, precipitating, and perpetuating factors of CRF. A modified categorization of this theoretical model is displayed in Table 1. The factors depicted there may contribute differently to the facets of CRF, eventually showing additive effects (Savina and Zaydiner 2019). Further, it is assumed that different courses of CRF during and after cancer treatment could classify CRF into different subtypes, dependent on the extent to which they associate with other PROs or patient characteristics (Cheng et al. 2024; Rosas et al. 2023; Schmidt et al. 2022a; Schmidt et al. 2024; Yuan et al. 2024). In this dissertation, the distinction between different contributing factors to CRF is based on their specific type or origin. It has been demonstrated that these types primarily include biological, clinical, sociodemographic, lifestyle, and psychosocial factors (Bower 2014). Overall, however, research is still in progress and the results presented here are often based on cross-sectional data (Bower 2019).

Table 1. Components of the 3P Model and corresponding examples

Component of the 3P Model	Examples of contributing characteristics
Predisposing factors	• Sociodemographic factors: biological sex, age • Psychosocial factors: childhood adversity, history of depression, trait anxiety, loneliness • Circadian dysregulation, body composition, genetic vulnerability, inflammation • Pain
Precipitating factors	• Inflammatory processes • Treatment-related factors: type of therapy, medication • Cancer tumor and diagnosis • Metabolic and cortisol dysregulation

Perpetuating factors	• Behavioral factors: physical inactivity, malnutrition • Treatment-related factors: maintenance therapy • Sleep disturbances, maladaptive coping such as catastrophizing

Note. Factors depicted in this table were classified according to Bower (2019) and Sleight et al. (2022).

A number of biological factors are suggested to play a role in the development and persistence of CRF. In this sense, mechanisms of the central nervous system can be impacted by cortisol dysregulation (for example, via the hypothalamic-pituitary-adrenal axis), circadian rhythm disruption, and inflammatory processes (García-González et al. 2023; O'Higgins et al. 2018). In the latter, especially elevated levels of the pro-inflammatory cytokines, e.g. Interleukin-6 (IL-6), have been associated with an increased likelihood of CRF prior, during, and after treatment (Bower 2014; Bower and Lamkin 2013; de Raaf et al. 2012). To date, the role of inflammatory processes in the development and persistence of CRF is under discussion (O'Higgins et al. 2018). Hormonal changes in the neuroendocrine system have also been suggested as potential contributors (Bower 2014; García-González et al. 2023). Dysregulations of adenosine triphosphate production (ATP) may result in a disrupted energy metabolism in the peripheral nervous system and therefore cause CRF (Thong et al. 2020). Besides, also genetic risk factors have been discussed to contribute to CRF (Bower 2014). The biological factors contributing to CRF remain inconclusive, partly because they could not be replicated across all cancer populations (Bower 2014; García-González et al. 2023; Thong et al. 2020).

With regard to clinical factors, the tumor itself and the treatment employed, including surgery, chemotherapy, radiotherapy, and immunotherapy, are considered to be relevant in the induction and worsening of CRF (Ma et al. 2020; Sleight et al. 2022). In terms of sociodemographic factors, higher BMI and female sex have been found to influence the risk of higher CRF levels (Ma et al. 2020; Ruiz-Casado et al. 2021). The association between BMI and CRF in general has been hypothesized to be related to increased inflammatory processes in obese patients and has shown particularly strong associations with physical CRF (Di Meglio et al. 2022; Inglis et al. 2021). However, studies focusing on pretreatment CRF and BMI found somewhat divergent results, as the majority did not demonstrate any association between the two measures (Bower et al. 2019; Pertl et al. 2014). Potential underlying mechanisms of the association between female sex and higher CRF burden remain unclear. However, women tend to report higher symptom burden not only for CRF, but for most PROs assessed in clinical trials (Hertler et al. 2020). With regard to age, study findings remain inconclusive. Most studies indicated that younger patients tend to report higher levels of CRF (Di Meglio et al. 2022), whereas others found results that contradict these findings (Ma et al. 2020). Perceived social

isolation and a feeling of loneliness have further been hypothesized as factors contributing to higher CRF (Bower 2019). Regarding education, inconclusive results have been demonstrated at least for pretreatment CRF, with findings indicating either no association or an association between lower levels of education and higher CRF levels (Bower et al. 2019; Goedendorp et al. 2013).

An unbalanced diet, malnutrition, and a lack of physical activity are considered potential lifestyle factors that may contribute to the onset and maintenance of CRF (Bower 2014). Dietary effects could impact metabolic regulations and therefore indirectly influence CRF (Sleight et al. 2022). Conversely, there is compelling evidence that physical activity during and after cancer therapy could prevent (the development of) chronic CRF and positively influence the level of CRF experienced (Hussey and Gupta 2022; Wu et al. 2023).

Overall, the lack of comprehensive longitudinal studies makes it difficult to draw conclusions about causal pathological mechanisms in the development and maintenance of CRF (Bower 2014). However, it is undebatable that there are multiple influencing factors from different origins contributing to CRF (Bower et al. 2019; Sleight et al. 2022). Further research is needed to gain a deeper understanding of the complex interplay of the different components that predispose to, precipitate, and/or perpetuate CRF in cancer patients. This is particularly true for the associations of CRF with other psychological factors, as these may form the basis of effective treatments and interventions (Cessna Palas et al. 2021; Henneghan 2016; Kirkhus et al. 2019). Accordingly, the following section presents some of the most relevant psychological factors related to CRF, including anxiety and depressive symptoms, sleep disturbance, and QoL. Other frequently reported PROs, such as pain and fear of cancer recurrence, are also associated with CRF (Kelada et al. 2019; Zhang et al. 2022). However, for reasons of parsimony and because they are beyond the scope of this dissertation, their relationship with CRF will not be discussed in detail.

1.3.3 Associations with other patient-reported outcomes

Studies have demonstrated that depressive symptoms and anxiety are consistently associated with CRF (Brown and Kroenke 2009; Oh and Seo 2011). When examining the relationship between depressive symptoms and CRF, the majority of studies have found significant associations between these two. More precisely, correlation coefficients have been shown to range from small to large across studies, leading to an overall moderate association from a meta-analytic perspective (Brown and Kroenke 2009). Depressive symptoms and CRF

showed consistently positive associations not only during, but also before treatment (Wang et al. 2023b). According to another meta-analysis, the average effect size of depressive symptoms on CRF was high and positive, indicating that higher levels of depressive symptoms were significantly associated with higher levels of CRF (Oh and Seo 2011). As depressive disorders and CRF share considerable symptom overlap, including tiredness, sleep disturbances, and lack of energy, these observed associations are not surprising (Bower 2014). Nevertheless, it is important, although not always easy, to distinguish CRF from depressive disorders, which might be a comorbid syndrome affecting about 15-25% of patients (Weber and O'Brien 2017). The ESMO guideline suggests the use of a two-question-test about the patients' experience of sadness, hopelessness, and diminished enjoyment of typical activities to help differentiate CRF from a potential depressive disorder (Fabi et al. 2020). Until today, it remains unclear if depressive symptoms lead to CRF or are caused by CRF, although some studies postulate that a (previous history of a) depressive disorder may be a predisposing risk factor for CRF (Bower 2014; Bower 2019; Ma et al. 2020; Schmidt et al. 2024).

The results of various studies have indicated that there is a significant relationship between anxiety and CRF, with anxiety accounting for approximately 23% of the variance in CRF (Brown and Kroenke 2009). Longitudinal studies revealed associations between trait anxiety and higher subsequent CRF levels in breast cancer patients, indicating a possible predisposing factor (Lockefeer and De Vries 2013; Servaes et al. 2007). However, some studies have also identified no associations between anxiety and CRF, suggesting that this relationship may be more dependent on other influencing factors than the association between depressive symptoms and CRF (Ma et al. 2020; Wang et al. 2024). Consistent with this, also the relationship between anxiety and pretreatment CRF remains unclear. While some studies have indicated that anxiety may be a predictor of pretreatment CRF, others have not identified an association between the two (Goedendorp et al. 2008; Wang et al. 2023b). Besides, childhood trauma and (lifetime) distress have been found to be associated with higher levels of CRF in certain cancer patient populations, both possibly also intertwined with depressive symptoms and anxiety (Bower 2014; Bower et al. 2014). This suggests that patients who have experienced potential traumatic events prior to a cancer diagnosis may be particularly vulnerable to the development of CRF. Other psychological factors that may perpetuate CRF include (dysfunctional) coping mechanisms such as the tendency to worry, catastrophizing, and engagement in negative self-statements, whereas higher acceptance and self-efficacy have shown to be associated with less CRF (Bower 2014; van Roozendaal et al. 2023; Wang et al. 2024). Overall, there have been indications for a close relationship between CRF, particularly emotional and cognitive CRF, with psychological distress and vulnerability (Di Meglio et al. 2022).

Sleep disturbances, such as insomnia or sleep disruption, are linked to CRF (Bower 2014; Bower 2019). Several studies have demonstrated that sleep problems were related to subsequent elevated CRF levels both during and after treatment (Jim et al. 2013; Liu et al. 2012) and have also been shown to be a perpetuating factor for CRF (Sleight et al. 2022). Moreover, a subjectively reported higher sleep quality was associated with lower CRF (Tian et al. 2016) and interventions aiming for an improvement in sleep quality also resulted in less CRF experienced (Dean 2022). In another study, circadian parameters such as late chronotype and low circadian amplitude were found to be associated with a higher symptom burden of CRF, depressive symptoms, and sleep problems in breast cancer survivors (de Rooij et al. 2023). Furthermore, studies analyzing symptom clusters and performing network analyses have demonstrated the co-occurrence of CRF and sleep problems (Guo et al. 2019; Schellekens et al. 2020). Overall, different explanatory approaches to the relationship between sleep and CRF have been proposed, including the discussion of common underlying biological mechanisms. However, despite these efforts, causal pathways remain challenging to identify (Bower et al. 2011; Dean 2022).

The aforementioned factors and associations can severely affect patients' QoL in many areas, such as physical, role, emotional, cognitive, and social functioning (Hofman et al. 2007; Muthanna et al. 2023). CRF itself was found to be among the strongest drivers of subsequent impaired QoL and seems to influence it independently of the site of origin, stage of disease, and stage of treatment (McCabe et al. 2015). Consequences of CRF early or prior to treatment can include a decreased willingness to complete cancer treatment and may result in a diminished therapy compliance (Hofman et al. 2007). The impact of CRF on QoL throughout the whole cancer trajectory can be experienced as a notable disruption to daily life, including occupational and leisure activities (Bower 2019). Consistent CRF burden in the aftermath of cancer therapy becomes visible in a reduced rate of cancer survivors returning back to work or only doing so with reduced working hours (Jones et al. 2023; Wolvers et al. 2018). Moreover, CRF results in higher costs for the healthcare system and the society at large (Jones et al. 2023). To combat or even prevent CRF, international guidelines are currently the best orientation available for the assessment, management, and treatment of CRF (Fabi et al. 2020; Howell et al. 2013; National Comprehensive Cancer Network 2023). An overview of these recommendations is provided in the following section and illustrated in Figure 3, which depicts the suggested flow of CRF management from the time of cancer diagnosis onwards.

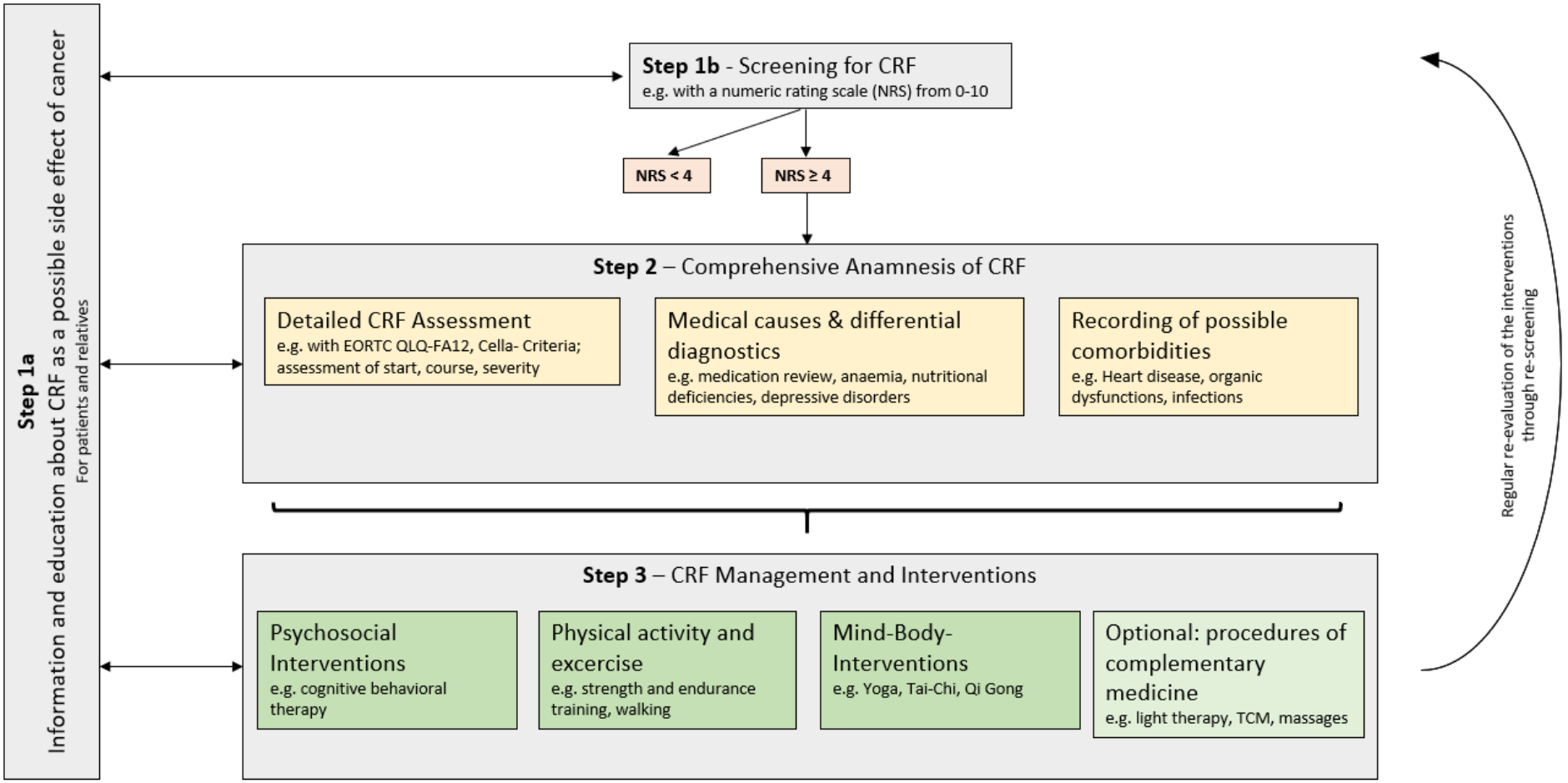


Figure 3. CRF assessment and management flow as recommended by international guidelines

Note. Figure translated and adapted from Blickle et al. (2024a). Reproduced with permission from Springer Nature. Cella-Criteria = Diagnostic Criteria for CRF proposed by Cella et al. (2001). NRS = Numeric Rating Scale, TCM = Traditional Chinese Medicine.

1.3.4 Assessment, management, and treatment

Assessment

Despite its high prevalence and the multiple negative associations with emotional distress and other side effects, CRF remains underdiagnosed and undertreated (Bower 2014; Milzer et al. 2024). Recent study results from Germany revealed for example that only 13% of cancer patients received any screening for CRF during their treatment (Milzer et al. 2024). This is in contrast to the international guideline recommendations, which unanimously suggest a systematic screening for and management of CRF from the time of a cancer diagnosis onwards, with regular monitoring throughout the cancer trajectory (Fabi et al. 2020; Howell et al. 2013; National Comprehensive Cancer Network 2023). A commonly suggested screening tool is a numeric rating scale (NRS) for CRF severity ranging from 0 to 10 (0= 'no fatigue' and 10 = 'worst fatigue'); e.g. 'How would you rate your exhaustion of the last seven days on a scale from 0 to 10?' (Fabi et al. 2020). On this scale, a value of 0 indicates no CRF, whereas values of 1-3 are interpreted as mild, 4-6 as moderate and 7-10 as severe CRF. A score of 4 or higher indicates at least moderate CRF symptom burden and, thus, warrants a more comprehensive diagnostic assessment of possible underlying causes of CRF (Fabi et al. 2020). Such an assessment may include laboratory tests to identify potential medical causes of CRF, such as anemia or thyroid disease. Furthermore, sleep disturbances, an unbalanced diet, and the use of concomitant medications should be investigated.

Validated questionnaires that assess CRF in more detail can also be used for further elaboration. Two recent reviews have consistently evaluated the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) as an effective instrument for assessing CRF (Campbell et al. 2022; Fisher et al. 2022; Yellen et al. 1997). The 13 items included in the FACIT-F assess the severity and impact of CRF on daily life and showed convincing psychometric properties. In Europe, another widely used questionnaire is the fatigue module of the EORTC quality of life questionnaire (EORTC QLQ-FA12; Weis et al. 2017). It assesses CRF multidimensionally with twelve items on the dimensions of physical, emotional, and cognitive fatigue and has received excellent psychometric properties in the review of Campbell and colleagues (2022). Other highly recommended questionnaires according to Fisher and colleagues (2022) are the Fatigue Short Form of the PROMIS and the Piper Fatigue Scale – Revised (Cella et al. 2016; Piper et al. 1998). The choice of one of the questionnaires may be guided by the purpose and the domains most relevant for the clinical context, for instance, if the objective is to identify the severity or the multidimensionality of CRF (Campbell et al. 2022). Additionally, the availability of time and human resources should be taken into consideration.

The US Fatigue Coalition has proposed Diagnostic Criteria for CRF (2001). Despite their inclusion in the International Classification of Diseases 10th Revision, Clinical Modification

(ICD-10-CM) under the term ‘neoplastic (malignant) related fatigue’, they are not available in the German version, indicating a lack of a gold standard to properly diagnose CRF. This mirrors the still insufficient awareness and inadequate care structures for CRF in Germany (Milzer et al. 2024).

Management and treatment

In addition to regular screening and, if necessary, comprehensive follow-up assessment of CRF during treatment and in the post-treatment period, the guidelines advise that all patients are provided with comprehensive education and information materials. These should comprise explanations of the pathology, courses, and consequences of CRF, aiming to encourage patients to address the symptoms and to identify support options for coping (Fabi et al. 2020; Howell et al. 2013; National Comprehensive Cancer Network 2023). By offering reassurance that they are not alone in experiencing this side effect, and by providing guidance on how to manage CRF symptoms, for example through open communication with HCPs, patients can be empowered to take an active role in their own care (Schmidt et al. 2022b). Other self-management options, such as active energy management or keeping a symptom diary, have been proposed to alleviate symptom burden and were perceived as helpful by many patients (Adriaans et al. 2021; Coolbrandt et al. 2017; Milzer et al. 2022). This emphasizes the advantages of PROMs in clinical practice and points out that higher knowledge about potential symptoms and their treatment options may allow patients to take a more active role in the management of their disease (Purcell et al. 2011).

Physical activity and exercise, yoga and (other) mind-body interventions, relaxation, and psychosocial interventions have been found to significantly reduce or even prevent CRF. In particular, the guidelines emphasize the effectiveness of sport and exercise for CRF (Fabi et al. 2020; Howell et al. 2013; National Comprehensive Cancer Network 2023). More precisely, a mix of moderate-to-vigorous strength and endurance training (alone or in combination) has been found to be highly efficacious in mitigating symptoms associated with CRF (Campbell et al. 2019; Schmidt et al. 2015). The American College of Sports Medicine (ACSM) reinforces these recommendations by suggesting moderate aerobic exercise for a minimum of twelve weeks with additional strength training twice a week (Bower et al. 2024; Campbell et al. 2019; Patel et al. 2019). Ideally, an exercise intervention program is designed in consultation with the treating physicians, adapted to the patient’s individual situation, and supervised by qualified trainers (Fabi et al. 2020; Howell et al. 2013; National Comprehensive Cancer Network 2023). Starting point for such interventions is always the patient’s individual health status, from which it is important to improve physical fitness step by step (Bower et al. 2024). It has further been demonstrated that yoga, along with other mind-body interventions such as Qi Gong or Tai-Chi, can have a beneficial impact on CRF (Bower et al. 2024; Fabi et al. 2020; Haussmann et al.

2022). Similarly, mindfulness-based interventions, including progressive muscle relaxation, guided imagery, and Mindfulness Based Stress Reduction (MBSR) have demonstrated efficacy in alleviating CRF symptoms (Haussmann et al. 2022). Besides, psychosocial interventions include a variety of intervention types to alleviate the burden of CRF. Cognitive behavioral therapy (CBT), in an individual or group setting, has been found to be the most effective intervention for managing the distress caused by CRF (Haussmann et al. 2022). Consequently, it is unanimously and strongly recommended in the guidelines (Fabi et al. 2020; Howell et al. 2013; National Comprehensive Cancer Network 2023). Complementary medicine interventions, such as acupuncture or acupressure from Traditional Chinese Medicine (TCM), massages, and light therapy have been found to have some positive effects on CRF (Fabi et al. 2020; Howell et al. 2013; National Comprehensive Cancer Network 2023). Their use in CRF treatment can be recommended depending on the individual needs and interests of the patient. In contrast to the aforementioned treatment approaches, the evidence base for pharmacological therapy remains inconclusive. There are hints that pharmacological agents such as methylphenidate or corticosteroids should only be prescribed in exceptional cases, with non-pharmacological interventions being the primary and more effective recommendation for CRF treatment (Fabi et al. 2020; Howell et al. 2013; Mustian et al. 2017; National Comprehensive Cancer Network 2023). As the use of medication (e.g. beta-blocker, antidepressants) to treat comorbid symptoms during therapy can lead to CRF, this should be constantly monitored by HCPs (Thong et al. 2020).

In total, a step-by-step approach in CRF management and treatment (see Figure 3) is important to provide patient-centered supportive care, while acknowledging that there is no ‘one size fits all’ solution (Henson et al. 2020). An appropriate and timely assessment lays the foundation for recognizing CRF as an individually experienced symptom that can manifest in different ways. As previously stated and in accordance with the guideline recommendations, it is particularly important to ensure that patients are provided with comprehensive information about CRF in order to facilitate self-management. A multimodal intervention approach, tailored to the individual patient’s needs, may be necessary to address the multidimensional nature of CRF, to alleviate the patient’s symptom burden, and to prevent chronification (Di Meglio et al. 2022). Unfortunately, due to a knowledge-to-practice gap and systemic barriers, implementation of CRF guidelines in clinical care remains challenging (Jones et al. 2021; Martin et al. 2021).

1.3.5 Research gaps

Patients experience an increased symptom burden, particularly CRF, even before the start of their planned cancer treatment, and especially when compared with healthy controls (Cella et al. 2002; Hinz et al. 2020). However, there is a lack of studies investigating the symptom burden of patients at the beginning of the cancer trajectory. This hinders to quantify the extent to which patients suffer from and differ in their symptoms from the general population, especially at that specific timepoint of the cancer course (Di Meglio et al. 2022; Goedendorp et al. 2013; Goedendorp et al. 2008; Pertl et al. 2014). Furthermore, although it is well known that CRF at the onset of cancer and its treatment is one of the strongest predictors of subsequent CRF burden (Di Meglio et al. 2022), research investigating pretreatment CRF and its associations with sociodemographic and psychosocial factors remains scarce. This is an intriguing observation, as the revelation of potential associations between pretreatment CRF and these factors could represent a promising step for the early detection of patients at high risk of developing CRF. A more detailed investigation of the specific burdens and interrelationships at the beginning of the cancer trajectory is therefore crucial. More specifically, the relationship between pretreatment CRF and anxiety remains equivocal. A number of studies have indicated positive associations, while others have found no association (Wang et al. 2023b). This dissertation will therefore address these research gaps by answering the resulting research questions (see the following section) in Manuscript III.

1.4 Research questions

The use of PROs has increased significantly in recent decades, suggesting an enhanced awareness for a more patient-centered approach in oncology care. The assessment of PROs allows for a better understanding of patients' side effects throughout the cancer trajectory and subsequent survivorship. Of relevance for the context of this dissertation, the assessment of PROs has led to the discovery of PTG as a positive long-term consequence in cancer patients and to more knowledge about CRF. However, both PROs, PTG and CRF, are complex and multidimensional, and their associations with other relevant PROs in the oncologic field remain incompletely understood. The overarching objective of this dissertation is therefore to gain new insights into the associations of these variables with other important PROs in cancer patients and survivors.

As stated in section 1.2.5, more longitudinal data and assessments in diverse cancer patient populations would facilitate a better understanding of the long-term influences and associations of PROs on PTG (Menger et al. 2021). To this end, a cancer survivor population

comprising the 15 most prevalent cancer entities of Germany was analyzed in Manuscript I. The extent of PTG and the potential influence of psycho-oncological determinants on PTG were investigated longitudinally. More precisely, the following research questions were answered:

- What is the extent of PTG in cancer survivors?
- Are emotional distress, pain, and CRF potential longitudinal determinants of PTG?
- Does CRF literacy, i.e. self-rated informedness about CRF, contribute to higher levels of PTG?

In Manuscript II, the association of PTG with HRQoL was analyzed, as existing literature has reported positive linear and quadratic associations, but also no associations between these constructs (Casellas-Grau et al. 2017; Liu et al. 2020; Tomich and Helgeson 2012). The potential moderating role of CRF in the association of PTG and HRQoL was also part of the analyses conducted. Therefore, the manuscript answered the questions:

- What is the nature of the association between HRQoL and PTG in cancer survivors?
- Does CRF moderate this association?

In Manuscript III, this dissertation aimed to contribute to a deeper understanding of (1) the pretreatment symptom burden in cancer patients compared to healthy controls and (2) the factors associated with pretreatment CRF. For the latter, sociodemographic factors and patient-reported psychosocial factors and their associations with pretreatment CRF were investigated. Consequently, the following research questions were answered:

- Do patients already suffer from clinically relevant CRF before treatment start and is their burden significantly higher compared to a healthy control sample?
- How are patients with clinically relevant pretreatment CRF characterized in terms of sociodemographic factors?
- Taking these sociodemographic factors into account, what are the associations between patients with and without clinically relevant CRF on various psychological factors?

1.5 General Methods

This dissertation is based on two research projects. The following sections provide a brief overview of the study designs and the study populations for each project, whereas some of this information is also included in the manuscripts that form part of the dissertation. Manuscript I and Manuscript II are based on data from the longitudinal FiX study (acronym for 'Fatigue in Germany – Examination of prevalence, severity, ad state of screening and treatment'). Data from the CogniFit study (acronym for 'Cognitive Function in patients with breast or gynecological Tumors') were analyzed to conduct Manuscript III. The specific statistical methods employed in each case are outlined in the respective manuscript.

1.5.1 The FiX study

Study design and participants

The FiX study is a longitudinal, observational study with two measurement timepoints. The main objective of the study was to assess the prevalence of CRF in cancer survivors. Secondary aims were to assess knowledge, perceptions, and perceived care of CRF. To achieve this, patients were randomly selected from the Epidemiological Cancer Registry of Baden-Württemberg in Germany between March 2018 and May 2019. Patients were eligible for study participation if they were at least 18 years old, able to understand the study documents, and had been diagnosed with one of the following primary tumors approximately two years previously: stomach, colon, rectum, liver, pancreas, lung, malignant melanoma, breast, endometrium, ovaries/cervix, prostate, kidney, bladder, non-Hodgkin lymphoma, or leukemia. A total of 11,113 patients were contacted and asked for permission to share their contact details with the FiX study staff (Schmidt et al. 2021). Of those contacted, 2,508 patients agreed to participate in the study and completed the first measurement timepoint (T0, approximately two years after cancer diagnosis). A further two years later, at T1, these patients were contacted once more for the second assessment. 1,835 patients completed the second questionnaires (Schmidt et al. 2021). 1,316 patients indicated that they were cancer-free at that time, i.e. they self-reported the absence of metastases, cancer recurrence or a secondary tumor. These self-reports were matched with the cancer registry data to verify accuracy. Details of the patient flow are shown in Figure 4. Ethical approval for the study was obtained from the Ethics Committee from the Medical Faculty of the University of Heidelberg (S-654/2016). The study was registered on ClinicalTrials.gov (identifier: NCT03318224).

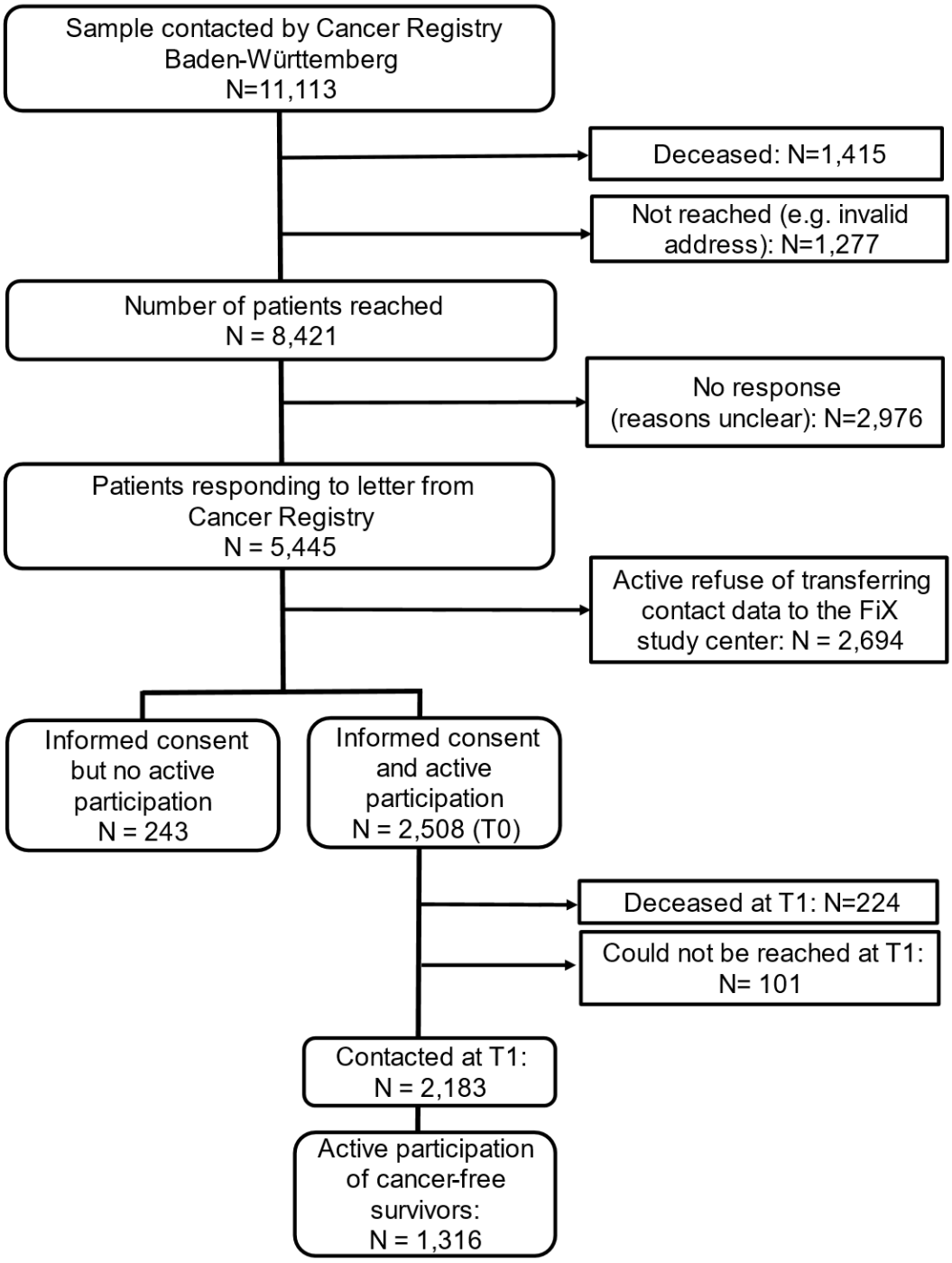


Figure 4. Patient flow of the FiX study

Note. Consolidated Statement of Reporting Trials (CONSORT) diagram adapted and modified from Schmidt et al. (2020).

Assessments

PROs were assessed at both measurement timepoints. A detailed overview of the validated questionnaires used at the respective timepoints is provided in Table 2. At T0, patients also

answered single-item questions about their knowledge of CRF and whether HCPs had discussed or educated patients about CRF on a six-point Likert scale (0 = ‘strongly disagree’ to 5 = ‘strongly agree’). Further, they were asked whether they had used any of the CRF-related support services or interventions, such as relaxation techniques, yoga or exercise. At T1, in addition to the validated questionnaires, patients were asked about the perceived burden of potential cancer-related side effects (ranging from 0 = ‘no burden’ to 4 = ‘extreme burden’) and whether they had received support to manage this symptom (0 = ‘good support’ to 3 = ‘poor support’). Moreover, age, tumor characteristics, and cancer therapy were extracted from the Epidemiological Cancer Registry.

Table 2. Validated questionnaires to assess PROs in the FiX study

Measurement timepoint	Validated questionnaires
T0	• Brief Fatigue Inventory (BFI; Mendoza et al. 1999) • EORTC QLQ-C30 (Fayers and Bottomley 2002) • EORTC QLQ-FA12 (Weis et al. 2017) • Patient Health Questionnaire (PHQ-4; Löwe et al. 2010)
T1	• EORTC QLQ-C30 (Fayers and Bottomley 2002) • EORTC QLQ-FA12 (Weis et al. 2017) • PHQ-4 (Löwe et al. 2010) • PTGI (Tedeschi and Calhun 1996)

Note. Assessments of T0 took place about two years after diagnosis, assessments of T1 about four years after diagnosis.

1.5.2 The CogniFit study

Study design and participants

The CogniFit study is a comparative longitudinal study. The main objective of this study was to investigate the influence of cancer therapies and potential psychosocial factors on the development of subjectively perceived and objectively measurable cognitive impairments. Participants were recruited at the National Center for Tumor Diseases (NCT) in Heidelberg between November 2018 and March 2023. In addition to the cohort of cancer patients (*N*=243), the CogniFit study also included a healthy control group (*N*=41) to investigate potential learning effects of repeated cognitive testing and to contextualize the clinical relevance of the patient data.

Data was collected at three measurement timepoints: before the start of a systemic therapy or radiotherapy (T0), 7-14 days after the end of that therapy (T1), and one year after T1 (T2). Patients were eligible for study inclusion if they were female, diagnosed with breast cancer or a gynecological tumor, at least 18 years and capable of consenting to the study (i.e. able to speak and read German). Patients were not allowed to participate if they had a systemic or radiotherapy within the last two years, were diagnosed with a neurodegenerative, neurological or psychological disease, or under medication that would affect cognitive performance. Healthy participants were required to meet the same inclusion and exclusion criteria, except for having been diagnosed with cancer. Additionally, they were ineligible if they had a previous known or treated cancer. Of note, only study patients with a diagnosis of breast cancer (*N*=232) were included in the analyses of Manuscript III. The study was approved by the Ethical Committee of the Medical Faculty of the University of Heidelberg (S-489/2018) and conducted according to the ethical standards of the Helsinki Declaration. CogniFit was registered via 'Deutsches Register Klinischer Studien' (trial number DRKS00015757).

Assessments

An overview of the PROs assessed at each measurement timepoint is provided in Table 3. Further, objective measures to assess cognitive function were applied, such as the Trail Making Test or the Hopkins Verbal Learning Test – Revised (Benedict et al. 1998; Bowie and Harvey 2006). Medical data (i.e. type of tumor and therapy, medications, comorbidities) were extracted from the clinical documentation system if patients consented to this. Blood and stool samples were collected at each timepoint. Patients also provided sociodemographic data and indicated if they used supportive care offers. Sleep and physical activity patterns were assessed by using an accelerometer. For Manuscript III, only patient-reported baseline data was analyzed.

Table 3. Validated questionnaires to assess PROs in the CogniFit study

Questionnaire	**T0**	**T1**	**T2**
• Functional Assessment of Cancer Therapy – Cognitive Function (FACT-cog; Wagner et al. 2009)	X	X	X
• State Trait Anxiety Inventory (STAI; Spielberger et al. 2017)	X	X	X
• Center for Epidemiologic Studies Depression Scale (CESD-R; Eaton et al. 2004)	X	X	X
• EORTC QLQ-FA12 (Weis et al. 2017)	X	X	X

• Pittsburgh Sleep Quality Index (PSQI; Buysse et al. 1989)	X	X	X
• Childhood Trauma Questionnaire (CTQ; Bernstein et al. 2003)		X	
• Return to work (Van Veldhoven et al. 2015)	X	X	X
• Quality of Working Life (de Jong et al. 2018)	X	X	X
• Pain using a Visual Analog Scale (VAS)	X	X	X

Note. Assessment of T0 took place before start of treatment, assessment of T1 took place 7-14 days after the end of that therapy, T2 took place one year after T1.

2 Manuscript I

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Contribution to the research questions of this dissertation:

Manuscript I presents the extent of PTG in cancer survivors of diverse cancer types. Further, it investigates the influence of common cancer-related side effects experienced two years after diagnosis, such as emotional distress, pain, and CRF, on PTG four years after diagnosis. The influence of informedness about CRF on PTG is examined.

Data used:

Data from the two measurement timepoints of the FiX study were analyzed longitudinally in Manuscript I. The study population consisted of 1,316 cancer survivors (see section 1.5.1).

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Post-traumatic growth in cancer survivors: What is its extent and what are important determinants?

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ABSTRACT

Background/Objective: The aim was to investigate the extent and longitudinal determinants of post-traumatic growth (PTG) in cancer survivors.
Methods: A sample of 1316 cancer survivors with various cancer types was examined using the EORTC QLQ-FA12 to assess fatigue, the EORTC QLQ-C30 pain items to assess pain and the Patient Health Questionnaire (PHQ-4) to assess emotional distress two years after diagnosis (t0). Additionally, patients rated how well they felt informed about fatigue at t0. PTG was assessed with the 21-item PTG-Inventory four years after diagnosis (t1) comprising the five subdimensions appreciation of life, relation to others, personal strengths, new possibilities and spiritual change.
Results: Regarding the extent of PTG, most positive developments were experienced in the PTG subdimension appreciation of life whereas the subdimension spiritual change was the least pronounced domain. Fatigue, pain and emotional distress were longitudinal but non-linear predictors of long-term PTG. Additionally, poor informedness about fatigue was associated with less PTG.
Conclusions: PTG can be perceived even years after a traumatic cancer event and is longitudinally associated with common cancer side effects like fatigue, emotional distress and pain. Further research into the role of individuals' informedness contributing to PTG is needed.

Introduction

The number of cancer survivors is increasing across Europe, requiring more intensive research into this cancer population (Kalager et al., 2021; Lagergren et al., 2019; Malvezzi et al., 2015). Cancer as a life-threating illness can have substantial negative impact on individuals' lives, not only during the acute treatment but also in the aftermath. Frequently reported sequelae are among others fatigue, depression, sleep problems, cognitive impairment, distress and reduced quality of life (Lagergren et al., 2019; Wu & Harden, 2015).

Individuals with a cancer diagnosis are forced to adapt their personal life circumstances. This can be accompanied or challenged by the aforementioned negative consequences on the one hand, but also result in positive long-term effects on the other hand. The latter recently gained growing attention in research, attempting to better understand the whole process of coping with cancer. The positive psychological change experienced after the struggle of a challenging life event, e.g. cancer, was defined as post-traumatic growth (PTG). PTG can be experienced in different important life domains resulting in the development of an increased appreciation of life, deeper relationships to others, more personal strengths, new possibilities and a higher spiritual thrive (Tedeschi & Calhoun, 1996, 2004). The theoretical framework is based on the assumption that PTG arises out of an individuals' integration of fundamental beliefs about oneself and the world into the new reality of life (Janoff-Bulman & McPherson Frantz, 1997; Tedeschi & Calhoun, 2004). Therefore, PTG can also be seen as a coping strategy (Tedeschi & Calhoun, 2004). It has further been proposed that cognitive processing of the trauma-causing event is crucial for its successful overcoming (Tedeschi & Calhoun, 1996). In line with this, study results suggested that cognitive processing, e.g. through deliberate rumination and positive refraiming are linked to higher PTG (Hill & Watkins, 2017; Taku et al., 2009). Although it seems difficult to identify specific factors that support or hinder these favorable processes, one component might be education, which has been shown to be positively linked to PTG (Chen et al., 2019). Moreover, PTG has been associated with socio-demographic characteristics in such that female sex and lower age

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are linked to higher levels of PTG (Boyle et al., 2017; Wu et al., 2019). Further studies indicated that psychosocial variables, e.g. more social support, optimism and a high amount of perceived stress of the cancer were associated with higher PTG (Sharp et al., 2018; Wu et al., 2019).

However, there are also some inconsistent findings regarding influencing factors of PTG. For instance, some studies found a positive association of PTG with emotional distress (Cordova et al., 2007) while others reported negative or no relationships (Dekel et al., 2012; Mystakidou et al., 2008). Furthermore, also curvilinear associations between PTG and emotional distress have been observed (Lechner et al., 2006).

Besides, fatigue appears to be understudied with regard to PTG although it is one of the most common side effects during cancer and its treatment (Fabi et al., 2020; Ma et al., 2020). Fatigue describes a deliberating subjective feeling of constant physical, emotional and mental exhaustion. It is reported by approximately 30 % of survivors even 5 years after cancer treatment (Fabi et al., 2020; Schmidt et al., 2022, 2018). It is possible that fatigue could have a significant impact on PTG also years after treatment, because it might affect the severity of trauma experienced. Another frequently reported, burdensome and sometimes long-term side effect of cancer treatment is pain (Zielińska et al., 2021). To our knowledge no studies exist that analyze the influence of pain on PTG, although it is plausible that pain could have an adverse impact on an individual's wellbeing and coping.

A review of Casellas-Grau et al. (2017) highlighted reasons for the inconclusive study results in determining PTG: They argued that PTG has often been analyzed only in cross-sectional study designs. Menger et al. (2020) also pointed out that longitudinal studies are needed to better understand the time courses of PTG. Considered together, it seems that there is still no full picture of PTG determinants, which underlines the need to foster more research in cancer populations, especially in cancer survivors (Mayer et al., 2017). To address the aforementioned research gaps, we examined the extent and the determinants of PTG in survivors of different cancer types and treatments. For this, we analyzed longitudinal data, considering sociodemographic variables, psychosocial and also modifiable factors at t0 (two years after cancer diagnosis) to predict PTG at t1 (four years after cancer diagnosis). In accordance with the assumptions of Tedeschi and Calhoun (2004), we hypothesized that higher levels in fatigue, emotional distress and pain at t0 as indicators of higher distress might lead to higher PTG at t1.

We further assumed that information about cancer sequelae such as fatigue might be helpful in guiding a more rational type of cognitive processing as it could influence individual's general cancer literacy. A lack of information about cancer and its consequences has been shown to be associated with a decreased wellbeing, strengthening the assumption that it might play an important role in coping with the disease (Brown et al., 2016; Husson et al., 2011). So, we hypothesized that feeling well informed about fatigue would lead to higher levels of PTG and would influence the relationship between fatigue and PTG.

Methods

Participants and procedures

About 2 years after cancer diagnosis (t0), 2508 patients who underwent different cancer treatments were enrolled in the FiX study (**F**atigue **i**n Germany – **E**xamination of prevalence, severity, and date of screening and treatment). Patients were randomly sampled from the Epidemiological Cancer Registry of Baden-Württemberg, Germany. Individuals older than 18 years and diagnosed with a primary tumor of stomach, colon, rectum, liver, pancreas, lung, malignant melanoma, breast, endometrium, ovaries/cervix, prostate, kidney, ladder, non-Hodgkin lymphoma or leukemia were eligible for the study. Details of the study have been described previously (Schmidt et al., 2021). A follow-up survey (t1) was conducted approximately two years later (four years after diagnosis), and was completed by 1316 cancer free survivors.

The FiX study was conducted in accordance with the ethical standards of the Helsinki Declaration. The study was approved by the Ethic Committee of the Medical Faculty of the University of Heidelberg (S654/2016). All participants have given written informed consent.

Instruments

PTG was assessed at t1 with the 21-item PTG inventory (PTGI) of Tedeschi and Calhoun (1996) to examine if changes in participants' life domains occurred as a result of cancer. This questionnaire consists of the 5 subscales appreciation of life, new possibilities, personal strengths, relation to others and spiritual change which can be summed up to a total PTG score. Since the subscales comprise different numbers of items, the values were transformed into a range of 0–100 % for better comparability. Higher percentages indicate higher perceived change respectively.

At t0, fatigue was assessed multidimensionally with the EORTC QLQ-FA12 (Weis et al., 2017). All 12 items were answered on a 4-point Likert scale. We calculated a total sum score of the 12 items (Kecke et al., 2017) and transformed it to a scale of 0 to 100. Higher values indicate higher levels of fatigue.

Emotional distress was assessed at t0 with the short version of the Patient Health Questionnaire (PHQ-4) (Löwe et al., 2010), consisting of two items measuring symptoms of anxiety and two items measuring symptoms of depression. Each item was answered on a 4-point Likert scale and then added up to a total score. Higher values indicate higher emotional distress.

Pain at t0 was measured according to the symptom scores based on the EORTC QLQ-C30 (Fayers, 2001). Higher scores represent higher symptom burden.

In addition to the t0-measurements, participants were asked whether they felt well informed about fatigue. Answers ranged from 1 = "not at all informed" to 4 = "very well informed". Participants could also state if they did not know how to answer the question.

Data/statistical analysis

Data analyses were performed using IBM SPSS statistics version 29. First, descriptive analyses for the 5 PTG subscales were performed. Then, statistical preconditions to perform regression analyses were checked. Cancer entity and cancer treatment (chemotherapy, radiotherapy, immune therapy, endocrine therapy, operation) were expected to be associated with PTG, but except chemotherapy they did neither show a significant effect on PTG nor influenced the other variables in the model significantly. Except chemotherapy, these factors were therefore not included in the final model for reasons of parsimony.

Before inclusion in the final model, fatigue, emotional distress and pain at t0 were log-transformed in order to achieve a better model fit. The model consisted of sociodemographic variables like age and sex, chemotherapy and psychosocial factors like emotional distress, fatigue and pain two years after cancer diagnosis to predict PTG four years after cancer diagnosis. In an additional step, we investigated the categorial variable "information about fatigue" (t0) as a potential predictor by adding it to the model. Further, it was tested whether the amount of information about fatigue would influence the fatigue-PTG association. These exploratory analyses were conducted to test potential relationship patterns of fatigue (t0), information about fatigue (t0), and PTG (t1) using the PROCESS macro for SPSS (Hayes, 2017). Missing data were not imputed as it has been found useful to use only complete cases for regression analysis if there are less than 5 % of cases with missing values (Urban et al., 2016). In our calculations of the regression analyses, the percentage of missing values was 3.3 % (43 of 1316).

Results

The analyzed sample consisted of 1316 cancer survivors and was fairly balanced regarding sex (51.4 % female). The mean age at follow-

up (t1) was 67.2 years (SD = 11.1). About one third (34.4 %) of the cancer free survivors had ever received chemotherapy. Further participant and variable characteristics are displayed in Table 1.

All PTG subscales showed good to very good internal consistencies (Cronbach's α = 0.85 to 0.92). Regarding the extent of PTG, most positive developments were experienced in appreciation of life (Median (Q1-Q3) = 47.0 % (20.0 %–66.7 %)), followed by an intensification of the relations to others (34.0 % (11.4 %–54.3 %)), personal strengths (30.0 % (5.0 %–55.0 %)) and new possibilities (24.0 % (8.0 %–44.0 %)). Least developments were reported in spiritual change (10.0 % (0.0 %–40.0 %)). The median of the total PTG score was 32.3 % (12.4 %–50.5 %). The non-parametric Friedman test indicated that the medians of all subgroups were significantly different from each other (overall χ^2 = 1329.86, $p < .001$). Fig. 1 displays the extent and distribution of the prescribed PTG subdimensions. The characteristics of the original (not 0–100 % transformed) scales are presented in Supplement 1.

The results of the linear regression analyses are shown in Table 2. Model 1 revealed that age, sex and prior chemotherapy were significant predictors of total PTG, indicating that lower age (B = −0.33, 95% Confidence Interval (CI) [−0.44; −0.22]), female sex (B = 2.60, 95% CI [.16; 5.03]) and receiving chemotherapy (B = 4.78, 95% CI [2.27; 7.30]) were associated with higher PTG. Further, fatigue (B = 1.98, 95% CI [.52; 3.43]), emotional distress (B = 1.80, 95% CI [.64; 2.97]) and pain (B = 0.74, 95% CI [.01; 1.47]) were positive longitudinal determinants of PTG, suggesting that higher levels in these variables contributed to higher PTG. All variables together explained 12.4 % of variance in PTG.

In Model 2 we added the item information about fatigue (t0) in our analysis, which explained an additional significant albeit small amount of variance in PTG (increase in explained variance by 1.8 %). Survivors who felt poorly informed about their fatigue reported significantly less positive changes in PTG than patients who felt well informed (Table 2).

Results of the exploratory mediation analysis are depicted in Supplement 2. The coefficients revealed that information about fatigue may partially mediate the relationship between fatigue at t0 and PTG at t1. Moderation analysis did not show an effect of information about fatigue on the relationship between fatigue and PTG.

Table 1
Patient and variable characteristics in the FiX-study.

Characteristics	*N*	%	Range	Mean (SD)	Median (Q1 – Q3)
Age			26.30 - 95.76	67.28 (11.05)	
Sex					
Male	639	48.6			
Female	677	51.4			
Chemotherapy					
Yes	452	34.4			
No	864	65.6			
Fatigue at t0			0.00 – 100.00	26.20 (22.34)	21.71 (8.33 – 41.67)
PHQ-4 at t0			0.00 – 100.00	19.48 (19.33)	16.67 (0.00 – 33.33)
EORTC pain at t0			0.00 – 100.00	21.23 (27.62)	0.00 (0.00 – 33.33)
Information about fatigue at t0				1.43 (1.48)	
0 not at all informed	343	26.1			
1	118	9.0			
2	140	10.6			
3	103	7.8			
4very well informed	120	9.1			
8missing value	58	4.4			
9I don't know	434	33.0			

Note. Q1-Q3 = Quartile 1 – Quartile 3; PHQ-4 = 4-item Patient Health Questionnaire; EORTC = European Organization for Research and Treatment of Cancer. t0= Baseline measure (two years after diagnosis).

Discussion

We found most positive developments of PTG in the domain appreciation of life whereas spiritual change was significantly the least pronounced domain. Previous literature reported consistently least changes in spiritual change, suggesting that this subdimension appears to be less important at least in Western countries (Holtmaat et al., 2017; Lelorain et al., 2010; Sharp et al., 2018; Thornton & Perez, 2006). Concerning the extent of PTG in the subdimensions, our sample showed mostly comparable mean scores to other studies. In direct comparison to the study of Lelorain et al. (2010), who also examined PTG in long-term disease-free survivors, our results revealed lower mean scores in PTG. However, it is noteworthy that PTG seems to be perceived even four years after cancer diagnosis.

Consistent with previous findings in the literature, we found lower age and female sex associated with higher levels of PTG (Boyle et al., 2017; Husson et al., 2011; Wu et al., 2019). It can be assumed that the disruption or trauma due to cancer diagnosis and its treatment affect life plans more in younger than in older individuals leading to higher PTG levels (Blank & Bellizzi, 2008; Manne et al., 2004). Females report more PTG than males, but reasons for that remain still speculative. However, different response patterns in patient-reported outcomes between females and males have been observed previously, indicating that women often report higher symptom burden (Hertler et al., 2020).

Except for chemotherapy, no other type of therapy had an effect on the extent of PTG. This could lead to the hypothesis that chemotherapy might have an additional distressing influence compared to not undergoing chemotherapy. Surprisingly, cancer entity did not show a significant effect on PTG either, indicating that PTG may occur regardless of cancer entity.

In line with our hypothesis, fatigue, emotional distress and pain seem to be relevant predictors of long-term PTG. This finding supports the assumptions of the PTG model by Tedeschi and Calhoun (1996) that distress is an important precondition to develop PTG. As we found the best model fit with log-transformed predictors, this could be interpreted as that their association with PTG is not linear. It seems that beyond certain points, higher symptom burden may no longer lead to a further increase in PTG. With regard to the existing inconclusive findings of the association of PTG and emotional distress, our results tend to support a positive, but non-linear relationship of these constructs. Consistent with that, Eisma et al. (2019) found high levels of distress limited the amount of experienced PTG in bereaved adults. Another study concluded that moderate levels of general stress are associated with highest PTG compared to low or high stress in cancer patients (Coroiu et al., 2016).

Our study is one of the first that investigated fatigue and pain as predictors of PTG in cancer survivors, showing significant log-linear associations. As fatigue is one of the most frequent sequelae of cancer (Fabi et al., 2020), future studies could especially aim for a better understanding of the mechanisms of fatigue leading to PTG. Given the relatively wide CIs of the estimates, it must be noted that our data does not yield sufficient precision for a clear prediction of PTG from the determinants considered. However, it provides insights into factors associated with PTG that may warrant further investigation.

Information about fatigue explained a small but significant additional amount of variance in the model. It might be argued that higher level of information about this frequent cancer side effect is important to help individuals make sense of their experiences. In particular, facts about the existence, prevalence and type of fatigue may be important initial information. Further information should include possible treatment options and advice on managing fatigue and could be provided through patient education programs (Du et al., 2015; Schmidt et al., 2022). It could also lead to a more rational cognitive processing about fatigue, reducing feelings of helplessness through facilitated self-empowerment and contributing to higher PTG (Brown et al., 2016;

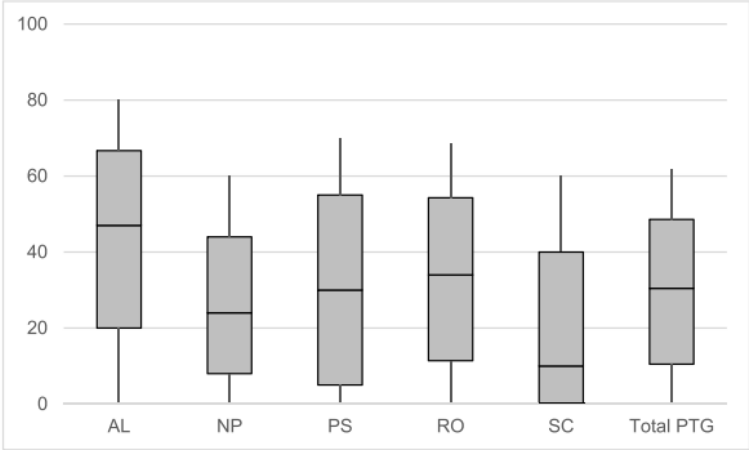


Fig. 1. Extent of the five post-traumatic growth subdimensions and the total score.
Note. AL = Appreciation of Life, NP = New Possibilities, PS = Personal Strengths, RO = Relation to Others; SC = Spiritual Change. Extents of the subdimensions are displayed with medians and Q1-Q3 Percentiles (in percent). Whiskers represent 10th and 90th percentiles.

Table 2
Exploration of determinants of post-traumatic growth with hierarchical multiple regression analysis.

Independent Variables	Model 1 R^2 =0.124			Model 2 R^2 =0.142		
	95 % CI			95 % CI		
	B	*LL*	*UL*	*B*	*LL*	*UL*
Age at t1	−0.33	−0.44	−0.22	−0.29	−0.40	−0.18
Sex (female vs. male)	2.60	.16	5.03	2.16	−0.27	4.60
Chemotherapy (yes vs. no)	4.78	2.27	7.30	3.91	1.39	6.44
Fatigue at t0	1.98	.52	3.43	2.01	.55	3.47
PHQ-4 at t0	1.80	.64	2.97	1.79	.64	2.94
EORTC pain at t0	0.74	.01	1.47	.70	−0.03	1.43
Information about fatigue at t0*:						
1 a little informed				1.81	−2.71	6.33
2				3.09	−1.20	7.37
3				4.73	−0.063	9.52
4 very well informed				9.61	5.06	14.16
9 I don't know				−0.13	−3.28	2.99

Note. Models included all listed variables simultaneously. *B* = unstandardized coefficients, CI = confidence interval, LL = lower limit, UL = upper limit, PHQ-4 = 4-item Patient Health Questionnaire. Fatigue, PHQ-4 and EORTC pain variables were log-transformed before analysis. t0 = two years after cancer diagnosis, t1 = four years after cancer diagnosis.
*reference category of "information about fatigue" was 0 = not at all informed.

Schmidt et al., 2022). This may underline the importance that providing adequate information about cancer and its side effects is crucial for patients and their coping with the disease (Brown et al., 2016; Husson et al., 2011). Aiming for a better understanding of the role of information about fatigue in the process of fatigue at t0 and PTG at t1, we found a potential partially mediating effect of information about fatigue. Due to the exploratory analysis, we cannot point to any causal interpretations here. Nevertheless, our results seem to support the theory of Tedeschi and Calhoun (2004): after experiencing the traumatic cancer event and its potential side effects, higher levels of information about fatigue could influence cognitive processing positively and thus mediate the impact of fatigue on PTG. Further research should clarify the role of patient informedness in the development of PTG.

Limitations of our study have to be mentioned. First, PTG contains self-reported data that was collected retrospectively. It is therefore possible that positive recollection bias might have distorted the response behavior. Second, the explained variance of our models is relatively small. This is an indication that further important factors contributing to PTG have not been taken into account. Studies showed that e.g. social support and positive appraisal are important factors in the development of PTG (Lelorain et al., 2012; Shand et al., 2015). Third, PTG was only assessed once, which does not allow a longitudinal development of PTG to be illustrated. Further, several individuals did not answer the question about fatigue informedness at all, thus these results have to be interpreted with care.

Nevertheless, our longitudinal study covering 15 different cancer entities allows for a broader picture of the extent of PTG and its longitudinal determinants in cancer survivors. In sum, PTG can be perceived even years after a traumatic cancer event and is associated with important cancer side effects like fatigue, emotional distress and pain. Our results further indicated that individuals' informedness also may play a role in the development of PTG, pointing to a modifiable factor during cancer treatment (Evans et al., 2022). This strengthens the existing recommendation to provide adequate education about manifestation and management of cancer side effects in clinical practice. Further research is warranted to explore the role of general cancer literacy in the development of PTG.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Karen Steindorf received a speaker's fee from Takeda.

Data availability

Data can be made available to scientific cooperation partners upon reasonable request.

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Supplementary materials

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3 Manuscript II

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Contribution to the research questions of this dissertation:

Manuscript II investigates the nature of the association between HRQoL and PTG in cancer survivors. Further, it examines the potential moderating role of CRF in this association.

Data used:

Data from the second measurement timepoint of the FiX study were analyzed in Manuscript II, comprising multiple regression analyses. The study population consisted of 1,316 cancer survivors (see section 1.5.1).

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RESEARCH ARTICLE

Posttraumatic growth and health-related quality of life in cancer survivors: Does fatigue moderate the link?

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Abstract

Interest in post-traumatic growth (PTG) as a predictor of health-related quality of life (HRQoL) is currently gaining attention. However, current evidence is still inconclusive on the nature of this relationship. The first objective of this study was to investigate the relationship between PTG and global HRQoL among cancer survivors. We further investigated the moderating role of fatigue in the association between PTG and global HRQoL. In the FiX study (Fatigue in Germany - Examination of prevalence, severity, and state of screening and treatment) cancer-related fatigue (EORTC QLQ-FA12), PTG inventory and global HRQoL (EORTC QLQ-C30) were assessed four years after cancer diagnosis in 1316 cancer-free survivors (mean age = 67.28, *SD* = 11.05, 51.4% female). Multiple linear regression analysis and moderation analysis were performed. The results showed that PTG had a convex quadratic relationship with global HRQoL ($p < 0.001$). Contrary to our hypothesis, fatigue did not moderate the relationship between PTG (linear and quadratic terms) and global HRQoL, neither when considering the overall PTG score nor for any PTG subdimension. In conclusion, PTG has a convex quadratic relationship with long-term global HRQoL that was not modified by persisting fatigue. Future statistical models investigating PTG and global HRQoL should take this non-linear relationship into account. Aiming to increase PTG might contribute to, but is likely not sufficient for high levels of global HRQoL in cancer survivors in the long run.

KEYWORDS
cancer survivors, fatigue, post-traumatic growth, psycho-oncology, quality of life, survivorship

Maria-Chidi C. Onyedibe and Patricia Blickle both authors contributed equally.

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1 | INTRODUCTION

Long-term health-related quality of life (HRQoL) is gaining increasing importance, as new therapeutic approaches not only allow cancer patients to live longer but also force them to face the long-term consequences of cancer and its treatment (Arndt et al., 2017; Berlinger & Flamm, 2009). Health-related quality of life is a multidimensional construct of subjective well-being that it is influenced by physical, emotional, social and cognitive factors (Götze et al., 2015; Schmidt et al., 2018; Velure et al., 2022) and has become an important indicator in understanding the long-term impacts of cancer and its treatment on individual's well-being (Firkins et al., 2020). An important psychosocial factor associated with HRQoL is post-traumatic growth (PTG; Hamdan et al., 2022; Sim et al., 2015), underlining the growing interest in investigating the possibility of cancer patients experiencing positive outcomes from their illness (Menger et al., 2021).

Post-traumatic growth is defined as a positive psychological change experienced as a result of struggling with highly challenging life events, such as a cancer diagnosis and its treatment. According to Tedeschi and Calhoun (1996), it can include a higher sense of personal strength, a deeper appreciation for life, closer relationships, new possibilities as well as a richer understanding of spiritual matters (Roepke, 2015; Tedeschi & Calhoun, 1996, 2004). Post-traumatic growth has been observed in a significant proportion of cancer survivors (Casellas-Grau et al., 2017; Turner et al., 2018), with moderate to high growth reported in approximately 60% of survivors (Jansen et al., 2011; Sharp et al., 2018). Theoretically, growth after a cancer experience can occur if the challenged fundamental assumptions about oneself and the world can successfully be adapted to the new circumstances. In this way, PTG can be seen as a result of an adaptive coping strategy (Janoff-Bulman & McPherson Frantz, 1997; Tedeschi & Calhoun, 2004).

Convincing evidence of a beneficial effect of PTG on (long-term) HRQoL would imply the relevance of measures or interventions to increase PTG. Yet, research in this area is inconclusive (Li, Wang, et al., 2019; Tomich & Helgeson, 2012). Whereas some studies found that PTG has a positive association with HRQoL (Harrington et al., 2010; Jansen et al., 2011; Liu et al., 2020), others found a negative association (Tomich & Helgeson, 2004). Bernard et al. (2022) found no linear association between PTG and HRQoL among palliative care patients. So, data on the PTG-HRQoL relationship is heterogeneous and, with respect to long-term effects, still scarce.

The contradictory results may be attributed to the nature of the relationship between PTG and HRQoL. While most studies investigated only linear associations, some studies suggested that the association of PTG with HRQoL-related constructs follows a quadratic function either convex or concave (Kleim & Ehlers, 2009; Lechner et al., 2006; Li, Wang, et al., 2019; Tomich & Helgeson, 2012). In particular, Tomich and Helgeson (2012) found a convex association between PTG and the physical health component score of the SF-36 six months after diagnosis. Thus, the evidence on the functional form of this association is still inconclusive. Further, the effect of PTG on HRQoL might be moderated by other factors, which could also contribute to the mixed results mentioned above. Hence, it is of interest to identify potential moderator variables of the PTG-HRQoL association, as the relationship between PTG and HRQoL seems to be more complex and dynamic than previously thought (Li, Sun, et al., 2019; Li, Wang, et al., 2019; Tomich & Helgeson, 2012).

Long-term HRQoL is strongly impacted by persisting cancer-related fatigue (Bower, 2014; Maki et al., 2022; Schmidt et al., 2018; Wu & Harden, 2015). Fatigue is a subjective feeling of physical, emotional and mental exhaustion that is reported by approximately 30% of survivors even 5 years after cancer treatment (Fabi et al., 2020; Schmidt et al., 2018, 2022). Diagnostic criteria to classify fatigue as an ICD-diagnosis have been proposed (Cella et al., 2001), indicating that fatigue can be perceived as a serious cancer-related disorder, whereas HRQoL is a broader subjective assessment of health and quality of life. Since fatigue is consistently associated with lower HRQoL, for example, because persisting fatigue affects every aspect of daily life and can interfere with patients' career and economic status (Minton et al., 2013), it is conceivable that a beneficial effect of PTG on long-term HRQoL is nullified by the overriding negative influence of persistent fatigue. Thus, fatigue might be a moderator of the long-term PTG-HRQoL association. To-date, a potential effect modification of the PTG-HRQoL relationship by persisting fatigue has not yet been investigated.

Therefore, we aimed to investigate the relationship of PTG with long-term HRQoL (about 4 years after diagnosis) under consideration of linear and quadratic functional associations, and potential moderating effects by persistent fatigue. We hypothesised a convex quadratic association between PTG and long-term HRQoL in cancer survivors. Further, we hypothesised that fatigue influences the relationship between PTG and HRQoL, as persisting fatigue might dominate the perception of HRQoL, for example, signalling out any benefits of PTG.

2 | METHODS

2.1 | Study design and population

The FiX study (Fatigue in Germany - Examination of prevalence, severity, and state of screening and treatment) is a longitudinal observational study. Cancer survivors were randomly selected via the Epidemiological Cancer Registry of Baden-Württemberg, a federal state in Germany, between March 2018 and May 2019. Individuals (≥18 years) diagnosed with a primary tumour in stomach, colon, rectum, liver, pancreas, lung, breast, cervix, ovaries, endometrium, prostate, kidney, or bladder, or with malignant melanoma, non-Hodgkin lymphoma or leukemia were eligible for study participation if having received or currently receiving at least one of the following treatments: surgery, chemotherapy, radiotherapy, hormone therapy, or immune therapy and being able to understand the study protocol. As reported by Schmidt et al. (2020), of 11,113 patients sampled by the Cancer Registry, 1277 could not be reached (e.g. unknown or invalid address), 1415 were deceased, 2694 actively refused that the Cancer Registry provide contact data to the study centre, and 2976 did not respond at all. Of the remaining patients, 2508 (29.8% of the potentially reached patients) gave informed

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consent to participate and completed the first survey around two years after cancer diagnosis (T0). At T0, we assessed HRQoL and fatigue. In a follow-up survey 2 years later (T1), the same variables as at T0 and additionally PTG were assessed. At T1, 224 patients were deceased, 101 could not be reached by postal mail (address no longer valid). Of the 2183 remaining contacted survivors, 1835 (84.1%) completed the HRQoL, fatigue and PTG questionnaires at T1. In the present analysis we included only the cancer-free survivors (N = 1316). All participants have given written informed consent.

2.2 | Measures

We used the 21-item posttraumatic growth inventory (PTGI) to assess posttraumatic growth (Tedeschi & Calhoun, 1996) at T1. The scale is divided into five subscales: appreciation of life (3 items), new possibilities (5 items), personal growth (4 items), relating to others (7 items), and spiritual change (2 items). Items were rated on a 6-point scale, ranging from 0 = "I did not experience this change as a result of my cancer" to 5 = "I experienced this change to a very great degree as a result of my cancer" (all transferred to a 0%–100% range). In this study we used the total score as well as the five sub-dimensions of PTG (all transferred to a 0%–100% range). Higher scores indicate greater PTG (Tedeschi & Calhoun, 1996). Previous research has confirmed the five-factor structure of the PTGI, however also provided support for the use of a PTGI total score (Lee et al., 2010; Palmer et al., 2012; Taku et al., 2008). The validated core questionnaire of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) was used to assess global HRQoL (Fayers, 2001). The global HRQoL score was derived from two 7-point response scales for overall health and QoL and linearly transformed to a 0%–100% score according to the EORTC scoring manual (Fayers, 2001). Higher scores indicate higher global HRQoL. Fatigue was assessed using the EORTC QLQ-FA12 (Weis et al., 2017). The FA12 has 12-items with four response categories for each item, coded from 1 to 4. The FA12 scores were transformed to a scale of 0%–100%, with higher scores indicating greater levels of fatigue. The total fatigue score, comprising the subdimensions physical, emotional and cognitive fatigue, was used for analysis in this study. The Cronbach's alpha was 0.96 for PTG total score, 0.93 for global HRQoL and 0.94 for the total fatigue score (EORTC QLQ-FA12). Date of birth (for calculating age at T1), gender, and cancer entity were derived from registry data. Cancer therapy was self-reported at T0 and T1 and supplemented by cancer registry data.

2.3 | Data analysis

Data was analysed using SPSS version 25. Multiple linear regression analyses were conducted with global HRQoL at T1 as dependent variable and PTG (total score and subdimensions) as the independent variable. Hereby, also quadratic terms of PTG were investigated. All models were adjusted for age, gender (1 = male, 2 = female) and global HRQoL at T0. The normality assumption for the residuals were met for all models. To test for the moderating effect of fatigue among the relationship of the five subdimensions of PTG and global HRQoL relationship, the Macro PROCESS for SPSS version 4.1 was used (Hayes, 2017). Missing data were not imputed.

3 | RESULTS

The age at T1 of the 639 male (48.6%) and 677 female (51.4%) cancer survivors ranged between 26.30 and 95.76 years with a mean age of 67.28 (SD = 11.05). Further characteristics of the sample can be found in Table 1. An overview of the zero-order correlations of the variables used in the analysis can be found in the Supplements S1.

In the hierarchical multiple regression, age, gender and global HRQoL at T0 were included in step 1 (Table 2). These three variables explained about 32% of the variance (ΔR^2 = 0.321, $p < 0.001$), with gender ($\beta = -0.087$, $p < 0.001$, 95% CI = −5.415, −1.668) and global HRQoL at T0 ($\beta = 0.557$, $p < 0.001$, 95% CI = 0.507, 0.595) significantly predicting global HRQoL at T1. The negative association between gender and global HRQoL indicated that men had higher global HRQoL scores compared to women. Age did not contribute significantly to the variance explanation ($\beta = -0.040$, 95% CI = −0.156, 0.011). The inclusion of total PTG (linear term) into the model in step 2 showed that it explained a small variance of 0.2% (ΔR^2 = 0.002, $p < 0.001$) and significantly predicted global HRQoL ($\beta = -0.047$, $p < 0.05$, 95% CI = −0.83, 0.000); In step 3, inclusion of PTG (quadratic term) contributed an additional variance of (ΔR^2 = 0.008, $p < 0.001$) and significantly predicted global HRQoL ($\beta = 0.303$, $p < 0.001$, 95% CI = 0.002, 0.005). Fatigue at T1 added in step 3 contributed about 23.4% variance explanation (ΔR^2 = 0.234, $p < 0.001$) and significantly predicted global HRQoL ($\beta = -0.590$, $p < 0.001$, 95% CI = −0.573, −0.493). Finally, the inclusion of the interaction terms of PTG (linear and quadratic) and fatigue in the model collectively contributed an explained variance of about 0.5% (ΔR^2 = 0.005, $p < 0.05$) with no significant prediction of global HRQoL (linear: $\beta = -0.071$, $p > 0.05$, 95% CI = −0.002, 0.005; quadratic: $\beta = 0.043$, $p > 0.05$, 95% CI = 0.000, 0.000). Adjusting in addition for cancer entity did not change the results.

Due to the nonsignificant moderating effect of fatigue on the relationship between PTG (total score) and global HRQoL, we performed further analyses (using PROCESS Macro) regarding the PTG sub-dimensions. The result showed that fatigue had no significant moderating effect on the association between any of the PTG subdimensions and global HRQoL These results are depicted in the Supplements S2.

4 | DISCUSSION

The purpose of this study was to investigate the relationship of PTG with global HRQoL under consideration of a potential moderating role of fatigue among 1316 cancer-free survivors about four years

TABLE 1 Demographic and clinical characteristics of study participants (at T1; approx. four years after diagnosis).

Characteristics	N	%	Mean	SD
Age	26.30–95.76		67.28	11.05
BMI	16.26–57.30		26.82	5.12
Time since diagnosis			4.4	0.8
Gender				
Male	639	48.6		
Female	677	51.4		
Primary tumour				
Breast	161	12.2		
Kidney	135	10.3		
Prostate	123	9.3		
Endometrium	115	8.7		
Non-Hodgkin lymphoma	104	7.9		
Colon	91	6.9		
Multiple primaries	94	7.1		
Malignant melanoma	95	7.2		
Rectum	85	6.5		
Bladder	77	5.9		
Leukemia	75	5.7		
Stomach	54	4.1		
Ovaries	51	3.9		
Others	14	1.1		
Received treatments				
Chemotherapy	452	34.3		
Radiotherapy	384	29.2		
Hormone therapy	229	17.4		
Immunotherapy	162	12.3		
Surgery	1148	85.2		

after a cancer diagnosis. We found a significant convex quadratic relationship between PTG and global HRQoL showing that survivors with higher PTG had better global HRQoL than those with low to moderate PTG, but also that survivors with very low or no PTG showed slightly higher levels of global HRQoL compared to individuals with moderate PTG. Our finding is consistent with previous studies in this field and strengthens the assumption that the PTG-HRQoL relation should not be considered as a linear association in statistical models as done in several previous studies (Kleim & Ehlers, 2009; Lechner et al., 2006; Tomich & Helgeson, 2004, 2012). This potentially explains the so-far inconclusive evidence in this field. An explanation for this convex quadratic relationship might be that patients who report no or low PTG probably experienced less stress during their cancer experience than people with moderate or high PTG (Lechner et al., 2006). According to the stress model of Lazarus and Folkman (1987), this may be because they appraised cancer as less threatening or because they had better and more resources, such as good coping strategies or psychosocial support, on which they could rely on (Lazarus & Folkman, 1987; Lechner et al., 2006). In line with that, Tedeschi and Calhoun (1996) pointed out, that the experience of PTG is dependent from the interpretation of an event as a serious adversity. Therefore, patients with moderate or high PTG levels might experience a higher threat by the disease (Lechner et al., 2006). At the same time, patients with moderate PTG levels might use worse coping strategies than patients with high PTG levels, resulting in an overall lower global HRQoL at T1 compared to patients with high PTG levels.

However, contrary to our hypothesis, fatigue had no significant moderating effect on the relationship between PTG and global HRQoL, neither when considering the overall PTG score nor for any subdimension of PTG. Hence, our results suggest that PTG may have a significant effect on long-term global HRQoL in cancer survivors irrespective of persisting fatigue levels.

4.1 | Clinical implications

The finding of a significant PTG - global HRQoL relationship that is robust against the influence of fatigue can be of clinical relevance, because any improvement in long-term global HRQoL is appreciated, especially for survivors who suffer from persisting fatigue. Since PTG can be regarded as a consequence of positive coping, there is a need to implore potential psychosocial interventions aimed at coping positively with cancer. Psychological interventions such as mindfulness skills for adaptive coping can support PTG in patients with cancer (Wong et al., 2022). Our results indicate that especially patients with moderate PTG levels could profit from these interventions, as they might help to perceive positive developments after cancer, finally leading to an increased HRQoL (Wong et al., 2022).

4.2 | Study limitations and strengths

In our study, PTG was evaluated 4 years after cancer diagnosis. Previous studies showed that PTG increased primarily in the first year after diagnosis, the time when one's assumptions about the world and oneself are likely to be challenged the most (Danhauer et al., 2013, 2015). So, the timing of our PTG assessment may be considered as too far away from the initial cancer diagnosis. This might have resulted in a weaker association of PTG and global HRQoL compared to assessments closer to diagnosis. However, considering PTG as a process that continues even years after cancer diagnosis and treatment and previous studies (Cormio et al., 2017; Scherer-Trame et al., 2022) investigating PTG in cancer patients up to four or 5 years after diagnosis may nevertheless indicate that the timing of the PTG assessment was adequate. Further, our sample may not be completely representative because

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TABLE 2 Summary of moderated hierarchical multiple regression analysis of the relationship between posttraumatic growth, fatigue and global health-related quality of life (HRQoL) (all at T1).

Variables	Step 1 ß (95% CI)	Step 2 ß (95% CI)	Step 3 ß (95% CI)	Step 4 ß (95% CI)	Step 5 ß (95% CI)
Covariates					
Age	−0.040 (−0.151, 0.011)	0.049 (−0.174, −0.003)*	−0.054 (−0.184, −0.014)*	−0.045 (−0.151, −0.012)*	−0.042 (−0.146, −0.009)*
Gender	−0.087 (−5.415, −1.668)***	−0.083 (−5.228, −1.488)***	−0.082 (−5.149, −1.429)**	−0.041 (−3.176, −0.148)*	−0.043 (−3.232, −0.234)*
HRQoL at T0	0.557 (0.507, 0.595)***	0.551 (0.499, 0.589)***	0.532 (0.480, 0.571)***	0.242 (0.196, 0.282)***	0.269 (0.219, 0.312)***
Main variables					
PTGt linear term		−0.047 (−0.83, 0.000)*	−0.340 (−0.432, −0.166)***	−0.080 (−0.179, 0.038)	−0.097 (−.223, .052)
PTGt quadratic term			0.303 (0.002, 0.005)***	0.132 (0.000, 0.003)*	0.088 (−0.001, 0.003)
Fatigue at T1				−0.590 (−0.573, −0.493)***	−0.626 (−0.612, −0.520)***
Interaction effects					
PTGt linear × Fatigue					0.071 (−0.002, 0.005)
PTGt quadratic × Fatigue					0.043 (0.000, 0.000)
Model summary					
R^2	0.321	0.323	0.332	0.566	0.571
ΔR^2	0.321***	0.002*	0.008***	0.234***	0.005*
Cohen's f^2	0.468	0.477	0.492	1.288	1.299

Note: The table contains standardized coefficients. Gender: male = 1, female = 2, PTGt = Posttraumatic growth total score, PTG= Independent variable, fatigue = moderator variable, global HRQoL = Dependent variable.

*$p < 0$ 0.05, **$p < 0.01$, ***$p < 0$ 0.001.

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patients who were extremely fatigued or traumatised may have been unable to participate in the survey, which could have led to fatigue being underreported. Moreover, as only individuals who participated at T1 were included in our analysis, this might also have contributed to an underestimation of fatigue as well as to an overestimation of global HRQoL at T1. This might be one reason why we found no moderating effect by fatigue. Possibly important covariates like socioeconomic status, psychoactive medications or stage of disease were not assessed in our study. Future studies should consider these variables, as it is possible that the findings would have been influenced by these characteristics. Despite the study limitations, the study has some methodological strengths. We investigated both linear and quadratic functions of PTG, which appear to better reflect the true associations of PTG and global HRQoL than using only linear models. Further, our study had a large sample size ($N = 1316$) and was spread across 15 different cancer entities. This allows for proper generalisation to the general cancer survivor population in Germany, not limited to a specific cancer entity.

5 | CONCLUSION

We found a significant convex quadratic relationship between PTG and global HRQoL even 4 years after cancer diagnosis which was not modified by fatigue. Future statistical models investigating PTG and global HRQoL should take this non-linear relationship into account to avoid misleading results by using linear models. Further, as high PTG was associated with better global HRQoL compared to only moderate PTG, it is perceivable that promoting PTG by appropriate interventions could be a way to improve global HRQoL. However, PTG might contribute to but is likely not sufficient for high levels of global HRQoL in cancer survivors in the long run.

AUTHOR CONTRIBUTIONS

Martina E. Schmidt and Karen Steindorf conceptualised, designed and managed study data acquisition, Maria-Chidi C. Onyedibe and Patricia Blickle performed the statistical analysis and drafted the manuscript, all authors critically revised the manuscript and contributed important intellectual content.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

Data can be made available to scientific cooperation partners upon reasonable request.

ETHICAL STATEMENT

This study was conducted in accordance with the ethical standards of the Helsinki Declaration. The study was approved by the Ethic Committee of the Medical Faculty of the University of Heidelberg (S654/2016). All patients have given written informed consent.

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4 Manuscript III

Blickle, P., Schmidt, M.E. and Steindorf, K. (2025). **Pretreatment Fatigue in Breast Cancer Patients: Comparison with Healthy Controls and Associations with Biopsychosocial Variables**. Cancer Med *14 (1)*, e70404, doi: 10.1002/cam4.70404.

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Manuscript III was published as an Open Access article in the Journal *Cancer Medicine.* The journal is published by *John Wiley & Sons Ltd.* It is an interdisciplinary oncology journal and publishes manuscripts from clinical cancer research, cancer biology, cancer prevention, and bioinformatics. In 2023, the journal's impact factor was 2.9, with a five-year impact factor of 3.9.

Contribution to the research questions of this dissertation:

Manuscript III compares the pretreatment symptom burden in newly diagnosed cancer patients with those in healthy controls. By applying TCIs, it further investigates the clinically relevant symptom burden in the patient group and analyses sociodemographic and psychosocial factors that may contribute to an increased likelihood of reporting clinically relevant CRF.

Data used:

Data from the baseline measurement timepoint of the CogniFit study was analyzed for Manuscript III. The analyzed study population consisted of 232 breast cancer patients and 41 healthy control participants (see section 1.5.2).

The supplementary material for this manuscript can be retrieved from: https://doi.org/10.1002/cam4.70404

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RESEARCH ARTICLE OPEN ACCESS

Pretreatment Fatigue in Breast Cancer Patients: Comparison With Healthy Controls and Associations With Biopsychosocial Variables

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Keywords: breast cancer patients | cancer | cancer-related fatigue | oncology | patient-reported outcomes | pretreatment fatigue | psychological factors | psycho-oncology | quality of life | supportive care

ABSTRACT

Objective: Cancer-related fatigue is one of the most common burdens of cancer patients. To date, most studies focused on fatigue during or after treatment. However, investigation of pretreatment fatigue is crucial to identify causal or risk factors other than cancer therapy and to enable timely fatigue management.

Methods: Two hundred and thirty-two breast cancer patients (mean age = 55.6) and 41 healthy participants (mean age = 49.3) were recruited via the National Center for Tumor Diseases (NCT) Heidelberg. Patient-reported outcomes were assessed with the EORTC QLQ-FA12 for fatigue, the EORTC QLQ-C30 for functioning, the STAI for anxiety, the CESD-R for depression and the PSQI for sleep disturbance. Descriptive analyses and logistic regression models were performed using baseline data before start of cancer treatment. The thresholds of clinical importance (TCI) were applied to test for clinically relevant fatigue.

Results: Compared to the healthy participants, patients scored significantly higher in physical, emotional, and total fatigue, in depression, in global health status and in all functioning scales except cognitive function (all $p < 0.01$). 48.7% of all patients reported clinically relevant fatigue. Being younger, being obese, having low education, or low social support was associated with a higher likelihood of clinically relevant fatigue before treatment. Higher depression and anxiety scores, poorer sleep quality and global health status, and impaired functioning seemed to get along with an increased likelihood of scoring above the TCI of fatigue (all $p < 0.001$).

Conclusions: Our study results suggest that fatigue screening, patient-centered fatigue education and psychosocial support may be needed already from the time of cancer diagnosis.

1 | Background

Cancer-related fatigue (CRF) is one of the most prevalent and burdensome side effects of cancer and cancer treatments. It manifests as a persistent feeling of physical, emotional, or cognitive weariness or exhaustion. It exhibits a disproportionate intensity relative to recent activity while impeding patient's ability to function [1]. Fatigue is not resolved by sleep or rest. Beside

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the fact that fatigue can lead to significant decrements in patients' quality of life (QoL), it has also been associated with lower recurrence-free and overall survival [2].

The pathogenesis of fatigue is complex and multifactorial. Several factors have been suggested to contribute to the development of fatigue: [3] the tumor itself, its treatment with chemotherapy, radiotherapy or immunotherapy and inflammatory processes, such as increased levels of inflammatory cytokines or cortisol dysregulation. Reduced energy metabolism or (neuro)endocrine changes can also cause fatigue. In addition to hormonal changes, an unbalanced diet and a lack of physical activity are discussed as possible influences on the development of fatigue. Psychological factors such as anxiety, depressive symptoms, sleep disturbance, and stress also appear to be important contributors to fatigue, although the extent and causal mechanisms are not fully understood [4, 5].

In the course of treatment, around 85% of patients experience fatigue, while approximately one third experiences fatigue for more than 5 years after their treatment [6–8]. Some studies showed that fatigue can also occur prior to initiation of cancer treatment, that is, before start of systemic or radiotherapy, reporting prevalence rates ranging from 14% to 24% [5, 9]. Pretreatment fatigue may be caused by the tumor itself, by tumor surgery or the stress and anxiety of being diagnosed. It seems to emerge as a key predictor influencing the level of fatigue after treatment, resulting in increased fatigue severity and burden in the aftermath [4, 10]. Identifying factors that contribute to or co-occur with pretreatment fatigue is crucial for alleviating this problem at an early stage, as fatigue can lead to poor cancer treatment adherence [8]. Moreover, investigation of pretreatment fatigue enables identification of risk factors or potential mechanisms that are independent of causal pathways related to therapy. However, compared to research on fatigue during or after cancer treatment, pretreatment fatigue has been less studied with still inconclusive evidence [4, 9–13].

Some sociodemographic factors have been associated with higher pretreatment fatigue, for example female sex, younger age and lower social support [12, 13]. Inconclusive associations have been found for education level, either showing no association with fatigue [4, 10] or suggesting that lower education is associated with higher fatigue [12]. Besides, higher body mass index (BMI) has been found to be associated with higher fatigue [14], but also showed no association with fatigue levels in other studies [10, 12].

Limited knowledge exists regarding the associations of pretreatment fatigue with other patient-reported outcomes (PROs). Goedendorp and her colleagues were one of the first to assess pretreatment fatigue in cancer patients and found depressed mood, impaired sleep quality and lower physical activity to be associated with higher fatigue levels [9]. Other studies linked higher levels of pretreatment stress to higher fatigue [15]. Anxiety has been shown to predict fatigue during cancer treatment [16], but the relation to pretreatment fatigue is less clear [9]. Depressive symptoms showed consistently high correlations with increased fatigue levels, before and during cancer treatment [17, 18]. One reason for this might be that fatigue and depressive symptoms share common behavior patterns, for example, tiredness and feeling exhausted. Therefore, it is not surprising that depressive symptoms have been found to be associated with higher levels of fatigue, although causal mechanisms are not yet fully understood and fatigue and depression do not necessarily go hand in hand [18].

Overall, a complete picture of fatigue and its associations with other burdens before start of cancer treatment is lacking. In addition, it remains unclear to what extent pretreatment fatigue in cancer patients differs from fatigue in the general population and thus, might be caused by cancer-related issues. Identifying factors that contribute to pretreatment fatigue could provide insights into the underlying mechanisms and help to better understand adjustment difficulties depending on patients' individual situations [12]. This is particularly important to provide appropriate support to affected and high-risk patients and to reduce the potential negative impact of fatigue on patients' quality of life and cancer treatment adherence [10].

To fill the research gaps mentioned above, the aims of this study were as follows: First, we wanted to find out whether patients already suffer from clinically relevant fatigue before the start of treatment and whether their burden was significantly higher compared to a healthy sample. Secondly, we were interested in how patients with clinically relevant pretreatment fatigue were characterized in terms of sociodemographic factors. Taking these sociodemographic factors into account, we then, thirdly, examined the associations between patients with and without clinically relevant fatigue on various psychological factors.

2 | Methods

2.1 | Participants

The COGNIFiT study (**COGNI**tive **F**unction **i**n patients with gynecological **T**umors) is a comparative longitudinal study with three measurement timepoints to examine the impact of cancer therapy on cognitive function. Participants were systematically screened and recruited at the National Center of Tumor Diseases (NCT) Heidelberg between November 2018 and March 2023. Eligibility criteria for patients were as follows: they were female, older than 18 years, able to speak and read German as well as be diagnosed with breast cancer or another gynecological tumor. Baseline assessments took place before start of systemic therapy (e.g., chemotherapy, immune therapy, endocrine therapy) and/or radiotherapy. Exclusion criteria were a diagnosis of a psychological, neurological or neurodegenerative illness and having undergone a cancer therapy within the last 2 years (except surgery). Overall, 243 patients were enrolled in the study after providing informed consent. Sample size calculation was based on the primary objective of the study to test for differences in cognitive impairments between different treatments.

To explore whether repetition of neurocognitive testing had any impact on the test results, healthy control participants were recruited via flyer and online advertisement in general practitioners' clinics around Heidelberg, Germany. They were

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required to meet the same criteria as patients except for having been diagnosed with a breast/gynecological tumor.

However, a comparison between patients and healthy controls was not the primary objective of the study and, accordingly, no power analysis was conducted for this. In the present analyses, we considered the baseline data, which were all assessed before start of systemic cancer treatment or radiotherapy.

The CogniFit study (registered via Deutsches Register Klinischer Studien (DRKS), trial number DRKS00015757) was conducted in accordance with the ethical standards of the Helsinki Declaration. The study was approved by the Ethic Committee of the Medical Faculty of the University of Heidelberg (S-489/2018).

2.2 | Assessments

Fatigue was assessed using the EORTC QLQ-FA12 (FA12). The FA12 has 12-items with responses on a 4-point Likert scale. The total fatigue score, and the three subdimensions comprising physical, emotional and cognitive fatigue were calculated and transformed to a scale of 0%–100% according to the scoring manual, with higher scores indicating greater levels of fatigue [19].

Depressive symptoms were measured with the revised 20-item Center for Epidemiologic Studies Depression Scale (CESD-R) [20, 21]. Higher scores indicate higher symptom burden. Total questionnaire scores range from 0 (no symptoms) to 80 (maximum symptoms). The frequently used cut-score of 16 was used to identify possibly depressed patients.

Anxiety was measured using the State Trait Anxiety Inventory (STAI), comprising 20 items [22]. To ensure comparability with other test values, the raw test values were converted into a 0%–100% scale and missing items were imputed [23].

The Pittsburg Sleep Quality Index (PSQI) consists of 19 items asking about sleep quality and sleep disturbances during the past month [24]. Items are divided into 7 subscales, of which the sleep quality subscale was used for the analyses as we considered impaired sleep quality the most relevant variable of the questionnaire with regard to pretreatment fatigue. Higher values on the 0–3 scale represent worse sleep quality.

The EORTC QLQ-C30 (C30) consists of 30 items divided into five function subscales (physical, role, emotional, cognitive and social), nine symptom subscales/items and a global health subscale [25]. Except the latter, all scales are answered on a 4-point Likert scale and transformed into a 0%–100% score according to the scoring manual. Patients with clinically relevant functional impairment or fatigue were identified using thresholds of clinical importance (TCI) from previous literature. The TCIs are based on three aspects of patients burden, that is, limitations in everyday life, requiring help or care, or worrying because of symptoms. As interpretation of the 0%–100% scores of the C30 can be challenging, this approach facilitates the interpretation of results by combining significant results with an estimation of their clinical relevance [26].

2.3 | Statistical Analyses

Data analyses were performed using IBM SPSS statistics version 29 and results were considered statistically significant if p was < 0.05. First, descriptive analyses for the PROs were performed separately for patients and healthy participants and differences between the two groups were tested using hierarchical regression analyses with bootstrapping. Bootstrapping was used as a robust statistical method to estimate the standard errors and the confidence intervals for each parameter irrespective of the underlying distribution of the variables.

Applying the TCI for the C30 fatigue score, patients were then divided into two groups: patients with clinically relevant fatigue (C30-fatigue > 39) and patients without (C30-fatigue ≤ 39) [26]. To estimate the associations between different sociodemographic variables and clinically relevant fatigue a multiple logistic regression analysis was calculated. Age and social support were entered in the model as continuous variables, whereas education (four levels), BMI (three levels; according to the World Health Organization's (WHO) BMI classification) and the statement if participants exercised in the year before diagnosis (yes/no) were entered as categorial variables. To estimate associations between PROs and fatigue, further logistic regression analyses were conducted. These models were adjusted for the sociodemographic variables that significantly contributed to the association with clinically relevant fatigue. Using only complete cases for regression analyses was considered appropriate as the number of missing data ranged from 0.44% to 2.63% of the study population [27].

3 | Results

Of the 243 patients enrolled, 236 were diagnosed with breast cancer. The remaining seven patients were diagnosed with other gynecological tumors and were therefore not included in the analyses. Of the 236 breast cancer patients, four did not provide any data on fatigue at all. Therefore, a total of 232 patients were included in the initial statistical analyses. A further four patients did not answer the C30 fatigue questions, so the logistic regressions based on the C30 TCI for fatigue included 228 patients.

The patient sample consisted of 98.7% women who were diagnosed with invasive breast cancer and 1.3% with ductal carcinoma in situ (DCIS). Their mean age was $M = 55.6$ years (SD = 11.6). More than one third (35.8%) of the patients had an academic education, that is, a university degree. Further 21.6% had a high school degree (referring to the German "(Fach-)Abitur" or a degree of a specialized school, that is, entitling access to universities), while less than half of the patients (42.7%) had a lower qualification than this. Most of the patients (85.4%) lived together with at least one person. The 41 healthy women were slightly younger ($M = 49.3$, SD = 9.8) and better educated compared to the patient sample, as 51.6% had an academic education and only ten women (24.4%) didn't have a high school degree. 40% of this population lived alone. Further sociodemographic characteristics of the study population are depicted in Table 1.

Table 2 displays the distributions of pretreatment fatigue and PROs in patients and healthy participants and the mean

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TABLE 1 | Sociodemographic characteristics of the study population.

	Patients ($N=232$)	Healthy participants ($N=41$)
Mean age (SD)	55.6 (11.6)	49.3 (9.8)
Breast cancer type	*N* (%)	*N* (%)
Invasive	229 (98.7%)	
In situ	3 (1.3%)	
Surgery before treatment	*N* (%)	
Yes	226 (97.4%)	
No	6 (2.6%)	
Educational level	*N* (%)	*N* (%)
Academic	83 (35.8%)	23 (56.1%)
Higher education	50 (21.6%)	8 (19.5%)
Moderate education	73 (31.5%)	9 (22.0%)
Basic or no education	26 (11.2%)	1 (2.4%)
BMI in kg/m^2: Mean (SD)	25.7 (5.4)	24.5 (4.4)
Underweight (< 18.5)	7 (3.0%)	—
Normal (≥ 18.5 and < 25)	122 (52.6%)	26 (63.4%)
Overweight (≥ 25 and < 30)	63 (27.2%)	11 (26.8%)
Obese (≥ 30)	40 (17.2%)	4 (9.7%)
Living alone (household)		
Yes	33 (14.6%)	16 (40%)
No	193 (85.4%)	24 (60%)

Note: Regarding living situation, six patients and one healthy participant did not answer the question.

differences adjusted for age, BMI and education level. Patients had significantly higher scores on the FA12 total fatigue score (adjusted mean difference = 9.99, 95% confidence interval (CI) [3.83, 15.76]) and on the subscales physical fatigue (12.77, 95% CI [3.94; 21.12]) and emotional fatigue (10.52, 95% CI [2.92; 17.60]), as well as a higher C30 fatigue score (15.96, 95% CI [6.52, 24.64]). Almost half of the patients (48.7%), compared to 17.1% of healthy participants, scored higher than the TCI of 39 on the C30 fatigue symptom subscale, indicating clinically relevant fatigue. Regarding the function scales of the C30, patients reported significantly higher impairment on the subscales physical, role, social, and emotional function (all $p < 0.01$), as well as a worse global health status. Besides, patients reported significantly more depressive symptoms compared to healthy participants (adjusted mean difference = 9.41, 95% CI [4.97, 13.74]), with 48.7% of patients (compared to 22% of healthy participants) scoring higher than the clinically relevant cut-score of the CESD-R.

With regard to sociodemographic variables (see Table 3), the odds for showing clinically relevant fatigue were higher for patients with no/basic education (OR = 2.87, 95% CI [1.05; 7.84]) or moderate education (OR = 2.79, 95% CI [1.39; 5.60]) compared to those with academic education, for those with lower social support (OR = 0.96; 95% CI [0.94; 0.99]) compared to those with higher social support, and also tended to be higher for younger compared to older patients (OR = 0.98; 95% CI [0.95; 1.00]). Obese patients (BMI ≥ 30) had higher odds for showing clinically relevant fatigue compared to patients with a normal BMI (OR = 2.56, 95% CI [1.14; 5.72]).

Table 4 shows the results of multiple logistic regression models to estimate associations of other PROs with clinically relevant fatigue in patients. Clinically relevant fatigue was associated with higher symptom burden regarding depression (OR = 1.17, 95% CI [1.12; 1.22]) and anxiety (OR = 1.10, 95% CI [1.07; 1.13]), poorer sleep quality (OR = 5.18, 95% CI [3.00; 8.93]), a worse global health status (OR = 0.90; 95% CI [0.88; 0.93]), as well as lower scores in all five function scales of the C30 (all $p < 0.001$). Figures 1–3 illustrate the distribution of symptom burden between patients with and without clinically relevant fatigue. Figures showing lower functioning in social, emotional, physical, role, and cognitive domains and global health status in patients with clinically relevant fatigue compared with those without are also provided in the Appendix (Figures S4a and S4b).

4 | Discussion

In patients, we found significantly higher scores for physical, emotional and total fatigue as well as for the fatigue subscale score of the C30 compared to healthy participants, even after adjusting for sociodemographic factors. These results point to a higher fatigue burden in patients already at the beginning of cancer treatment.

Our patient sample showed lower fatigue scores in all FA12 dimensions as well as in the total score compared to patients already under treatment [28]. Nevertheless, almost half of our breast cancer patients scored worse than the TCI for clinically relevant fatigue even before starting therapy, indicating supportive care needs. More precisely, scoring higher than the TCI represents a significant limitation to the patient's daily life due to the perceived symptom burden, causes worry to patients or their families, or requires help or care [26]. As it is well-known that fatigue symptoms tend to worsen with treatment, these results may only indicate the beginning of the fatigue burden, emphasizing the need to educate patients and their relatives about fatigue at an early stage.

Our results support findings from previous literature, which found that lower age and low social support are associated with higher fatigue [12, 29]. With regard to the inconclusive findings to date on whether education and BMI play a role in pretreatment fatigue [4, 10, 12, 14], our data suggest that they do. These findings may guide health care professionals in identifying patients at high risk of developing fatigue prior to treatment. For example, as BMI is a modifiable factor, advice on diet and physical activity could not only reduce weight, but also prevent the development or worsening of fatigue [30]. As lower education also appears to be a risk factor for fatigue, providing adequate and easily understandable information about cancer and its side effects could be an important pillar of supportive cancer care.

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TABLE 2 | Distributions of patient-reported outcomes and adjusted mean differences between patients and healthy controls.

Dependent variable	Patients mean (SD)	Patients scoring worse than cut-score/ TCI[a]	Mean (SD) controls	Controls scoring worse than cut-score/ TCI	Adjusted mean difference [95% CI]	*T*-test	*p*
EORTC QLQ-FA12							
Total fatigue	28.42 (22.82)	n.a.	16.73 (15.65)	n.a.	**9.99 [3.83, 15.76]**	**2.62**	**0.009**
Physical fatigue	39.94 (28.30)	n.a.	24.23 (21.02)	n.a.	**12.77 [3.94, 21.12]**	**2.71**	**0.007**
Emotional fatigue	25.60 (28.78)	n.a.	15.18 (19.04)	n.a.	**10.52 [2.92, 17.60]**	**2.17**	**0.031**
Cognitive fatigue	11.58 (18.80)	n.a.	5.69 (10.28)	n.a.	5.85 [1.45, 9.99]	1.89	0.060
EORTC QLQ-C30							
Fatigue	40.84 (27.44)	48.7%	22.49 (24.28)	17.1%	**15.96 [6.52, 24.64]**	**3.45**	**< 0.001**
Physical function	80.56 (19.97)	47.4%	92.85 (13.20)	12.2%	**−8.70 [−13.08, −3.85]**	**−2.74**	**0.007**
Role function	62.19 (31.83)	39.6%	92.28 (15.85)	4.9%	**−28.98 [−35.43, −22.29]**	**−5.54**	**< 0.001**
Social function	72.66 (30.18)	26.3%	94.17 (13.89)	5.0%	**−21.06 [−27.24, −14.86]**	**−4.21**	**< 0.001**
Cognitive function	77.68 (24.51)	37.4%	85.77 (19.21)	24.4%	−6.28 [−12.91, 0.77]	−1.52	0.129
Emotional function	55.62 (26.35)	65.5%	71.75 (20.49)	51.2%	**−16.54 [−24.07, −9.16]**	**−3.68**	**< 0.001**
Global health status	61.60 (20.76)	n.a.	81.10 (12.91)	n.a.	**−16.75 [−21.93, −11.49]**	**−4.91**	**< 0.001**
Depression (CESD-R)							
Total score	20.54 (19.07)	48.7%	9.31 (11.14)	22%	**9.41 [4.97, 13.74]**	**3.01**	**0.003**
Anxiety (STAI)							
Total score %	32.44 (19.56)	n.a.	25.94 (17.48)	n.a.	6.68 [0.44, 12.79]	1.92	0.056
Sleep quality	1.39 (0.73)	n.a.	1.15 (0.53)	n.a.	0.174 [−0.05, 0.38]	1.47	0.149

Note: We calculated separate models for all listed dependent variables. All models were adjusted for age, BMI and education. Bootstrapping based on 5000 bootstrap samples was used to calculate the coefficients and the confidence intervals, as residuals were not normally distributed. Significant results ($p < 0.05$) were marked in bold.

Abbreviations: CESD-R = Center for Epidemiological Studies Depression Scale—Revised, CI = confidence interval, n.a. = not applicable, when no cut-scores or thresholds of clinical importance were defined for these variables, STAI = State Trait Anxiety Inventory.

[a]TCI = thresholds of clinical importance for the EORTC QLQ C30 subscales [26]. Cut-score for the CESD-R = 16 [20, 21].

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TABLE 3 | Logistic regression analysis to estimate associations of sociodemographic variables with clinically relevant fatigue in 228 breast cancer patients before treatment.

Dependent variable: clinically relevant fatigue (yes vs. no)[a]	OR [95% CI]	*p*
Age	0.98 [0.95; 1.00]	0.054
Social support	0.96 [0.94; 0.99]	0.001
Exercise before diagnosis		
Yes	Ref	
No	1.07 [0.57; 2.02]	0.835
Educational level		
Academic	Ref	
Higher education	1.78 [0.83; 3.84]	0.140
Moderate education	2.79 [1.39; 5.60]	0.004
No or basic education	2.87 [1.05; 7.84]	0.039
BMI		
Normal[b] (BMI < 25)	Ref	
Overweight (BMI ≥ 25 and < 30)	0.77 [0.39; 1.49]	0.402
Obese (BMI ≥ 30)	2.56 [1.14; 5.72]	0.022

Note: All listed variables were included simultaneously. R^2 (Nagelkerke) = 0.172.
Abbreviations: BMI = body mass index, CI = confidence interval (based on 1000 bootstrap samples), OR = odds ratio.
[a]Based on the threshold of clinical importance for the EORTC QLQ-C30 subscales [26].
[b]The seven patients with BMI ranging between 16 and 18 were also included in this category for reasons of parsimony.

In the patient group, higher depression and anxiety scores and poorer sleep quality seemed to get along with an increased likelihood of scoring above the TCI of fatigue. In light of previous inconclusive findings, our results may suggest that anxiety already plays a significant role in pretreatment fatigue levels. This assumption is underlined by a recent systematic review by Cheng and colleagues, who also found that anxiety and depression were associated with higher odds of experiencing increased fatigue [31]. Other studies have reported similar findings, emphasizing that psychological factors in general play an important role in pretreatment fatigue [9, 10].

The significantly higher depression score in patients compared to healthy participants leads to the interpretation that a cancer diagnosis can cause tremendous emotional distress [10]. The fact that we only included individuals with no pre-diagnosed mental illness in our study makes it even more likely that the cancer diagnosis/surgery was the cause of the increased symptom burden. Using the classical cut score of 16 [20, 21], almost half of the patients reported a clinically relevant symptom burden of depression. This is a considerably high number of people who may be depressed. However, this number may be overestimated, as research has shown that the cut score of 16 may lack specificity in some study populations, and 22% of our healthy participants scored above this score [32]. Nevertheless, pretreatment signs of depression should be taken seriously, as they are a strong predictor of poorer well-being during and after treatment [33].

Regarding the mean scores of the C30 function subscales, we found slightly lower, but still comparable values in our patient sample compared to the reference values of early breast cancer patients prior to treatment [34]. The mean scores of the healthy sample were comparable to the German norm values [35]. Patients with clinically relevant fatigue scored worse on

TABLE 4 | Separate logistic regression models to estimate associations of patient-reported outcomes with clinically relevant fatigue in 228 breast cancer patients before treatment.

Dependent variable: clinically relevant fatigue (yes vs. no)	OR [95% CI]	*p*	Pseudo R^2 (Nagelkerke)
Depression (total score)	1.17 [1.12; 1.22]	< 0.001	0.63
Anxiety (total score)	1.10 [1.07; 1.13]	< 0.001	0.51
Sleep quality[a]	5.18 [3.00; 8.93]	< 0.001	0.36
EORTC QLQ C30			
Physical function	0.91 [0.89; 0.94]	< 0.001	0.48
Role function	0.95 [0.93; 0.96]	< 0.001	0.52
Social function	0.94 [0.93; 0.96]	< 0.001	0.51
Cognitive function	0.93 [0.91; 0.95]	< 0.001	0.48
Emotional function	0.93 [0.91; 0.95]	< 0.001	0.58
Global health status	0.90 [0.88; 0.93]	< 0.001	0.57

Note: Each line represents a separate model, adjusted for age, social support, BMI and education. Depressive symptoms were measured with the Center for Epidemiologic Studies Depression Scale – Revised (CESD-R, ranging from 0 to 80), anxiety was measured with the State Trait Anxiety Inventory (STAI, ranging from 0% to 100%); sleep quality was measured with a subscale (ranging from 0 to 3) of the Pittsburg Sleep Quality Index (PSQI).
Abbreviations: CI = Confidence Interval (based on 1000 bootstrap samples), OR = Odds Ratio.
[a]Higher scores on this scale indicate poorer sleep quality.

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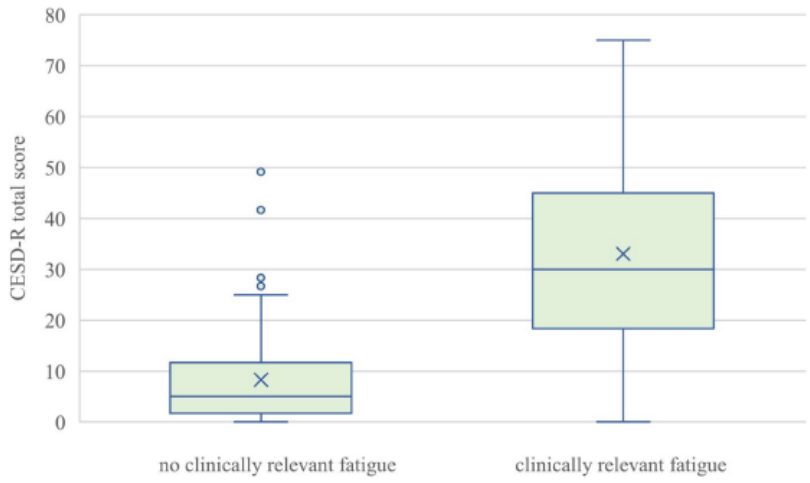


FIGURE 1 | Distribution of depressive symptoms between patients with and without clinically relevant fatigue. CESD-R = Center for Epidemiologic Studies Depression Scale—Revised.

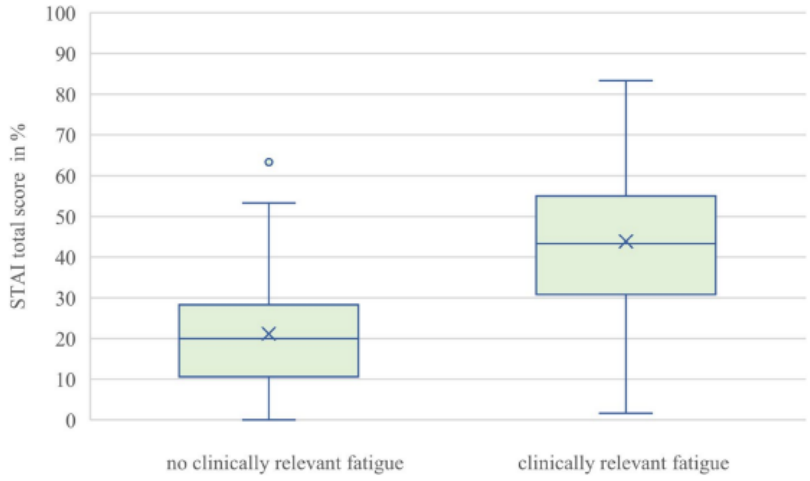


FIGURE 2 | Distribution of anxiety symptoms between patients with and without clinically relevant fatigue. STAI = State Trait Anxiety Inventory.

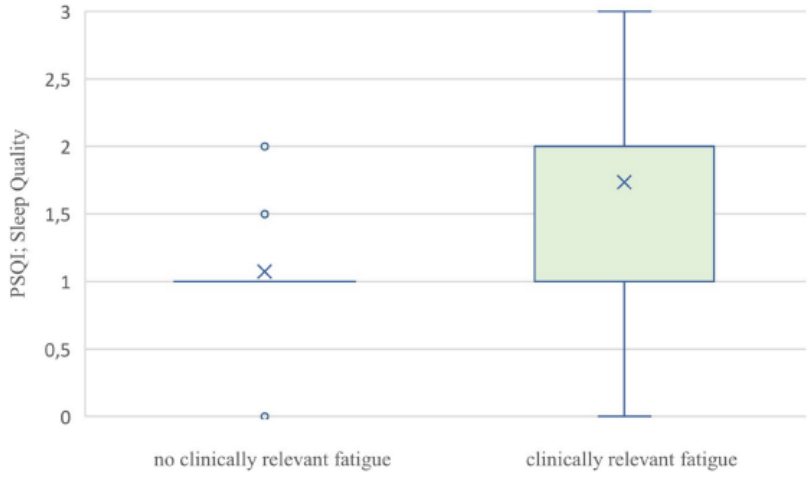


FIGURE 3 | Distribution of impaired sleep quality between patients with and without clinically relevant fatigue. PSQI = Pittsburg Sleep Quality Index; subscale Sleep Quality.

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all function subscales than those without, pointing to a potentially significant negative impact of pretreatment fatigue on other life domains and the global health status. Underlying common causes, such as increased distress levels, may account for this association.

Overall, our results show that fatigue does not occur alone but mostly clusters with other psychological and functional factors [3, 31]. Almost half of breast cancer patients in our study experienced clinically relevant fatigue already before start of treatment. Thus, their fatigue was caused by other factors than radio- or systemic therapies. Although we cannot point to any causal relationships here, the data suggest that the TCI of fatigue can reliably distinguish between patients regarding overall symptom burden. It might therefore be promising if future research investigates TCIs for the FA12 subscales to provide a more nuanced picture of pretreatment fatigue burden in cancer patients.

4.1 | Clinical Implications

Our findings highlight the importance of screening patients for fatigue even before they start cancer treatment and providing them with comprehensive information about this distressing side effect [10, 30]. More specifically, the provision of easy-to-understand educational information appears not only to reduce symptoms, but also to facilitate positive outcomes and is in line with international guideline recommendations [1, 30, 36, 37]. Appropriate information should include a description of symptoms and effective treatment options, such as physical activity or mind–body exercises [1, 30].

As social support is also known to be a great resource for cancer patients and to have a positive influence on treatment (adherence), providing support to socially disadvantaged people seems particularly important. Here, for example, cognitive behavioral therapy to help patients address emotional distress and cope with their diagnosis has been shown to be effective [38].

As our results also suggest that psychological mechanisms appear to be triggered by the diagnosis, psychosocial treatments/interventions should be offered to affected patients prior to starting treatment [39]. This may not only help to manage psychological distress but may also have a positive effect on fatigue levels [30, 40].

In summary, the provision of educational, emotional and psychosocial support, including cognitive behavioral therapy, may address patients' concerns and needs prior to treatment initiation, potentially reducing psychological distress, improving sleep quality and reducing fatigue. If time constraints in routine clinical practice require prioritization, it may be possible to focus on high-risk patients as characterized here.

4.2 | Study Limitations

Some limitations of the study need to be considered. First, the study population was limited to patients diagnosed with breast cancer. Therefore, it remains an open question whether the findings can be extrapolated to other cancer entities. Given the different sample sizes and characteristics of patients and healthy controls, the statistical differences observed in the results must be interpreted with caution. In addition, as we only examined patient-reported burden cross-sectionally, causal interpretations of our findings cannot be made and adjustment for pre-diagnosis fatigue was not possible. All data analyzed were self-reported; however, they were assessed using validated questionnaires and showed marked differences in psychological symptom burden between clinically relevant fatigued and non-fatigued patients.

5 | Conclusions

To ensure an adequate fatigue management, fatigue screening, patient-centered education on fatigue and psychosocial support may be needed already from the time of cancer diagnosis. Providing coping and symptom management strategies prior to starting cancer treatment may be an important step in preventing further exacerbation or chronicity of fatigue.

Author Contributions

Patricia Blickle: formal analysis (lead), writing – original draft (lead). **Martina E. Schmidt:** conceptualization (equal), formal analysis (supporting), project administration (equal), writing – original draft (supporting). **Karen Steindorf:** conceptualization (equal), investigation (equal), project administration (equal), writing – original draft (supporting).

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Conflicts of Interest

Martina E. Schmidt and Patricia Blickle declare no conflicts of interest. Karen Steindorf received honararies and travel refunds for talks with some relation to the context of the manuscript from the companies Takeda and Adviva medical equipment.

Data Availability Statement

Data can be made available to scientific cooperation partners upon reasonable request.

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5 Discussion

The main findings of the examined research questions are outlined in the following section 5.1. Thereafter, sections 5.2. and 5.3 situate the findings within the current scientific context. Taking into account the strengths and limitations outlined in section 5.4, directions for future developments and clinical implications are discussed in section 5.5. Finally, an overall conclusion is provided (section 5.6).

5.1 Overview of the main findings

The findings from Manuscript I indicated that PTG can be experienced by cancer-free cancer survivors even four years after the potentially traumatic cancer event. ‘Appreciation of life’ was identified as the most pronounced dimension of PTG in this study population. It was demonstrated that common cancer-related side effects, including emotional distress, pain, and CRF, were longitudinally associated with PTG. Further, the study found that survivors who reported feeling poorly informed about CRF exhibited lower PTG levels compared to those who felt well informed about CRF.

Statistical analyses in Manuscript II revealed a convex quadratic association between PTG and HRQoL in cancer survivors. Furthermore, the findings corroborated the established influence of CRF on (HR)QoL as evidenced by previous research. The results did not demonstrate a moderating effect of CRF on the association between PTG and HRQoL.

In addition to PTG and the role of CRF in cancer survivors, this dissertation investigated pretreatment CRF in breast cancer patients. The results of Manuscript III indicated that patients experienced a substantial amount of pretreatment CRF, a level that was significantly higher than that observed in healthy individuals. This pattern was similar in other variables, such as functioning and depressive symptoms. In terms of sociodemographic factors, patients who were younger or obese, had a lower level of education, and lower social support were more likely to score above the TCI for clinically relevant CRF. Psychosocial factors contributing to the likelihood of scoring above the TCI included more depressive symptoms and anxiety, poorer sleep quality, poorer functioning, and poorer overall health status.

5.2 Post-traumatic growth

As indicated by the findings of Manuscript I, the extent of PTG among cancer survivors participating in the FiX study appeared to be modest to moderate when compared to the potential total scores of PTG. The magnitude of PTG was broadly comparable with the results of other studies investigating PTG in cancer-free survivors, albeit at a lower level across all subdimensions and the total score (Cormio et al. 2017; Lelorain et al. 2010). One reason for this may be that past studies included a higher proportion of female cancer survivors (Cormio et al. 2017; Lelorain et al. 2010). Given that previous research has indicated that women tend to report higher PTG levels than men (Jaarsma et al. 2006; Liu et al. 2021; Zwahlen et al. 2010), this could explain the observed difference. Various studies have revealed most changes in the domain of ‘appreciation of life’ (Husson et al. 2017; Jansen et al. 2011; Sim et al. 2015) and least changes in ‘spiritual change’ (Lelorain et al. 2010; Sharp et al. 2018), and the results of Manuscript I were in line with this. Furthermore, consistent with previous literature, the results supported the hypothesis that younger patients tend to report higher PTG levels than older individuals (Boyle et al. 2017; Widows et al. 2005; Wu et al. 2019). The finding that receiving chemotherapy may result in elevated levels of PTG underscored the burdensome impact of chemotherapy on patients and added new evidence to the so far conflicting study results (Baník and Gajdošová 2014; Casellas-Grau et al. 2017; Jansen et al. 2011; Lelorain et al. 2010; Mols et al. 2009). In view of the inconclusive findings regarding the influence of education or health literacy on PTG, the results from Manuscript I provided indirect support for the hypothesis that patients with higher levels of informedness report higher PTG values. This assumption could be inferred from the reported positive influence of informedness about CRF on PTG levels.

A synthesis of the results of the longitudinal regression analyses presented in Manuscript I suggested that a certain increase in symptom burden, due to emotional distress, pain, or CRF was associated with an increased perception of subsequent PTG. Hereby, new insights into the predictive potential of cancer-related side effects on PTG were revealed. Contrary to the findings of some studies in this field which did not identify a significant association between PTG and emotional distress (Casellas-Grau et al. 2017; Cormio et al. 2017; Leong Abdullah et al. 2015), the findings of Manuscript I indicated that emotional distress may be a contributing factor in the determination of subsequent levels of PTG. A potential explanation for this observed difference may be the longitudinal nature of the analyses conducted (Menger et al. 2021). Other explanations can be based on the assumptions of some previous research and are in line with the ideas of the theoretical PTG model (see Introduction section 1.2.2). Firstly, emotional distress may be a prerequisite to develop subsequent PTG (Tedeschi and Calhoun

1996; Tedeschi and Calhoun 2004), and, secondly, both emotional distress and PTG may be dimensions that can coexist (Lelorain et al. 2010; Sumalla et al. 2009; Tedeschi and Calhoun 1996; Tedeschi and Calhoun 2004). In addition, it appeared that pain and CRF levels also contributed to PTG. With regard to the association between pain and PTG, the results of Manuscript I indicated somewhat contradictory results compared to a previous intervention study (Arefian and Asgari-Mobarakeh 2024). In the intervention group of this study, which was designed to reduce the burden of pain symptoms through an educational intervention, a subsequent increase in PTG scores was observed. This increase was associated with significantly lower pain scores than in the control group (Arefian and Asgari-Mobarakeh 2024). Interpreting the results of this study and of Manuscript I within the theoretical framework of Tedeschi and Calhoun (1996; 2004), it may be argued that PTG is a dynamic process that can be influenced by interventions, even if these interventions are primarily aimed at alleviating physical symptoms. This in turn may influence the perception of PTG through cognitive restructuring and processing, pointing to the complex interplay between symptoms and their (perceived) influence on broader health outcomes (Costa et al. 2016). Overall, it might well be that an initially higher pain symptom burden contributes to the development of PTG, as it may represent an indication of the severity of the disease and its side effects (Tedeschi and Calhoun 1996; Tedeschi and Calhoun 2004). The alleviation of this symptom burden through educational efforts may, in turn, facilitate the perception of the potential positive outcomes of cancer, such as PTG (Arefian and Asgari-Mobarakeh 2024). As higher CRF levels also contributed to some extent to higher subsequent PTG levels, this can be interpreted as further support for the theoretical framework of Tedeschi and Calhoun (1996; 2004). Despite the interpretation within this framework, another assumption regarding underlying causes for this association could be based on inflammatory processes. Studies investigating the underlying biological mechanisms of CRF (García-González et al. 2023; O'Higgins et al. 2018), as well as studies aiming to identify potential biological mechanisms for PTG (Sierra-Murguía et al. 2024), both hypothesized that these processes contribute to the respective PRO. However, it can be considered highly speculative to assume a causal association between PTG and CRF through inflammatory processes, as no study has yet investigated this.

The results of Manuscript II demonstrated a statistically significant, convex quadratic association between PTG and HRQoL. One potential interpretation of this finding might be that survivors reporting no or low levels of PTG might have perceived their disease as less threatening than survivors with moderate or high PTG (Lechner et al. 2006; Tedeschi and Calhoun 1996; Tedeschi and Calhoun 2004). At the same time, survivors who reported moderate levels of PTG might have used less adaptive coping strategies and might have had less personal resources in comparison to those with higher PTG levels, which could have

negatively impacted their levels of HRQoL (Lechner et al. 2006; Tedeschi and Calhoun 1996; Tedeschi and Calhoun 2004). As recommended by previous research (Menger et al. 2021), a diverse and comprehensive study sample was examined. However, the investigation of the association between PTG and HRQoL remained challenging, as the findings presented in Manuscript II indicated a relatively weak association. Given the ambiguity that has been observed in this association over recent decades, it can be argued that this may be due to the highly individualized processes that enable individuals to perceive critical life events as either challenging or threatening (Costa et al. 2016; Tedeschi and Calhoun 1996; Tedeschi and Calhoun 2004). Furthermore, the findings of this manuscript revealed a significant negative impact of CRF on HRQoL. This reinforced the conclusions of previous research, that CRF can be a burdensome and long-term side effect, contributing to unfavorable outcomes such as diminished HRQoL even years after the cancer diagnosis (Bower 2014; Minton et al. 2013; Ruiz-Casado et al. 2021). Additionally, the regression model demonstrated that HRQoL, assessed two years after the cancer diagnosis, can function as a potential predictor for subsequent HRQoL, assessed another two years later. This finding showed consistency with existing literature, suggesting that timely measurements of HRQoL could serve as an indicator of its future development (Gao et al. 2023; Schulte et al. 2022). Despite previous studies suggesting that the association between PTG and HRQoL may be influenced by additional factors (Li et al. 2019), the findings of Manuscript II did not identify CRF as such a factor. This indicated that the association between PTG and HRQoL existed independently of the CRF level of the cancer survivors, irrespective of whether the moderation analyses were conducted with the PTG total score or with the PTG subdimensions as the dependent variable.

Taken together, the results of Manuscript I and II suggested further evidence for the theoretical framework put forth by Tedeschi and Calhoun (1996; 2004), that a traumatic (cancer) experience can lead to positive psychological changes. These changes seemed to be perceptible even four years after the event, were associated with cancer-specific side effects, and did not necessarily imply an increase in HRQoL. Overall, both manuscripts highlighted PTG as an important, albeit understudied, PRO in cancer survivors.

5.3 Cancer-related fatigue

In line with previous results, the findings of Manuscript III yielded higher symptom scores in cancer patients compared to healthy participants in most domains assessed (Cella et al. 2002; Hinz et al. 2020). The significantly elevated symptom burden observed in the C30-functioning scales (with the exception of cognitive function) and the increased prevalence of depressive symptoms among patients in comparison with healthy participants were to be anticipated in

light of the findings of previous studies (Arndt et al. 2017; Mitchell et al. 2013). With regard to CRF, patients and healthy participants expressed significantly different levels of CRF in the total, physical, and emotional dimensions, but not in the cognitive dimension. This underscored the importance of considering the various dimensions of CRF to achieve a comprehensive understanding of its complexity in patients. As demonstrated by a substantial number of patients scoring above the respective TCIs, the findings of Manuscript III further shed new light on the extent of clinically relevant symptom burden from the time of cancer diagnosis onwards. In particular, the high prevalence of clinically relevant pretreatment CRF in patients stood out. This finding reinforced existing recommendations outlined in international guidelines that screening for CRF should be performed early in the cancer trajectory, ideally following the diagnosis of cancer (Fabi et al. 2020; Howell et al. 2013; National Comprehensive Cancer Network 2023).

With regard to sociodemographic factors, younger age, higher BMI, lower education, and lower social support tended to increase the likelihood of scoring above the TCI for CRF, highlighting important characteristics of patients that may be at elevated risk to develop CRF. In terms of age, the study results suggested that younger age could increase the likelihood of clinically relevant CRF. This finding was consistent with the results of studies specifically examining the relationship between age and pretreatment CRF (Bower et al. 2019; Rosas et al. 2023) and provided new evidence to support previous inconclusive findings investigating this association at various timepoints during the cancer course (Di Meglio et al. 2022; Ma et al. 2020). Moreover, despite the existence of some studies that did not report an association between pretreatment CRF and BMI, the observation that obesity could increase the likelihood of pretreatment CRF was in alignment with the findings that high BMI was associated with an elevated risk of developing higher CRF levels during and after treatment (Ma et al. 2020; Ruiz-Casado et al. 2021). As recent study results indicated that BMI can also influence the amount of long-term CRF (Kastelein et al. 2025), high BMI could be considered as a prospective risk factor for CRF. In light of previous conflicting results regarding the association between pretreatment CRF and education (Bower et al. 2019; Goedendorp et al. 2013), the results of Manuscript III indicated that low education levels were associated with a higher likelihood for clinically relevant pretreatment CRF levels. Therefore, low education could also be considered a potential risk factor for developing CRF. Lastly, the findings supported the existing literature, which found that lower social support was associated with higher CRF levels (Bower et al. 2019).

In view of inconclusive results regarding the association of anxiety and CRF (Goedendorp et al. 2008; Hughes et al. 2020), findings of Manuscript III were of particular interest. They

indicated that, on average, patients did not report significantly higher levels of anxiety than healthy participants prior to treatment. However, when subgroups of patients were analyzed, for example according to their level of pretreatment CRF, clear differences between the levels of anxiety could be seen. This might indicate that even pretreatment CRF is already associated with specific symptoms, such as anxiety. Existing literature performing cluster analyses have already identified anxiety as an important factor contributing to the development and severity of CRF (Schellekens et al. 2020; Schmidt et al. 2022a). Notably, these cluster analyses and network approaches were primarily conducted with PROs during or after cancer treatment (Baussard et al. 2024; Schellekens et al. 2020; van Roozendaal et al. 2023). The findings of Manuscript III suggested that these prospective clusters begin to develop already prior to treatment. Given that the CogniFit study exclusively included patients without a previously diagnosed psychological disorder, this could reinforce the assumption that the reported anxiety only developed subsequent to the receipt of a cancer diagnosis. In addition to anxiety, other important factors potentially clustering with pretreatment CRF may be depressive symptoms, impaired sleep quality, lower functioning, and a worse global health status, as indicated by the findings of Manuscript III. In view of the findings of previous studies, which largely found similar associations of these factors with CRF during or following treatment, these results were not unexpected (de Rooij et al. 2023; Hofman et al. 2007; Muthanna et al. 2023; Schellekens et al. 2020). In particular, as almost half of the patients scored above the cut-off for clinically relevant depressive symptom burden (Eaton et al. 2004), this indicated a further frequent burden prior to treatment. Given the high correlation with CRF, differential diagnosis between these two symptoms should be taken into consideration by HCPs (Fabi et al. 2020). It may be suggested that this differential diagnostic assessment should be initiated at the earliest timepoint possible in the cancer experience, if patients are faced with symptoms of exhaustion with an unclear underlying cause.

5.4 Strengths and limitations

This dissertation provided valuable insights for both PTG and CRF research. In addition to the limitations mentioned in the respective manuscripts, it is important to note further strengths and limitations that have not been addressed previously. Strengths and limitations are primarily discussed in relation to the characteristics of the two study samples, the nature of PROs and its assessment, and the statistical methods applied.

Firstly, potential limitations of Manuscript I and II should be noted. Regarding the study population from the FiX study, only cancer-free survivors have been analyzed, which might have limited the generalizability of the results. One might argue that the level of PTG could

depend on the severity of the disease. Although research in this area is scarce, a recent systematic review and meta-analysis found higher PTG levels in stage four cancer patients compared to patients in less advanced stages (Marziliano et al. 2020). Therefore, a different extent of PTG may have been observed if survivors who were not cancer-free were included. Furthermore, the temporal course of PTG and its development over time could not be displayed, as PTG was only assessed once in the FiX study. As depicted in the CONSORT diagram in Figure 4, the response rate at the follow-up assessment in the FiX study (measurement timepoint T1) decreased to some extent due to study dropouts. This may have caused a selection bias in the sense that rather less burdened survivors participated in the survey, leading to a potential underestimation of the real symptom burden of cancer survivors. It is also important to note that the variables for measuring the experienced symptom burden in the FiX study were recorded two years after diagnosis. According to the theoretical framework of PTG, the assessment of an earlier symptom burden, for example measured closely to the end of acute treatment, may have served as a more robust indicator for the subsequent PTG levels. This could be due to the fact that the cognitive processing of the traumatic event may have already taken place during treatment, but the positive perception of PTG had not yet become the new 'normal' (Tedeschi and Calhoun 1996). The relatively limited explanatory power of the regression models in Manuscript I indicated that additional variables may have been significant in understanding the development of PTG. As previously outlined in the Introduction of this dissertation (see section 1.2.2) and mentioned in Manuscript I, social support plays an important role in the development of PTG. Consequently, it could be important to consider this factor in the construction of prediction and regression models for PTG (Ma et al. 2022; McDonough et al. 2014). Notwithstanding the aforementioned limitations, Manuscript I and II were able to investigate (longitudinal) associations in a diverse study sample covering the 15 most prevalent cancer entities in Germany. In total, 1,316 individuals were included in the analyses, enabling a comprehensive picture of the investigated associations in cancer survivors. In addition to these favorable characteristics, the study’s utilization of systematic and representative sampling via a statewide cancer registry can be regarded as a significant strength (Schmidt et al. 2020). Moreover, the theory-driven approach rooted in the PTG framework (Tedeschi and Calhoun 1996; Tedeschi and Calhoun 2004) and the longitudinal assessment of the variables of interest in Manuscript I allowed for causal interpretation of the results. Hereby, new insights into the predictive potential of cancer-related side effects on PTG could be revealed, as it was one of the first studies to investigate these associations. The results of both manuscripts, I and II, led to the contribution of novel and important aspects regarding the association between common cancer-related side effects and PTG as discussed in section 5.2 of this dissertation.

Potential limitations should also be noted for Manuscript III. It may be likely that mainly motivated patients interested in research decided to participate in the CogniFit study. Moreover, the analyzed study population consisted exclusively of patients with breast cancer, most of whom were predominantly well-educated. These characteristics raise concerns about the representativeness of the sample for all cancer patients. Further, all analyses performed in Manuscript III were cross-sectional in nature. As a result, it was not possible to draw any causal inferences from the observed associations between CRF and sociodemographic and psychosocial factors. Nevertheless, the results added novel insights into the pretreatment burden of breast cancer patients compared to healthy participants. Furthermore, the findings shed new light on so far inconclusive associations, for example between pretreatment CRF and anxiety. As the eligibility criteria only permitted the inclusion of patients who had not been diagnosed with a neurodegenerative, neurological or psychological disease, the study was able to rule out the possibility that the psychological burden shown was due to clinically relevant psychological burden that already existed before the cancer diagnosis. This resulted in an elimination of a potential confounding variable. Moreover, the CogniFit study included a healthy participant group as a control comparison and is among the first to measure the extent of clinically relevant symptoms by applying existing thresholds (Eaton et al. 2004; Giesinger et al. 2020). These are considerable strengths of the study, especially given that, in the limited number of existing studies conducted on pretreatment CRF, a control comparison was usually not included (Di Meglio et al. 2022; Goedendorp et al. 2013; Goedendorp et al. 2008; Pertl et al. 2014).

In view of the self-reported data analyzed in all three manuscripts, it should be noted that PROs are generally subjective in their nature and may therefore be impacted by memory or recall bias, whereby patients may not accurately recall the extent of their symptom burden (Zini and Banfi 2021). Other types of bias may also have influenced patient responses. Of importance for the interpretation of the results presented in this dissertation is the fatigue bias. This bias may occur when patients become tired and start to give inaccurate answers due to the length of a survey (Zini and Banfi 2021). It might be assumed that the likelihood of the fatigue bias increases when patient's CRF levels are high, contributing to potentially distorted response patterns. However, the amount of this potential confounding bias could not be quantified. Nevertheless, PROMs are the best methodology currently available for evaluating diverse aspects of a patient's subjective health status beyond the traditional outcome measures (Campbell et al. 2022). A paper-pencil approach was chosen to collect PRO data of both the FiX and the CogniFit study. This offered benefits such as high compliance rates and accessibility for all patients, regardless of their familiarity with digital technology (Meirte et al. 2020). In consideration of the PROMs used in both studies, the majority of these were in the

form of standardized and previously validated questionnaires (such as the measurement of PTG, CRF, HRQoL, anxiety, depressive symptoms, pain, and sleep; as depicted in section 1.5.1 and section 1.5.2). This ensured that reliable measurements could take place, contributing to valid results. Regarding statistical analyses, all calculations were adjusted for potentially confounding factors. However, not all potential covariates and contributing factors could be assessed. Beside the fact that social support might have been an additional explanatory variable in the context of PTG (in Manuscript I and II), medical characteristics such as tumor stage or the type and number of planned cancer treatment(s) could have influenced the levels of pretreatment CRF in Manuscript III. Despite these limitations, it should be emphasized that throughout all three manuscripts incorporated in this dissertation, advanced statistical techniques were used to facilitate a comprehensive understanding of the research objectives. Multivariate statistical approaches, such as multiple hierarchical and logistic regression analyses, were applied. Where appropriate, bootstrapping techniques were used in the regression analyses to ensure that the study results were as robust as possible regarding potential normal distribution violation.

5.5 Outlook and clinical implications

This section builds on the discussion of the findings within the broader scientific context (sections 5.2 and 5.3) and the outline of the strengths and limitations (section 5.4) of this dissertation. Following a presentation of potential future developments for PRO(M) research, it aims to highlight clinical implications arising from the results of the manuscripts included in this dissertation.

Although PROs are being utilized more frequently in research, further efforts are required to incorporate them into standard clinical care. It has been shown that the integration of digital ePROMs into clinical practice has the potential to facilitate regular assessments and monitoring of common, cancer-related symptoms (Yamaguchi et al. 2024). Further, recent studies have demonstrated that ePRO systems may serve as an educational resource to increase patient engagement, empowerment, and self-management (Covvey et al. 2019; Yamaguchi et al. 2024). These findings are underlined by results of Purcell et al. (2011) who found that an increased symptom knowledge enables patients to adopt a more active role in their disease management. Therefore, regular ePRO assessments in clinical practice could offer approaches to increase symptom recognition and interactive care between patient and HCP (Balitsky et al. 2024). In addition, cancer-related side effects could be prevented from becoming chronic, as timely symptom recognition could also lead to timely interventions (Yamaguchi et al. 2024). In view of the findings of Manuscript I, Manuscript III, and the CRF

guideline recommendations, this is of significant interest. While Manuscript I indicated that CRF literacy or education may contribute to higher PTG, results of Manuscript III underscored the recommendations from international guidelines to inform about CRF from the time of a cancer diagnosis onwards to enhance patient self-management (Fabi et al. 2020; National Comprehensive Cancer Network 2023). In light of the clinically relevant symptom burden prior to treatment (Manuscript III), approaches to facilitate the provision of timely interventions seem beneficial.

In addition to the significance of (e)PROMs in the context of monitoring and observing patient symptoms during active treatment, previous studies have acknowledged that further research is required to establish appropriate timeframes for the monitoring of prevalent side effects during the survivorship period (Rubinstein et al. 2017). This is due to the insufficient knowledge about and limited implementation of PROMs during this particular phase of the cancer trajectory (Di Maio et al. 2022; Rubinstein et al. 2017). The results of Manuscript I and II suggested that it may be beneficial to also assess positive long-term consequences of the cancer disease, such as PTG. Moreover, a deeper understanding of the underlying mechanisms that enhance PTG and adaptive coping strategies would be beneficial. This may be particularly relevant because the traumatic experience of cancer is not environmental, but internal in nature and involves an uncertain future rather than a demanding past experience (Kolokotroni et al. 2014). This represents a contrast to other traumatic experiences that have been studied in the context of PTG (Kolokotroni et al. 2014). Considering the limitations of the FiX study mentioned in section 5.4, future studies could assess the development of PTG in cancer survivors starting from the point of cancer treatment completion onwards, with assessments at multiple measurement timepoints. It has been proposed that treatment completion may be an appropriate starting point, as patients are better able to reflect on their experiences after the acute processing phase of the diagnosis (Tedeschi and Calhoun 1996; Tedeschi and Calhoun 2004). Moreover, it could be promising to include both cancer-free survivors and cancer patients, in order to take into account potential variations in PTG development depending on the stage of the disease (Marziliano et al. 2020). In view of the convex association between HRQoL and PTG found in Manuscript II and regarding the inconclusive results observed in recent decades, subgroup analyses, incorporating specific patient characteristics, could prove beneficial in investigating the potentially disparate nature of this association. As indicated by the findings of Manuscript II, men tend to report higher levels of HRQoL than women. At the same time, women tend to report higher levels of PTG (Blickle et al. 2024b). Therefore, one potential approach to such subgroup analyses would be to differentiate according to the patient's sex.

Psychological approaches, containing elements of mindfulness-based interventions and acceptance and commitment therapy, have been found to alleviate cancer-related emotional distress and have yielded a positive impact on PTG and QoL (Casellas-Grau et al. 2014; Tian et al. 2024). More precisely, study results have demonstrated that the development of adaptive coping strategies, for example the constructive rumination of disease-related thoughts, the articulation of internal thoughts, and the concentration on meaningful aspects of patient's lives can be supported by interventions and enhance PTG (Tian et al. 2024). At the same time, such interventions are able to improve (HR)QoL, and therefore, with regard to all manuscripts included in this dissertation, suggest a promising approach to increase the overall well-being of patients and survivors. However, it seems that not all patients might benefit from such interventions to the same extent (Casellas-Grau et al. 2014). Consequently, and suggested by the results of Manuscript I, information about cancer-related side effects such as CRF and its management could serve as an initial (resource-friendly and easily accessible) step towards enhancing every patients' knowledge about the side effects of the disease (Arefian and Asgari-Mobarakeh 2024). This, in turn, may facilitate patient empowerment and potentially pave the way for PTG development (Purcell et al. 2011). Overall, the investigation of PTG in cancer survivors appears to be an evolving research field. As indicated by Manuscript I and II and discussed in section 5.2, emotional distress, pain, CRF, and HRQoL contributed to and were associated with PTG. All factors would benefit from further research regarding their association with PTG. The investigation into these associations should consider the respective non-linear nature, i.e. the log-transformed associations (as illustrated in Manuscript I), or the quadratic association of HRQoL and PTG (as illustrated in Manuscript II). Furthermore, with regard to the latter, prospective research could investigate whether alternative analyses of this association would yield different results. For instance, one option would be to analyze CRF as a predictor of HRQoL, moderated by PTG levels. It could be interesting to explore the potential buffering PTG effects on this robust association, as this may provide valuable insights into the underlying mechanisms. Further research may disentangle the described associations in an even more concrete way, for example by also including the investigation of biological mechanisms contributing to the development of PTG (Sierra-Murguía et al. 2024).

In light of recent CRF research developments, the findings of Manuscript III supported the importance of evolving CRF prediction models, where an overarching analysis of PROs and electronic health records are combined. The objective of such prediction models is twofold: firstly, to provide insights into the underlying mechanisms of CRF, and, secondly, to provide suggestions for appropriate approaches to its management and treatment (Zhang et al. 2024). However, caution has to be taken in clinically applying these models, as their methodological foundation remains limited (Zhang et al. 2024). This is primarily due to the currently limited

understanding of CRF mechanisms and risk factors, as outlined in the Introduction of this dissertation, so that the employment of more accurate CRF prediction models in clinical practice is a subject of ongoing research (Santoso et al. 2022). However, study results such as those presented in Manuscript III are important in order to contribute more data to the development of prediction models for (CRF) symptom burden already from diagnosis onwards. Furthermore, sociodemographic factors, such as younger age and BMI, offer the advantage of providing indications of potential risk factors for CRF without the necessity for direct questioning of the patients. Therefore, when human and time resources are scarce in clinical settings, these characteristics could help HCPs to identify patients who are most likely to be at increased risk of developing CRF. Moreover, the need for timely and regular screening or assessment of CRF from cancer diagnosis onwards was highlighted by the results of Manuscript III. However, to date, there are no concrete recommendations regarding the frequency of CRF screening, the timepoints, and the cut-offs, which are tailored to specific patient and treatment characteristics (Fabi et al. 2020; Howell et al. 2013; National Comprehensive Cancer Network 2023). These unresolved questions are currently being investigated in an ongoing observational and longitudinal study at the German Cancer Research Center Heidelberg and the NCT Heidelberg. Its primary objective is to provide evidence for the design of an effective CRF screening tool for clinical practice (Blickle et al. 2023). Taking the recommendations for CRF management a step further (Fabi et al. 2020; Howell et al. 2013; National Comprehensive Cancer Network 2023), the results of Manuscript III suggested that information about common cancer-related side effects and their management options should be provided in an easily understandable way. Such provision of information and education about CRF from the cancer diagnosis onwards should include physical, emotional, cognitive, and social consequences of CRF. An important pillar in combating CRF is to also support self-management as suggested by the guidelines (Fabi et al. 2020; Howell et al. 2013; National Comprehensive Cancer Network 2023). This may include the use of a CRF symptom and energy management diary, and the encouragement of patients to openly address the symptoms experienced to HCPs (Agbejule et al. 2023; Milzer et al. 2022; Pearson et al. 2023). One example for a self-management tool covering the aforementioned aspects is the *Untire* mobile app to combat CRF (Spahrkäs et al. 2020). It has demonstrated significant improvements in CRF levels of patients using this app over a twelve-week period (Spahrkäs et al. 2020). In view of the findings of Manuscript III, it could be assumed that the implementation of such digital tools may already be beneficial from the point of cancer diagnosis onwards, if supportive care needs due to an augmented symptom burden are identified. Moreover, the findings indicated the need for supportive care from the time of cancer diagnosis, not only for CRF, but also for other common psychological factors, such as anxiety or depressive symptoms. In order to reduce psychological distress prior to treatment, it may

be beneficial to teach patients appropriate coping strategies. It is hypothesized that this approach assists in reducing the subjective symptom experience, thereby enhancing patients' tolerance for the upcoming treatment procedures (Pertl et al. 2014). Furthermore, given that low social support can operate as a concomitant risk factor for potential pretreatment CRF, the delivery of such (educational) training programs in group settings may be a conceivable proposition. Another psychological factor in Manuscript III that was associated with a higher likelihood of clinically relevant CRF before treatment was poor sleep quality. As CBT interventions have indicated that they can largely improve CRF in cancer survivors, and these effects were accounted for mostly by an alleviation of sleep problems, it could be hypothesized that CBT interventions prove beneficial already early in the course of cancer (Greeley et al. 2025).

Beyond that, there is a need to further understand the complex interplay of factors that contribute to the development and persistence of CRF. The use of existing models, such as the 3P model, may guide further interdisciplinary research ideas to identify specific risk factors dependent on patient characteristics (Sleight et al. 2022). More precisely, the in-depth investigation of biomarkers and metabolomics in combination with behavioral (intervention) studies appears to be a promising area for future research, with the potential to enhance the understanding of the underlying CRF mechanisms (Sleight et al. 2022). The findings of Manuscript III indicated that such research should be particularly encouraged with regard to the comprehension of pretreatment CRF.

5.6 Conclusions

In order to ensure the provision of quality cancer management and to measure cancer-related side effects during the patient's journey, which usually begins at the time of diagnosis and continues through the survivorship period, the patient's perspective has become a central component in oncological care (Silveira et al. 2022). To date, significant progress in PRO measurement and assessment have led to a better understanding of both negative and positive cancer-related side effects, such as CRF and PTG. The overarching objective of this dissertation was to gain new insights into the associations of these factors with other important PROs in cancer patients and survivors. In this context, the dissertation contributed to a refined picture of the longitudinal associations between common cancer-related side effects, such as emotional distress, pain, and CRF with PTG in cancer survivors. It also provided new insights into the quadratic and convex association between HRQoL and PTG, and revealed the extent of pretreatment symptom burden with a focus on CRF and its associated factors in breast cancer patients. With the assistance of continuous digital developments and an ongoing

implementation of (e)PROMs into clinical practice, it is anticipated that the understanding of common side effects, their associations, and, consequently, approaches for their alleviation, will continue to develop and improve. Collaborative and interdisciplinary efforts in research and clinical settings may support this, ultimately contributing to better symptom management and overall QoL in cancer patients and survivors.

6 Summary

Patient-reported outcomes (PROs) are subjective statements about a patient's health status, that are made directly by the patient without interpretation by others. PROs can cover the full spectrum of the patient's self-reported data, by providing information of the concomitant symptoms of the cancer and its treatment, as well as well-being in the subsequent survivorship period. In recent decades, PROs have become an increasingly important element in oncology. They provide valuable insights, especially into common, but invisible sequelae, such as cancer-related fatigue (CRF), but also support the understanding of positive long-term effects, such as post-traumatic growth (PTG). To date, despite the fact that PTG has received increasing attention in recent research, associations of PTG with common PROs in cancer survivors are still unclear. Moreover, it appears that PTG may influence patients' HRQoL, but the nature of this relationship remains inconclusive. In addition to PTG as a favorable long-term outcome, investigation into one of the most burdensome PROs in oncology, CRF, has revealed that it rarely appears alone, but in complex and incompletely understood interactions with other (patient-reported) factors. Furthermore, there is evidence that CRF occurs already prior to cancer treatment, but few studies have investigated CRF at this specific time. The overarching aim of this cumulative dissertation was therefore to make novel contributions to the field by providing findings regarding the associations of CRF and PTG with important cancer-related side effects and health related quality of life (HRQoL).

Three scientific publications, based on two research projects, the FiX study and the CogniFit study, were included in this dissertation. The analyses of the FiX study incorporated 1,316 cancer survivors of the 15 most prevalent cancer entities in Germany that were assessed longitudinally at two measurement timepoints. The results of multiple regression analyses of the first manuscript revealed that PTG may be influenced by common cancer-related side effects, such as emotional distress, pain, and CRF, suggesting log-linear determinants of subsequent PTG levels. Furthermore, it appeared that informedness about CRF contributed significantly to the variance explained in PTG (total R^2 = 14.2%), indicating that survivors who felt well informed about CRF exhibited higher levels in PTG compared to those who felt poorly informed about CRF. Secondly, in a further manuscript analyzing the same study population from the FiX study, this dissertation provided support for the hypothesis that the cross-sectional association between HRQoL and PTG may be quadratic, suggesting a convex shape (β = 0.303, p < 0.001, 95% CI [0.002, 0.005]). In addition, this association seemed not to be moderated by CRF. Nevertheless, the results corroborated existing findings that CRF substantially impacts HRQoL levels (β = −0.590, p < 0.001, 95% CI [−0.573, −0.493]). In sum, the findings of Manuscript I and II provided support for the theoretical assumptions regarding

PTG development, that positive and negative consequences can coexist. Thirdly, a manuscript reporting results of the CogniFit study, in which a total of 232 breast cancer patients prior to treatment and 41 healthy controls were analyzed, was included in this dissertation. It revealed significantly higher levels of most symptoms, such as impaired functioning or sleep problems, in patients compared to healthy controls. Further, a substantial part of patients suffered from a clinically relevant pretreatment symptom burden, particularly pretreatment CRF (48.7%). Logistic regression analyses, restricted to the patient sample, indicated that various sociodemographic factors (younger age, obesity, having low social support, having low education), psychosocial factors (high levels of depressive symptoms and anxiety, and lower levels of sleep quality and functioning), and overall health status increased the risk of scoring above the threshold of clinical importance for clinically relevant CRF.

Overall, this dissertation provides new insights into different associations of PROs in two cancer populations. As presented in the first manuscript, longitudinal associations of emotional distress, CRF, and pain with PTG could be revealed, thereby indicating cancer-specific determinants of PTG. The quadratic, albeit rather weak association between PTG and HRQoL found in the second manuscript suggests that higher levels of PTG do not necessarily imply higher HRQoL and that this association exists independently of CRF levels. Moreover, the results of the third manuscript of this dissertation indicate that symptom burden, especially CRF, exist in breast cancer patients already prior to treatment in a clinically relevant severity and is associated with various sociodemographic and psychosocial factors. These results support the recommendations of the international guidelines to screen for and inform about CRF in a timely manner. Consequently, the provision of supportive care for CRF and other prevalent symptoms could be initiated at the time of cancer diagnosis, with the aim of enhancing patients' tolerance for forthcoming treatment procedures. Future research into pretreatment symptom clustering of CRF and into underlying causal mechanisms contributing to PTG may prove beneficial, ultimately enhancing patients’ and survivors’ quality of life by incorporating their perspective through PROs.

7 Zusammenfassung

Patientenberichtete Endpunkte (PROs) sind subjektive Aussagen über den eigenen Gesundheitszustand, die direkt von Patient*innen gegeben werden und ohne Interpretation durch andere erfolgen. PROs reichen von Informationen über mögliche Begleiterscheinungen der Krebserkrankung und ihrer Behandlung bis hin zu Angaben zum Wohlbefinden in der anschließenden Überlebensphase. In den letzten Jahrzehnten haben PROs in der Onkologie zunehmend an Bedeutung gewonnen. Sie liefern vor allem wertvolle Information über häufige, aber unsichtbare Folgeerscheinungen, wie z. B. krebsbedingte Fatigue (CRF), erweitern aber auch das Verständnis über positive Langzeiteffekte, wie z. B. posttraumatisches Wachstum (PTG). Obwohl PTG in der jüngeren Forschung zunehmend Beachtung findet, sind die Zusammenhänge zwischen PTG und krebsspezifischen PROs bei Krebsüberlebenden bislang noch unklar. Zudem scheint es zwar, dass PTG die gesundheitsbezogene Lebensqualität (HRQoL) der Patient*innen beeinflussen kann, aber bisherige Studien liefern widersprüchliche Ergebnisse hinsichtlich der Art dieser Beziehung. Neben PTG als positivem Langzeiteffekt, legen Studien zu einer der belastendsten Krebsnebenwirkungen, der CRF, nahe, dass sie selten allein auftritt, sondern vielmehr in komplexen, bislang unvollständig verstandenen, Wechselwirkungen mit anderen (von Patient*innen berichteten) Faktoren steht. Darüber hinaus deuten bisherige Daten darauf hin, dass CRF bereits vor Beginn einer Krebstherapie auftreten kann, jedoch gibt es bislang nur wenige Studien, die CRF zu diesem spezifischen Zeitpunkt untersuchen. Das übergeordnete Ziel dieser kumulativen Dissertation war es daher, neue Erkenntnisse über die Zusammenhänge von CRF und PTG mit wichtigen krebsbedingten Nebenwirkungen und der gesundheitsbezogenen Lebensqualität (HRQoL) zu gewinnen.

Drei wissenschaftliche Publikationen, die auf zwei Forschungsprojekten basieren, der FiX-Studie und der CogniFit-Studie, sind in die vorliegende Dissertation eingeflossen. In die Analysen der FiX-Studie wurden 1.316 Krebsüberlebende der 15 häufigsten Krebsarten in Deutschland einbezogen, die zu zwei Messzeitpunkten untersucht wurden. Die Ergebnisse multipler Regressionsanalysen des ersten Manuskripts zeigten, dass PTG durch häufige krebsbedingte Nebenwirkungen wie emotionale Belastung, Schmerzen und CRF determiniert werden kann, was auf loglineare Einflussfaktoren auf PTG hinweist. Darüber hinaus zeigte sich, dass die Informiertheit über CRF signifikant zur erklärten Varianz in PTG beitrug (Gesamt-R^2 = 14,2 %), was zeigte, dass Überlebende, die sich gut über CRF informiert fühlten, höhere PTG-Werte aufwiesen als diejenigen, die sich schlecht über CRF informiert fühlten. Zudem unterstützten die Ergebnisse eines weiteren Manuskripts, das dieselbe Stichprobe der FiX-Studie analysierte, die Hypothese, dass der querschnittliche Zusammenhang von HRQoL und PTG quadratisch und konvex zu sein scheint (ß = 0.303, $p < 0.001$, 95% CI [0.002, 0.005]).

Dieser Zusammenhang wurde nicht durch CRF moderiert. Dennoch bestätigten die Ergebnisse bisherige Befunde, dass CRF einen signifikanten Einfluss auf das Ausmaß der HRQoL hat ($\beta = -0.590$, $p < 0.001$, 95% CI [-0.573, -0.493]). Insgesamt lieferten die Ergebnisse von Manuskript I und II Unterstützung für die theoretischen Annahmen zur Entstehung von PTG, dass positive und negative Folgen einer Krebserkrankung koexistieren können. Ein weiteres, drittes Manuskript in dieser Dissertation basierte auf Daten der CogniFit-Studie und analysierte 232 Brustkrebspatientinnen vor Behandlungsbeginn und 41 gesunde Kontrollprobandinnen. Dabei zeigte sich, dass die meisten Symptome, wie unter anderem funktionelle Einschränkungen oder Schlafprobleme, bei den Patientinnen deutlich stärker ausgeprägt waren als bei den gesunden Kontrollprobandinnen. Zudem litt ein erheblicher Anteil der Patientinnen bereits vor der Behandlung unter einer klinisch relevanten Symptombelastung, insbesondere unter CRF (48,7 %). Logistische Regressionsanalysen der Patientinnendaten ergaben, dass verschiedene soziodemografische Faktoren (jüngeres Alter, Übergewicht, geringe soziale Unterstützung, niedriges Bildungsniveau), psychosoziale Faktoren (hohe Depressivitäts- und Angstwerte sowie schlechtere Schlafqualität und Funktionsfähigkeit) und ein reduzierter allgemeiner Gesundheitszustand das Risiko erhöhten, den Schwellenwert für klinisch relevante CRF zu überschreiten.

Insgesamt liefert diese Dissertation neue Erkenntnisse über die verschiedenen Assoziationen von PROs anhand zweier Patient*innenstichproben. Basierend auf den Analysen des ersten Manuskripts konnten längsschnittliche Zusammenhänge von emotionaler Belastung, Schmerz und CRF mit PTG identifiziert werden, die somit krebsspezifische Einflussfaktoren auf PTG darstellen. Der im zweiten Manuskript gefundene quadratische, wenn auch eher schwache Zusammenhang zwischen PTG und HRQoL deutet darauf hin, dass höhere PTG-Werte nicht notwendigerweise mit einer höheren HRQoL einhergehen und dass dieser Zusammenhang unabhängig von CRF-Werten besteht. Darüber hinaus zeigten die Ergebnisse des dritten Manuskripts dieser Dissertation, dass die Symptombelastung, insbesondere CRF, bei Brustkrebspatientinnen bereits vor der Behandlung in einem klinisch relevanten Ausmaß vorliegt und mit verschiedenen soziodemografischen und psychosozialen Faktoren zusammenhängt. Diese Ergebnisse stützen die Empfehlungen internationaler Leitlinien, CRF frühzeitig zu erfassen und darüber aufzuklären. Dadurch könnte bereits zum Zeitpunkt der Diagnose mit supportiven Maßnahmen bei CRF und anderen Symptomen begonnen werden, um die Toleranz gegenüber anstehenden Therapien zu erhöhen. Zukünftige Forschung zu Symptomzusammenhängen von CRF vor Behandlungsbeginn sowie zu zugrundeliegenden kausalen Mechanismen, die zu PTG beitragen, könnten vielversprechend sein und letztendlich zu einer Verbesserung der Lebensqualität von Patient*innen und Überlebenden beitragen, indem ihre Perspektive durch PROs einbezogen wird.

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9 Personal contribution to data acquisition, data assessment, and publications

My personal contribution to the three publications included in this cumulative dissertation is declared in detail in the following. Overall, the contribution was significant in all three publications. The main responsibilities comprised the analysis of data and the composition of manuscripts. The following paragraphs provide detailed information on the involvement in the various stages of the research process.

Blickle, P., Schmidt, M. E. and Steindorf, K. (2024). **Post-traumatic growth in cancer survivors: What is its extent and what are important determinants?** Int J Clin Health Psychol *24 (1),* 100418, doi: 10.1016/j.ijchp.2023.100418.

Following a comprehensive literature research on the subject of PTG and its research gaps, the design and the concept of Manuscript I was developed by me. Through continuous scientific dialogue with the other two authors of the manuscript, the concrete research questions and specific contents were further refined. As the data collection for the FiX study had already been completed by the time I started my position as a doctoral candidate, I did not participate in the ethics application, the study's setup, or the data collection process. However, I contributed to the finalization of the database and conducted all statistical analyses necessary to answer the research questions. Furthermore, I was responsible for the interpretation of all statistical results and the scientific exchange regarding the discussion of the results with the co-authors. The initial manuscript was drafted by me, including the preparation of the tables and figures of the manuscript, and subsequently revised following feedback from the co-authors. Finally, I was responsible for the entire submission and revision process, supported by the co-authors.

Onyedibe, M. C.*, Blickle, P.*, Schmidt, M. E. and Steindorf, K. (2024). **Posttraumatic growth and health-related quality of life in cancer survivors: Does fatigue moderate the link?** Stress Health *40 (2),* e3299, doi: 10.1002/smi.3299.

*shared first authorship

The conceptual framework and design of Manuscript II were developed in conjunction with Dr. Onyedibe and Dr. Schmidt. Through continuous scientific dialogue with all authors of the manuscript, the concrete research questions and specific contents were further refined. As the data collection for the FiX study had already been completed by the time I started my position as a doctoral candidate, I did not participate in the ethics application, the study's setup, or the data collection process. With regard to the statistical analyses, I provided support to Dr. Onyedibe in conducting the analyses necessary to address the respective research questions, and I undertook a number of analyses independently. The interpretation of the statistical analyses was led by myself, with the valuable feedback of all contributing authors. Drafting the manuscript was shared equally between the two first authors, with me leading the scientific discussions within the author team and contributing significantly to the discussion section. Subsequent to the submission of the manuscript, I was responsible for the majority of the external peer review process, which also included addressing the comments of the reviewers.

Blickle, P., Schmidt, M.E. and Steindorf, K. (2025). **Pretreatment Fatigue in Breast Cancer Patients: Comparison with Healthy Controls and Associations with Biopsychosocial Variables**. Cancer Med *14 (1)*, e70404, doi: 10.1002/cam4.70404.

The conceptualization and design of Manuscript III was developed by the study team and realized by Dr. Schmidt and me. The corresponding literature research was conducted by me, with an ongoing scientific dialogue with the other two authors. As the data collection for the CogniFit study was already ongoing when I started my position as a doctoral candidate, I did not participate in the ethics application, the study's setup, or the data collection process. However, I contributed to the data finalization of the database of the first measurement timepoint, and conducted all statistical analyses to answer the defined research questions. Furthermore, the responsibility for interpreting all statistical results, preparing the tables and figures displayed in the manuscript, and facilitating the scientific exchange to discuss the results with the co-authors, fell upon me. The initial manuscript was drafted by me and supported by valuable feedback from the co-authors. The submission process was managed by me, including the incorporation of revisions received after external peer review.

Further manuscripts and publications were created during my time as a doctoral candidate, to which I made significant contributions. These manuscripts were not incorporated into this cumulative dissertation, but cited:

- Schmidt, M.E., Blickle, P. and Steindorf, K. (2022). **Cancer-related fatigue: Identification of hallmarks to enable refined treatment approaches**. Psycho-Oncology *31 (12),* 2169-2176, doi: 10.1002/pon.6061.
- Blickle, P., Haussmann, A., Holzner, B., Berger, A. K., Steindorf, K. and Schmidt, M. E. (2023). **Providing the basis for a patient-centred and effective screening for cancer-related fatigue (MERLIN study): design of a longitudinal observational study**. BMJ Open *13 (9)*, e073802, doi: 10.1136/bmjopen-2023-073802.
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10 Curriculum Vitae

Personal Information

Name	Patricia Blickle
Date of Birth	11 June 1994
Place of birth	Saarbrücken, Germany
Nationality	German

University Education and academic degrees

01/2022 – present	University of Heidelberg, Germany Doctoral Candidate (Dr. sc. hum)
10/2019 – 12/2021	University of Cologne, Germany Master of Science, Psychology
10/2015 – 04/2019	Saarland University, Germany Bachelor of Science, Psychology

Professional Employment

01/2022 – present	German Cancer Research Center (DKFZ) Heidelberg, and National Center of Tumor Diseases (NCT), Heidelberg, Germany *Doctoral Candidate*
08/2020 – 12/2021	University Hospital Cologne, Department of Psychiatry and Psychotherapy; Center for memory disorders, Cologne, Germany *Research Student*
07/2019 – 08/2019	BG Nordsee Rehaklinik, department of psychosocial counseling, St. Peter Ording, Germany *Intern*
11/2015 – 07/2017 12/2017 – 03/2019	SaarLB – Landesbank Saar, HR department, Saarbrücken, Germany *Working student*

Additional Training

03/2024 – 04/2024	Yoga und Krebs, Cologne, Germany *Advanced Yoga teacher training focusing on needs of cancer patients*
02/2023 – 12/2023	International Society for Systemic Therapy e.V., Heidelberg, Germany *Training in Systemic Therapy and Counseling*
05/2019 – 06/2019	Bali Yoga School, Ubud, Indonesia *Yoga Teacher training, 200hrs*

Awards

01/2025	EORTC Quality of Life group *Travel grant for attendance of the EORTC Quality of Life in Cancer Clinical Trials Conference*
02/2024	Kammler Academy, Yoga und Krebs *Scholarship for an advanced Yoga Teacher Training to specialize in the treatment of cancer patients*
09/2023	Congress of the Psycho-Oncology Working Group of the German Cancer Society (DKG) *Poster Prize*

11 Acknowledgements

After three years of working as a PhD student in the Division of Physical Activity, Prevention, and Cancer at the German Cancer Research Center, I am thrilled to have completed my dissertation, marking the end of this phase in my life.

Moving to Heidelberg in January 2022 to start my PhD was an exciting step after finishing university. I was really looking forward to it, although I wasn't really sure what would wait for me. However, the welcoming and caring atmosphere in our team and the people I have met here have made it easy for me to arrive at this place I now call home and to find my way through the different ups and downs throughout the last years.

First of all, I would like to thank my supervisor Prof. Dr. Karen Steindorf for allowing me to start this journey at her division, for providing guidance and support whenever I needed it the most, and for trusting always in my abilities and encouraging me to do so as well. Further, I would like to thank Dr. Martina Schmidt for helping me find my way through the - sometimes confusing - jungle of data analysis, for her support in any study management regards and for encouraging me and others to implement our research results in clinical practice. This dissertation would not have been feasible without you both and I am very much looking forward to continuing to work with you!

Furthermore, I would like to thank all my colleagues and PhD fellows in our division. Thank you for always making sure that 1) I consume enough coffee (Marlena, Alex, Alina), 2) I eat enough chocolate (Truong, Julian), but also enjoy the Obstzeit (Truong), and 3) I don’t forget to also enjoy the cultural highlights in Heidelberg (Mona).

Last but not least, I would like to express my gratitude to the most important people in my life: Thank you, Mama & Papa, for believing in me and supporting me unconditionally, thank you Robin, Hanni & Paul, for always standing aside and behind me at the same time, and thanks to all 5 of you for being my home. A special thanks to Luca, for being my everyday highlight and for supporting me in so many regards, and to Franzi and Jana, for being my rocks in the waves since so many years. Further, a big thank you to all my friends in and out of Heidelberg who make my life so joyful, colorful, and exciting and who remind me daily of the most important things in life.

Each and every one of you has helped me to follow this path and to complete this dissertation project - and I could not be more grateful.

12 Eidesstattliche Versicherung

1. Bei der eingereichten Dissertation zu dem Thema

OVERARCHING ANALYSES OF PATIENT-REPORTED OUTCOMES IN VARIOUS CANCER PATIENT POPULATIONS

handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

3. Die Arbeit oder Teile davon habe ich bislang nicht an einer Hochschule des In- oder Auslands als Bestandteil einer Prüfungs- oder Qualifikationsleistung vorgelegt.

4. Die Richtigkeit der vorstehenden Erklärungen bestätige ich.

5. Die Bedeutung der eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unrichtigen oder unvollständigen eidesstattlichen Versicherung sind mir bekannt. Ich versichere an Eides statt, dass ich nach bestem Wissen die reine Wahrheit erklärt und nichts verschwiegen habe.



Heidelberg, 03.03.2025 _____

Ort und Datum Unterschrift

13 Angaben zu verwendeten KI-basierten elektronischen Hilfsmitteln

Zur Dokumentation der verwendeten Hilfsmittel ist der schriftlichen Ausarbeitung ein besonderer Anhang hinzugefügt, der eine Liste und Beschreibung aller verwendeter KI-basierter Hilfsmittel enthält. Der besondere Anhang zur Dokumentation der verwendeten Hilfsmittel erfüllt folgende Kriterien:

1. Auflistung der Ziele, für die die KI-basierten Hilfsmittel in der vorliegenden Arbeit eingesetzt wurden.
2. Dokumentation der Verwendungsweise der KI-basierten Hilfsmittel.
3. Nennung der Kapitel und Abschnitte der vorliegenden Arbeit, in denen die KI-basierten Hilfsmittel eingesetzt wurden, um Inhalte zu erzeugen.

Der Gebrauch dieser Hilfsmittel inklusive Art, Ziel und Umfang des Gebrauchs wurde mit meiner offiziellen Betreuerin, Frau Prof. Dr. Karen Steindorf, abgesprochen.

Mir ist bewusst, dass insbesondere der Versuch einer nicht dokumentierten Nutzung KI-basierter Hilfsmittel als Täuschungsversuch zu werten ist:

Gem. § 16 Abs. 2 der Promotionsordnung „Dr. med. / dent.“: „Ergibt sich vor Aushändigung der Promotionsurkunde, dass der Kandidat/die Kandidatin bei einer Promotionsleistung getäuscht hat, so können einzelne oder alle Promotionsleistungen für ungültig erklärt werden. In schweren Fällen kann die Zulassung zum Promotionsverfahren zurückgenommen werden.”

Und § 16 Abs. 2 der Promotionsordnung „Dr. sc. hum.“: „Ergibt sich vor Aushändigung der Promotionsurkunde, dass der Doktorand / Doktorandin bei einer Promotionsleistung getäuscht hat, so kann der Promotionsausschuss diese Promotionsleistung oder alle bisher erbrachten Promotionsleistungen für ungültig erklären. In besonders schweren Fällen kann der Promotionsausschuss die Annahme als Doktorand / Doktorandin endgültig widerrufen.



Heidelberg, 03.03.2025 _____

Ort und Datum Unterschrift

Anhang zur Dokumentation der verwendeten KI-basierten elektronischen Hilfsmittel

Dieser Anhang zur Dokumentation der verwendeten Hilfsmittel enthält eine Liste und Beschreibung aller verwendeter KI-basierter Hilfsmittel. Er erfüllt folgende Kriterien:

1. **Auflistung der Ziele, für die die KI-basierten Hilfsmittel in der vorliegenden Arbeit eingesetzt wurden:**
    - Literaturrecherche (perplexity.ai)
    - Optimierung/Korrektur englischer Sätze (deepL write)

2. **Dokumentation der Verwendungsweise der KI-basierten Hilfsmittel:**
    - Gezielte Suche nach einzelnen Papern mithilfe von perplexity.ai
    - Anpassung englischer Formulierungen durch Überprüfung eigener Sätze in deepL write

3. **Nennung der Kapitel und Abschnitte der vorliegenden Arbeit, in denen die KI-basierten Hilfsmittel eingesetzt wurden, um Inhalte zu erzeugen:**
    - Kapitel 1.1.–1.5. sowie Kapitel 5.1–5.5.: sprachliche Anpassungen/Optimierungen mithilfe von deepL write
    - Kapitel 1.1. und Kapitel 5.5.: gezielte Literaturrecherche von Papern mithilfe von perplexity.ai



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