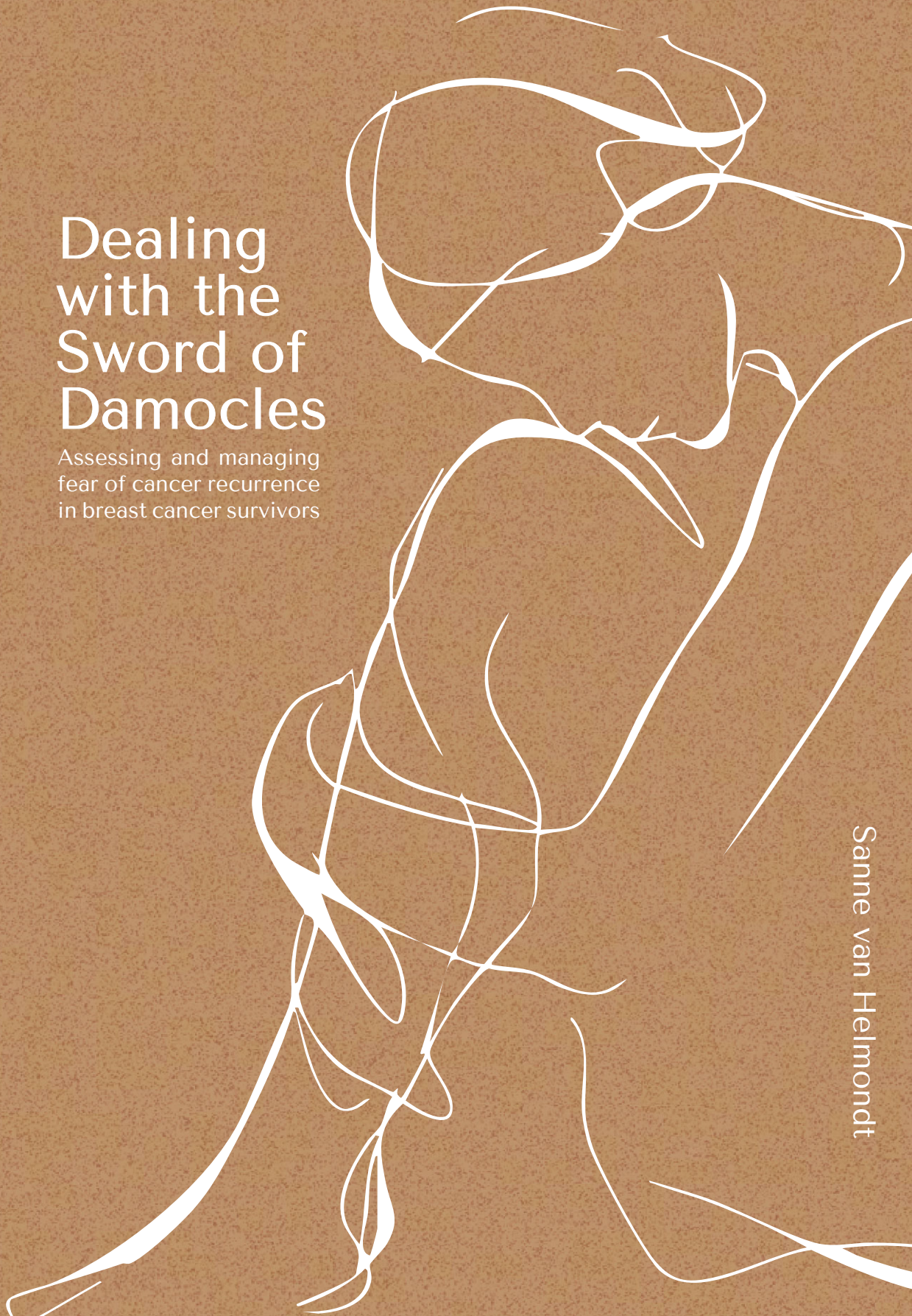
Dealing with the Sword of Damocles

Assessing and managing fear of cancer recurrence in breast cancer survivors



Sanne van Helmondt

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“It does not matter how slowly you go, so long as you do not stop.”
– Confucius

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General introduction

Fear of cancer recurrence

Cancer refers to a large group of diseases that can start in almost any organ or tissue of the body, which is characterized by the development of abnormal cells that divide uncontrollably and have the ability to infiltrate and destroy normal body tissue and to spread to other parts of the body.[1] Cancer has a high incidence of more than 115.000 new patients each year in the Netherlands for all cancer diagnoses, and the number one cause of death in the Netherlands (in 2020).[2, 3] Advances in cancer screening, detection, and treatment have resulted in a significantly improved survival of cancer patients.[2, 4] In the Netherlands, 65% of the patients diagnosed with any cancer are living five or more years beyond their diagnosis.[2] Breast cancer is the most prevalent cancer type among women in the Netherlands.[5] The survival of breast cancer patients is considerably higher than in the total cancer sample: 88% of the patients diagnosed with breast cancer are living five or more years beyond their diagnosis.[5]

As a result, there is a large and increasing group of breast cancer survivors that have to cope with the long-term consequences of cancer. Fear of cancer recurrence (FCR) is one of the most common long-term psychological consequences of surviving (breast) cancer.[6, 7] The threat of cancer recurrence is often metaphorically referred to as the "Sword of Damocles", which hangs over the head of cancer survivors and their families for the rest of their lives.[8, 9] Originally, FCR was defined by Vickberg (2003) as "the fear that the cancer will return or progress in the same organ or in another part of the body".[10] Because this definition did not refer to the multidimensional nature of FCR, a new expert-based definition FCR was proposed in 2016: "fear, worry, or concern about cancer returning or progressing".[11, 12] This new definition of FCR reflects the broad spectrum in which patients experience FCR.[12] FCR is a normal reaction to the cancer experience which at a certain point becomes problematic or pathological.[12]

Studies about FCR prevalence are inconclusive; a systematic review reported 39 to 97% of cancer survivors have some level of FCR, 22 to 87% have a moderate to high level of FCR, and 0 to 15% have a high level of FCR.[13] In a recently published sizeable individual participant data meta-analysis, Luigjes et al. (2022) reported that many (42%) breast cancer survivors experience some FCR, and that a substantial proportion (22%) experiences a high level of FCR.[14] In younger (15-39 years at cancer diagnosis) cancer survivors FCR is experienced more often; a systematic review reported 29 to 85% have some degree of FCR, 31 to 49% have a moderate to high level of FCR, and 13% to 62% have high level of FCR.[15] In younger (18-45 years) survivors of early-stage breast cancer, clinical levels of FCR were reported in 70%.[16] High levels of FCR may negatively affect mood, quality of life, health outcomes, self-examining-, cancer-screening-, and follow-up behavior, and may increase healthcare use and costs.[13, 16–20] FCR can be triggered by internal triggers, including pain, physical symptoms, treatment side effects, fatigue, and changes in appearance, or by external triggers such as doctor appointments,

hearing about someone else having cancer, and annual mammograms.[13, 19, 21, 22] Fear of cancer recurrence (FCR) is considered the most common unmet need among cancer survivors.[13, 23–25]

Duration and course of FCR

As mentioned above, FCR is a long-term psychological consequence of surviving (breast) cancer and cancer survivors still suffer from FCR many years after the initial diagnosis.[6, 26–29] To date, there is consensus that FCR, without any intervention, is relatively stable over time; levels of FCR in long-term cancer survivors are comparable to those of short-term survivors.[6, 13] The vast majority of cross-sectional studies exploring the relationship between FCR severity and time since diagnosis or cancer treatment in breast cancer survivors did not find a significant relationship, which means that FCR remains stable over time.[13] This finding was confirmed by longitudinal studies assessing the course of FCR in breast cancer patients within periods ranging from three months to six years: five studies found no change over time [13, 30–34], and seven studies found a decrease of FCR after the diagnosis or cancer treatment, and a stable course on the long-term.[7, 13, 27, 35–39]

Recently, an increasingly number of papers about classes and trajectories in FCR have been published.[7, 40–47] The number of classes and trajectories in these studies range from one to eight, and all studies reported different combinations of FCR trajectories. [7, 40–47] Some trajectories were repeatedly reported, such as stable low[42, 47] and stable high FCR trajectories. [7, 42, 43, 47] But mostly, the results of these studies were inconsistent. Also, comparison of these studies is hampered by the use of different study designs, for example duration of the studies, outcome measures, and statistical methods. Therefore, there is a need for research about FCR classes and the course of FCR. Knowledge about classes and trajectories can contribute to development and improvement of tailored interventions for FCR. Moreover, trajectories could be used in intervention studies to determine which patients benefit most from the intervention.

Theoretical frameworks of FCR

Before the start of this project, the research on theoretical frameworks of FCR was scarce. The most prominent theoretical framework for conceptualizing FCR was, and still is, an adaptation of Leventhal's Common-Sense Model of Illness by Lee-Jones and colleagues.[11, 48] Therefore, this model was used as the theoretical framework in the present study.

Leventhal's Common-Sense Model of Illness was originally proposed to help understand adherence to treatment regimens, and as a side issue, their model may be useful both for conceptualizing and intervening in psychological problems, such

as panic disorders and hypochondriasis.[48] In short, the model proposes that every individual has an illness representation, triggered by identifying somatic experiences, or symptoms, and interpreting somatic sensations by using cognitive ("objective") and emotional ("subjective") processing systems.[48] When there is an illness threat, these cognitive and emotional processing systems act in parallel to inform the person how they should act, through the procedures they use for coping with threats and feelings, and the criteria they use to evaluate the coping outcomes.[48] Representations, coping procedures, and evaluation criteria are affected by self and social context, and may be inaccurate.[11, 48] Leventhal's Common-Sense Model of Illness is not cancer or FCR specific.

Lee Jones and colleagues adapted Leventhal's model to a theoretical model to help understanding FCR.[11] Their visual representation of this model can be found in Figure 1. In their model, it was hypothesized that a person's fear of recurrence will vary depending on his/her illness representation.[11] Lee-Jones and colleagues proposed their framework based on the available literature, beginning with triggers (or antecedents) of FCR, which can lead to its consequences through certain cognitions, beliefs and emotions. Triggers include internal cues, such as somatic stimuli which can be interpreted as symptoms or indicators of cancer recurrence, and external cues, such as hospital appointments, chance exposure to magazine articles related to cancer, or concerned family members. Lee-Jones and colleagues state that FCR consists of cognitions, beliefs, and emotions. **Cognitions** include a patient's past experience with cancer and its treatment, a patient's knowledge base about cancer, and doubts about the elimination of the cancer. These cognitions form the patient's perception of his/her personal risk to a recurrence. Patients who **believe** themselves to be at higher risk of the cancer returning will have **emotions** like (worrying) thoughts about recurrence of the disease, anxiety about cancer itself, and remorse over not opting for more aggressive treatments in the past. These cognitions, beliefs, and emotions cause a fear response: FCR. Possible consequences of high fear of recurrence include behavioral responses, such as (excessive) body checking for signs or symptoms of cancer, seeking advice and reassurance, and limited planning for the future. Psychological consequences include misinterpretation of neutral bodily symptoms, an increase in somatic anxiety and increased propensity to panic attacks. This theoretical framework for conceptualizing FCR from Lee-Jones and colleagues is most often cited and forms the basis for several measures and interventions for FCR, as well as for the current project (some examples in the references).[49–54] In this dissertation, the theoretical framework was used for developing a new intervention for FCR, see chapters 4-6.

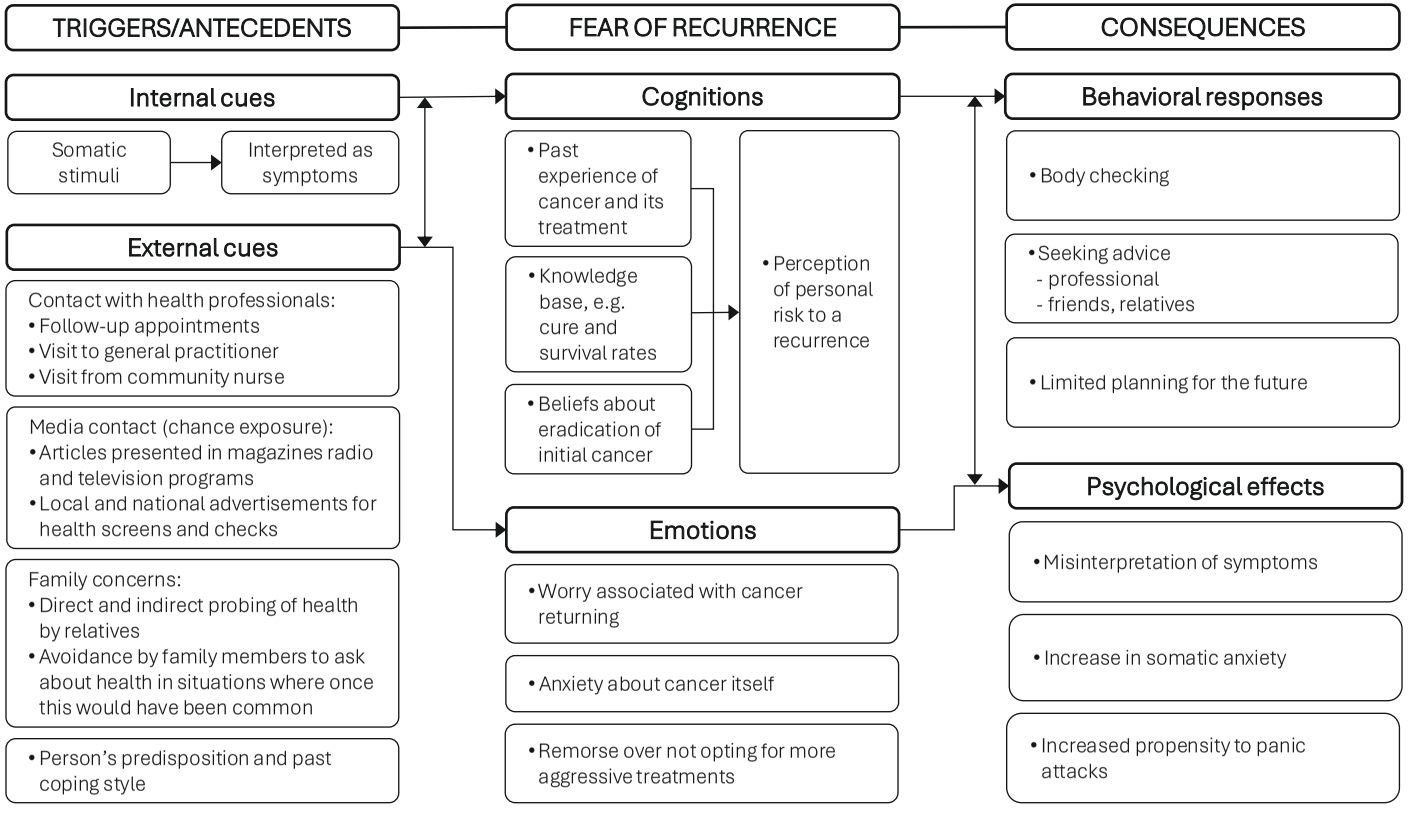

Figure 1. Lee-Jones' adaption of Leventhal's Common-Sense Model of Illness to a theoretical model for conceptualizing fear of cancer recurrence. Adapted from Lee-Jones et al., 1997.

Years later, some new theoretical frameworks for conceptualizing FCR were developed, some based on Leventhal's Common-Sense Model and often attuned to the focus of the researchers.[55–58] These new theoretical frameworks for conceptualizing FCR will not be discussed in detail, because this dissertation is based on the adaptation of Leventhal's Common-Sense Model by Lee-Jones.[11, 48]

Factors correlated with fear of cancer recurrence

There is a growing number of studies on factors that are relevant to the development process of FCR, such as correlates or predictors. Identifying and understanding potential risk factors for developing FCR is important, for example for the development of interventions to prevent or reduce FCR. Figure 2 gives an overview of factors that are investigated in relation to FCR. The factors are classified into several groups (i.e., demographic factors, medical and treatment related factors, physical factors, psychosocial factors, coping, quality of life, and healthcare factors) according to conceptual similarity. A comprehensive enumeration of all factors is described in this paragraph.

Demographic factors

Concerning demographic factors, age is the most evident factor associated with FCR. There is strong evidence for this relationship, indicating that younger age is associated with higher FCR, in both mixed and breast cancer samples. [6, 13, 22, 59–63] There is limited evidence for the association of FCR with partnership, children, and parenting stress.[6, 22, 59] Cancer survivors who have a partner report less FCR than those without a partner, and cancer survivors with children (regardless of their children's age) or parenting stress have higher FCR than those without.[6, 22, 59] For all other demographic factors investigated, there is no association with FCR or the evidence is inconsistent.[6, 7, 13, 22, 29, 59, 61, 62, 64]

Physical, medical and treatment related factors

Concerning physical factors, poorer general health is related to higher levels of FCR, as well as more frequent or a higher number of physical symptoms.[6, 13, 22, 29, 62] Moreover, there is limited evidence that experiencing new or ongoing medical side effects is associated with greater FCR.[6, 13, 22, 29] For example, neurotoxic and severe surgical side effects are significantly correlated with higher FCR.[61, 62]

Concerning medical factors, menopausal status is the only factor associated with FCR. There is moderate evidence that menopausal status is negatively associated with FCR.[13, 29] Although this seems to be in line with the negative association between age and FCR, this needs to be interpreted with caution because the confounding effect of age was not explored.[29]

Concerning specific physical symptoms, there is strong evidence that fatigue and pain are positively associated with FCR, although a small number of studies find them to be unrelated.[13, 29, 60, 62] The evidence for the association between FCR and comorbidities, cancer stage or cancer severity, and treatment type (e.g., chemotherapy, radiotherapy, surgery) is inconsistent; some studies report no relationships while others find a positive relationship for these factors with FCR. [6, 7, 13, 22, 29, 59–62, 65, 66] Likewise, for time since diagnosis, most studies report no significant association between time since diagnosis and FCR, while some other studies report fewer years of survivorship contributing to higher levels of FCR.[6, 22, 29, 59, 60] For other factors, such as length of treatment and a family history of (breast) cancer, no association with FCR is found.[13, 29, 61]

Psychosocial factors

Several psychosocial factors have an association with FCR. Psychological distress and psychological morbidity are associated with higher FCR, and change in distress levels predicted FCR severity over time.[13, 15, 22, 29, 59, 60, 67] Also, family distress is positively associated with FCR and concurrent family stressors are predictive of elevated FCR.[6, 22] Furthermore, anxiety, anxiety disorders (including generalized anxiety disorder and post-traumatic stress disorder symptoms), and cancer specific anxiety are positively associated with FCR.[6, 13, 29, 60, 61] Contradictory, uncertainty and rumination are negatively associated with FCR.[6, 60] A recent review stated that FCR, although associated with various forms of anxiety, is an independent phenomenon.[59]

Risk perception is significantly associated with FCR; patients who overestimate their risk of recurrence report greater FCR than patients who underestimate their risk of recurrence.[13, 22, 29, 61] Furthermore, illness perceptions, including perceptions of more severe consequences and stronger emotional representations, are associated with FCR, as well as conceptualizing cancer as a chronic illness.[22] Also, body image or appearance is positively associated with FCR.[13, 29] Optimism, self-esteem, and sense of coherence are negatively associated with FCR and the first two are a predictor of lower FCR over time.[6, 13, 22, 29, 60, 62] Concerning personality, neuroticism is positively associated with FCR.[6, 22, 60, 62]

Inconsistent evidence is found for low mood and depression, some studies found a positive association with FCR, while other studies found them to be unrelated.[13, 22, 29, 60, 61] Also findings concerning social support are inconclusive; some studies report that social support is negatively associated with FCR, while others (including one review) found that social support and FCR are unrelated.[6, 13, 22, 29, 59–62] Patients who experience less social support and the lack of important dialogue are associated with higher FCR.[59, 62]

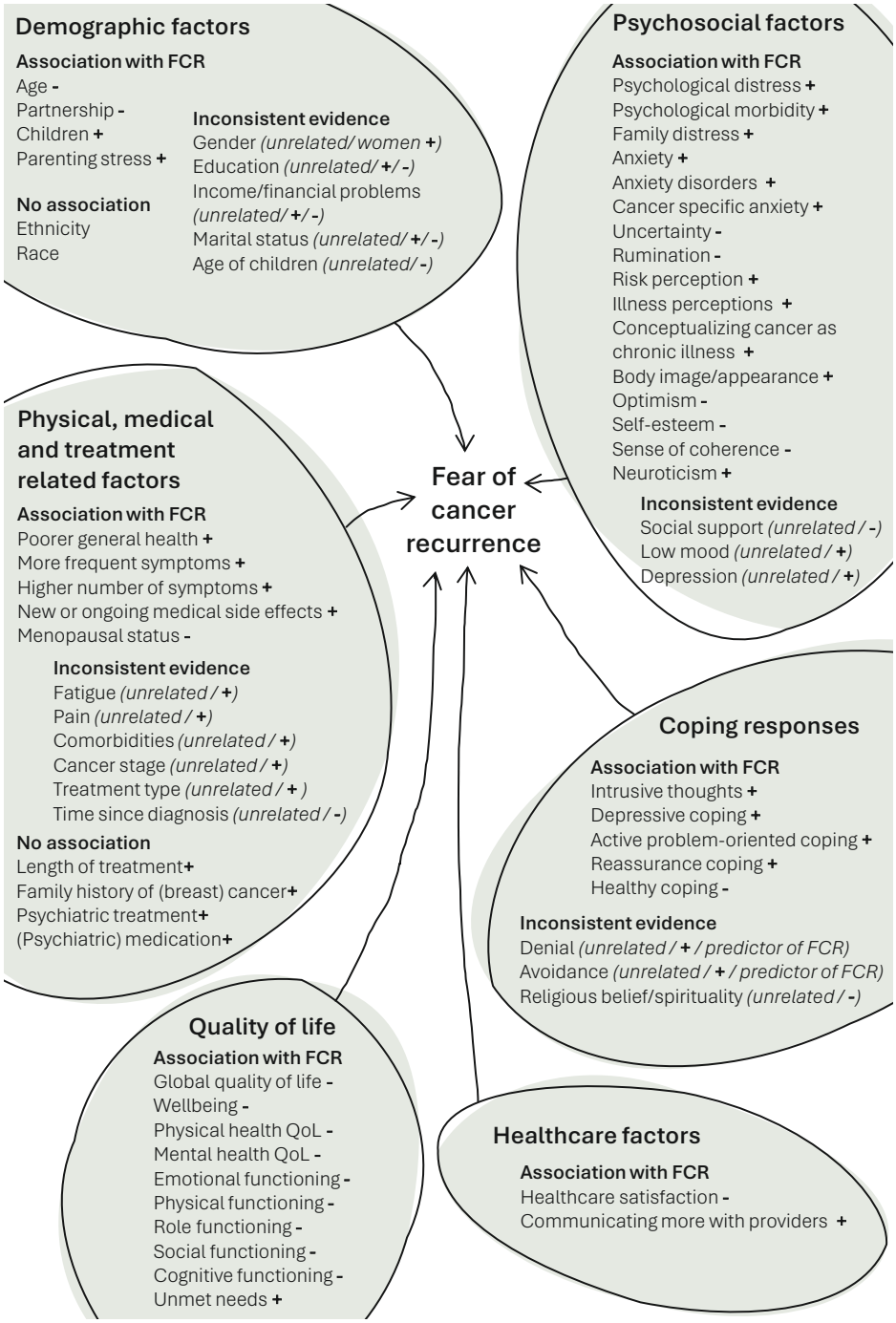

Figure 2. An overview of factors that are investigated in relation to fear of cancer recurrence. + positive association, - negative association, unrelated: no association, FCR: fear of cancer recurrence.

Coping responses

Concerning coping responses, only healthy coping is related to lower levels of FCR.[62] Furthermore, intrusive thoughts and cognitions, depressive coping, active problem-oriented coping and reassurance coping are positively associated with FCR.[6, 13, 22, 60] Inconsistent evidence is found for avoidance and denial; while some studies find a positive association with FCR and that avoidance and denial were a predictor of future FCR, other studies report that they were unrelated.[6, 13, 22, 29, 60] Also for religious belief and spirituality, inconclusive results are reported (both negative associations and unrelated).[13, 29]

Other factors

Furthermore, several factors concerning quality of life and healthcare factors associated to FCR are reported and displayed in Figure 2. These factors are not within the scope of our research and will therefore not be discussed in detail. As you may have noticed, for several factors in Figure 2 the evidence was inconclusive. For these factors, more research may be needed to clarify the association between these factors and FCR.

As described above and showed in Figure 2, there is inconsistent evidence for a considerable number of factors that are investigated in relation to FCR. For most factors, some studies find no relationship, while other studies find a positive or a negative relation between the factor and FCR. We need to perform multiple regression analysis on large datasets, to analyze the combined and independent contributions of multiple potential determinants and get more consistent findings. Moreover, more longitudinal research, for example latent growth curve models (LGCM) or experience sampling method (ESM), is needed, as it will give us more insight into the development of FCR in relation to the risk factors. In this study, we have included some of these factors of which the evidence is inconsistent (i.e., education, depressive symptoms, social support, and treatment type) in our LGCM. Since psychological distress is associated with higher FCR, it is also included in one of our papers. Moreover, since younger age is strongly associated with higher FCR, in this study we investigate a self-help intervention for fear of cancer recurrence aimed at young breast cancer survivors.

Assessment of FCR

Good, concise, reliable and valid measures to assess FCR are needed. For example, to be able to assess the prevalence of the problem and to study the effectiveness of interventions. It is also important to be able to measure what challenges patients face in this area and how they cope, as input for psychological treatment. To date, more than 30 FCR measures have been developed.[13, 68] First, there are FCR-specific subscales of more comprehensive quality of life or psycho-social measures (n=11).[13, 68] Furthermore, there are brief FCR-specific measures, 2 to 10 items, such as the Cancer Worry Scale

(CWS) and the Fear of Recurrence Scale (FRS) (n=17).[13, 68] Lastly, there are longer, multi-dimensional measures of more than 10 items, such as the Concerns About Recurrence Scale (CARS) and the Fear of Cancer Recurrence Inventory (FCRI) (n=4).[13, 68] Many of these measures have limitations, such as limited availability of psychometric data, been used in just one study or a few studies, only available in one language, or cancer site specific, which all results in limited generalizability.[13, 68] Generalizability is important because it allows researchers to make inferences for a broader patient population, by only studying a sample of it. Also, the current lack of gold-standard diagnostic criteria for FCR limits comparison between studies, as well as the capacity to adequately evaluate the criterion validity of the different FCR scales, the development of screening tools for FCR and the development of specific FCR interventions.[68] One study has attempted to establish a clinical cut-off score for the FCRI Severity subscale, by using a face-to-face semi-structured interview of FCR (specially designed for this purpose) as a gold-standard measure.[68, 69] However, although rigorous methodology is used in this study, this diagnostic interview has not been validated.[68, 69] The CARS, FCRI, and CWS are identified as the three most frequently used scales to measure FCR.[10, 70–72]

At the start of this project, Dutch translations of FCR measures were scarce. Because the FCRI was one of the most comprehensive multidimensional FCR measures at that time (and it still is), and already available in several languages, we decided to translate and validate the FCRI for this project.[71] More recently, questions have been raised about the appropriateness of measuring FCR using a multidimensional rather than unidimensional approach.[73] For example, the FCRI consists of seven subscales, including fear, triggers, consequences and coping strategies.[71] Despite the fact that these subscales capture important information, an aggregated score across all subscales represents an uninterpretable combination of concepts.[73] Therefore, a multidimensional questionnaire like the FCRI is best used when you want to know something in a differentiated way about FCR. For example, as input for therapy. The different concepts cannot be combined into a single score. To measure FCR for research purposes, it is better to use a unidimensional questionnaire. Therefore, in this project, we used the severity subscale of the FCRI as the primary outcome measure for FCR. In chapters 2 and 3 of this dissertation, the psychometric qualities of the Dutch version of the FCRI (FCRI-NL) were investigated. In chapters 5 and 6 of this dissertation, we used the severity subscale of the FCRI-NL for evaluation purposes.

Management of FCR

Because high levels of FCR can have a considerable impact on the lives of (breast-) cancer survivors and may reduce quality of life and health outcomes and increase healthcare costs, there is a need for cost-effective interventions to reduce FCR.[13, 17, 20]

In the past years, an increasing number of psychosocial interventions for FCR have been developed, with different treatment methods (e.g., cognitive behavioral therapy (CBT), Mindfulness-Based Stress Reduction (MBSR), meta-cognitive therapy, acceptance and commitment therapy (ACT)) and different delivery methods (e.g., therapist-guided vs. self-management, individual vs. group, face-to-face vs. online/blended).[13, 74, 75] In 2011, Völker and colleagues proposed a stepped-care model for treating FCR, in which normalization, psycho-education and self-management are followed by face-to-face CBT.[76] Recently, a similar but more extensive stepped-care model for managing FCR was proposed.[77] In the first step of this model, oncologists normalize FCR, provide reassurance and accurate prognostic information, and specify the likely symptoms associated with FCR in patients with a "normal" level of FCR.[77] In the second step, patients with mild-moderate FCR are encouraged to follow an efficacious minimal intervention, and in the third step, those with moderate to high symptoms are referred to brief nurse-led interventions.[77] In the fourth step, cancer survivors with a severe level of FCR are referred to face-to-face evidence-based interventions delivered by mental health specialists.[77] Since FCR is common, but only a minority of cancer survivors experience severe FCR, a stepped-care approach may help to prevent sub-clinical FCR from deteriorating into a clinical level of FCR, and at the same time also to reduce costs.

Concerning the effectiveness of interventions for reducing FCR, several systematic reviews and meta-analyses have been published. Three recent papers will be discussed, they include overlapping studies but all have a slightly different focus.[78–80] Tauber and colleagues (2019) found a small but robust effect of psychological interventions for FCR in 23 controlled trials with mixed samples, both immediately after the intervention and at follow-up.[78] Larger effects are associated with shorter time to follow-up and group based formats, and effects of contemporary CBTs are larger than those of traditional CBTs.[78] Traditional CBTs are directed at changing the content of thoughts and behavior, while in the contemporary CBTs the emphasis is more on changing the relation with thought instead of the content of thoughts. Lyu et al. (2022) found similar results in 16 randomized controlled trials (RCTs) with breast cancer samples. They also report that interventions with three to eight sessions are effective, while interventions with nine or more sessions are not.[79] Park and colleagues (2022) found that most interventions for reducing FCR are effective in 17 RCTs with breast cancer samples.[80] RCTs with face-to-face interventions of at least one month seemed to be more effective than those with a brief online or telephone format.[80]

Last years, there was an increase in the use of eHealth, for instance online (guided) interventions, blended interventions, or online self-help programs. However, the effectiveness of online interventions for cancer patients is still unclear.[81] To my knowledge, no systematic reviews or meta-analyses concerning the effectiveness of internet-delivered interventions for reducing FCR in breast cancer patients have been published yet. Some systematic reviews about the effectiveness of internet-delivered

interventions for reducing anxiety in breast cancer patients have been published, but FCR is a construct that is conceptually different from anxiety, so I will not discuss these reviews.[82] Some studies about the effectiveness of internet-delivered interventions for reducing FCR have been published, they have reported some evidence for blended cognitive behavior therapy.[83–85] The only study investigating a self-management intervention is a feasibility study that found that iConquerFear, a five-module self-guided digital FCR intervention, is a feasible and potentially efficacious intervention for reducing FCR in breast cancer survivors.[86]

At the start of this project, in 2013, the literature about interventions for FCR was limited. Some interventions were being developed, but easily accessible and cost-effective interventions were scarce.[13, 74, 75] Therefore, we started the CAncer REcurrence Self-help Training (CAREST) RCT to investigate the effectiveness of an online self-help training based on evidence-based CBT to reduce FCR.

Outline of the dissertation

This dissertation starts with the prevalence, theoretical frameworks, duration and course of FCR, and factors associated with FCR. Moreover, a general overview of assessment methods for FCR and interventions for managing FCR is given. The main objectives of the studies presented in this thesis were to translate the FCRI and investigate its psychometric properties, and to investigate the effectiveness of a CBT-based online self-help training to reduce FCR, compared to care as usual. Therefore, this dissertation consists of two parts.

Part one: Assessment of fear of cancer recurrence
As described above, Dutch FCR measures were scarce at the start of this project. Therefore, in chapter 2, one of the most comprehensively described multidimensional FCR measures at that time, the FCRI, was translated into Dutch. Also, the factor structure and the psychometric properties of the FCRI-NL are investigated. In chapter 3 we aimed to improve the FCRI and its usability through investigating the factor structure. Therefore, we did a comprehensive comparison of the factor structure results of all translations. Moreover, we explored and improved the structure of the Dutch FCRI-NL and tested this new factor structure in two new patient samples.

Part two: Managing fear of cancer recurrence in breast cancer survivors
In the second part of this dissertation, the potential effectiveness of CBT-based online self-help training for FCR is addressed. Chapter 4 describes the study protocol of the CAREST (CAncer Recurrence Self-help Training) trial: a randomized controlled trial (RCT) investigating the effectiveness of CBT-based online self-help training for FCR in Dutch women with curatively treated breast cancer (breast cancer survivors). This chapter includes a short literature overview about FCR and its treatment, the CAREST

study design, and a description of the CBT-based online self-help training for FCR "Less fear after cancer". In chapter 5 the first results of the CAREST trial, the effectiveness of our CBT-based online self-help training to reduce FCR after 3 and 9 months, are described and discussed. Chapter 6 describes and discusses the long-term (24 months) effectiveness of our CBT-based online self-help training to reduce FCR and psychological distress (PD). In this chapter we also evaluate the relation between FCR and PD across time, and we identify subgroups representing different change trajectories in FCR over time and their predictors. In chapter 7 the experiences of Dutch breast cancer survivors with the online self-help training for FCR are qualitatively described, by means of a thematic analysis of facilitators and barriers.

Concluding this dissertation, chapter 8 contains a general discussion of the studies presented in this dissertation and discusses implications for further research. Chapter 9 summarizes the most important findings in both English and Dutch.

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02

Translation and validation of the Dutch version of the Fear of Cancer Recurrence Inventory (FCRI-NL)

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Abstract

Objective

The study objectives are to translate the FCRI in Dutch, and to explore the factor structure and the psychometric qualities of the Dutch translation of the Fear of Cancer Recurrence Inventory (FCRI-NL).

Method

The original French-Canadian FCRI had been forward-backward translated into English by the developers, and this method was also used to translate the English version of the FCRI into Dutch. Patients were recruited via patient organizations between July 2011 and October 2013. To replicate the original 7-factor structure of the FCRI, confirmatory factor analysis (CFA) was performed. To examine the psychometric qualities, reliability (Cronbach's alpha), test-retest reliability (intra-class correlations; ICC), and convergent and divergent validity (Spearman's correlations) were calculated.

Results

From 290 cancer patients, 255 (88%) were eligible for analysis (aged 51.0 ± 9.8 years, 88.6% women). CFA showed a reasonable yet suboptimal fit of the hypothesized model to the data. The FCRI-NL has good reliability (Cronbach's α = .93 for the total scale and α = .75-.92 for the subscales) and test-retest reliability (ICC=.84 for the total scale and ICC=.56-.87 for the subscales). Convergent (r= .53-.66 for the FCRI-NL and r=.48-.57 for the FCRI-SF-NL) and divergent (r= -.20- -.07 for the FCRI-NL and r= -.28- -.17 for the FCRI-SF-NL) validity was demonstrated.

Conclusion

The FCRI-NL seems to have sufficient psychometric properties. However, the FCRI-NL total score should be interpreted with caution. The Severity subscale (FCRI-SF-NL) may be a valuable screening tool for fear of cancer recurrence severity in clinical care.

Introduction

Fear of cancer recurrence (FCR) is one of the most reported long-term consequences of surviving cancer.[1] Elevated levels of FCR represent a continuing problem in cancer patients, for ten years or more after diagnosis.[2–4] In 2015, the International Expert Special Interest Group on FCR (FORwaRdS) redefined FCR as "fear, worry, or concern about cancer returning or progressing", which is broader than previous definitions and more suitable for all types and stages of cancer.[5] This definition also shows that FCR ranges from normal or healthy levels of concerns about cancer recurrence to clinical levels of FCR.[5] Across different cancer types, 39-97% of cancer survivors reported some degree of FCR, 22-87% reported moderate to high degree of FCR and 0-15% reported a high degree of FCR.[6] A growing body of research recognizes FCR as a multi-dimensional construct, including intrusive thoughts, physical sensations, psychological distress, coping strategies, and functioning impairments.[7–9]

Currently, at least 32 assessment instruments for FCR have been developed.[6, 10] Of these, 11 are subscales of comprehensive measures, 17 are brief questionnaires (2–10 items), and four are longer (multi-dimensional) questionnaires (10+ items).[6, 10] However, many of these scales have limited generalizability due to limited psychometric data and/or have been used in few studies.[6, 10] Other limitations are that measures are only available in one language and/or are cancer site specific, which impedes comparison across cancer populations.[6, 10] Currently, the Fear of Cancer Recurrence Inventory (FCRI) is one of the best measures available.[10] The FCRI was developed by a committee of experts in psycho-oncology, based on their definition of FCR, on DSM-IV diagnostic criteria of anxiety and somatoform disorders and on a cognitive-behavioral conceptualization of FCR inspired by the model developed by Lee-Jones et al.[8, 11] The original version of the FCRI was developed in French-Canadian and contains 42 items measuring seven factors (Triggers, Severity, Psychological Distress, Coping Strategies, Functioning Impairments, Insight, and Reassurance).[8] In the initial article it was stated that a higher score on the total scale indicates higher levels of FCR.[8] The FCRI was validated in a sample of 600 participants who had been treated for breast, prostate, lung, or colorectal cancer, and it demonstrated good reliability and validity (reliability Cronbach's $\alpha = 0.95$; test-retest reliability $r\,(287) = 0.89$, $p < 0.001$).[8] The psychometric properties of the English version of the FCRI were similar to those of the original French-Canadian version (reliability Cronbach's $\alpha = 0.96$; test-retest reliability $r\,(135) = 0.88$, $p < 0.001$; ICC = 0.94, $p < 0.001$).[7] Simard and Savard recommend more validation studies in other cultures and languages.[8] Recently, an empirically validated cut-off score was determined for the Severity subscale of the FCRI, making it usable as a short form of the FCRI (FCRI-SF) to screen for clinical levels of FCR.[12] The Severity subscale is strongly associated with the FCRI total score and seems the most accurately representation of FCR severity, the other subscales represent related aspects, such as antecedents (e.g., Triggers), modifiers (e.g., Coping Strategies), or consequences (e.g. Functioning

Impairments), which give important clinical information about FCR.[12, 13] There is some disagreement about the interpretation of the FCRI. While the authors of the original version of the FCRI recommend to measure FCR with the total FCRI scale or use the Severity subscale for screening purposes, Costa and colleagues recommend separate interpretation of the subscale scores.[8, 14]

FORwaRdS recently reported a lack of translations of FCR measures and stated that we need cross-culturally validated measures.[15] To make the FCRI available in Dutch speaking countries, the FCRI was translated into Dutch (FCRI-NL). We will refer to the Dutch translation of the FCRI-SF as FCRI-SF-NL. The present study describes the translation and validation of the FCRI-NL (i) by performing a confirmatory factor analysis (CFA) to investigate whether the multidimensional seven factor structure of the original FCRI could be confirmed and (ii) by assessing internal consistency, test-retest reliability, and convergent and divergent validity of the FCRI-NL and its subscales. We hypothesized that confirmatory analysis would show a good fit and that the FCRI-NL would demonstrate good psychometric qualities.

Method

Translation process

The original FCRI had been forward-backward translated into English by the developers, and this method was also used to translate the English version of the FCRI into Dutch (FCRI-NL).[7, 8] Forward translations were done by two independent native Dutch translators (AV, CV). Semantics of these two versions were evaluated by an expert panel consisting of the two translators and a researcher/psychologist expert in psycho-oncology (all bilingual; two of them had clinical experience in psycho-oncology) (AV, CV, JL). Discrepancies (N=45) between the two translations were discussed and resolved (best translation was selected (N=18) or an alternative translation was proposed (N=27)). Mostly minor modifications were made. One difficult issue and important modification was the Dutch translation of “cancer recurrence”. This term occurs a lot in the questionnaire, therefore many items needed modification. The focus was on clinical meaningfulness rather than literal equivalence. At the end of the expert meeting, a single translation of the FCRI-NL was agreed upon. After the translation of the FCRI-NL was agreed upon, backward translations were made by two independent native English translators blind to the original version (SD, MY). The expert team evaluated the backward translations and four important points were discussed. The first two concerned the lack of backward translation of the word “anxiety”. A possible explanation could be, that there are more words for anxiety in the English language than in the Dutch language. Consensus was reached about this point, all experts agreed that the initial Dutch translation was the best choice. Concerning the third point of discussion, the experts considered a slightly different translation for the word “disrupt”, but eventually they decided the initial translation was better. Regarding

the fourth discussion point they proposed a better translation of item 34 and agreed to use the new translation. Consensus was reached on the final version of the FCRI-NL.

Pilot-testing

The FCRI-NL was pilot-tested in ten patients with different types of cancer receiving therapy at the Helen Dowling Institute for cancer-related psychological distress. Participants were recruited by therapists after their treatment session; they assessed if filling out the questionnaire would not be too stressful for the patients. Written informed consent was obtained from all participants. All participants stated that the questions were clear and understandable. Nine participants had clinical levels of FCR. Participants filled out the questionnaires in a clinical setting, therefore detailed demographic and medical information was not assessed to minimize patient burden. Additionally, two independent members of the Dutch Lymphoma Patients Society (LVN) were asked to provide comments on the questionnaire. They did not report ambiguities either and made some valuable suggestions for adjustments, which were discussed by the expert panel. The expert panel decided to stay as close as possible to the original FCRI. Finally, therapists indicated that the FCRI-NL provided them with valuable information for clinical practice.

Participants

For testing the psychometric properties of the FCRI-NL and the FCRI-SF-NL, patients were recruited with an opt-in recruitment method through an email newsletter from the Dutch Federation for Cancer Patients Organizations, and through websites of the Dutch Lymphoma Patients Society and the Lung Cancer Information Center between July 2011 and October 2013. Inclusion criteria were: 1) any type of cancer diagnoses in the past 10 years; 2) cancer was successfully treated; 3) end of treatment ≥1 years ago; 4) ≥18 years old; and 5) sufficient command of the Dutch language. The exclusion criterion was cancer recurrence.

Materials

At the time of data collection there was no validated measure for FCR available yet. Therefore, we used questionnaires measuring constructs related to FCR, namely several forms of anxiety, for determining convergent validity. Divergent validity was examined using subscales from a measure for personality traits (i.e., extraversion, openness to experience, conscientiousness, and agreeableness), which are presumed to be distinct from FCR.

Fear of Cancer Recurrence Inventory-Dutch version (FCRI-NL).[8] The 42 items are rated on a 5-point Likert scale ranging from 0 (not at all or never) to 4 (a great deal or all the time).[8] The score of item 13 ‘‘I believe that I am cured and the cancer will not come back’’ must be reversed before summation.[8] A total score can be obtained for each subscale and for the total scale by summing the items.[12] In the original version a score of

13 or higher on the Severity subscale (FCRI-short form; FCRI-SF) is an optimal cutoff for detecting the presence of clinically significant FCR (with high sensitivity), which makes it a brief and rapid screening instrument.[12] A cutoff score of 16 or higher is an optimal cutoff for the purpose of differentiating between clinical and nonclinical levels FCR (higher specificity).[12] The FCRI-SF has a strong correlation with the total score of the FCRI (r = 0.84) and it demonstrated good reliability and validity (reliability Cronbach's α = 0.89; test-retest reliability r (287) = 0.80, p < 0.001).[8]

The State Trait Anxiety Inventory, version Dutch Y (STAI-DY).[16, 17] The STAI-DY measures state anxiety and trait anxiety and consists of two 20-item subscales. Each item is rated on a 4-point Likert scale ranging from 0 (not at all/almost never) to 3 (very much so/almost always). The psychometric properties of the STAI-DY are satisfactory. Both subscales of the STAI-DY were used for examining convergent validity.

Profile of Moods States (POMS)-Dutch (shortened version).[18] The POMS-Dutch (shortened version) measures affective mood-states (depression, anger, fatigue, vigor, and tension) and consists of 32 items with a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). The POMS-Dutch (shortened version) has been found to be a reliable and valid instrument. The tension subscale of the POMS was used for examining convergent validity.

Agoraphobic Cognition Questionnaire (ACQ)-Dutch version.[19, 20] The ACQ measures the frequency of certain thoughts concerning negative consequences of experiencing anxiety, and it consists of 14 statements which are rated on a 5-point Likert scale ranging from 1 (thought never occurs) to 5 (thought always occurs). The total score was computed by averaging responses across the individual items. The original ACQ has been found to be reliable. The ACQ was used for examining convergent validity.

The Big Five Inventory (BFI)-Dutch version.[21] The BFI measures the Big Five personality factors and consists of 44 items with a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). The BFI consists of 5 subscales: Extraversion, Neuroticism, Conscientiousness, Agreeableness, and Openness to Experience. The Dutch version of the BFI has been found to be of sufficient psychometric quality. The Neuroticism subscale of the BFI was used for examining convergent validity, and the remaining subscales of the BFI were used for examining divergent validity.

Procedure

Via the e-mail newsletter described in the Participants section, patients could access the questionnaire through a link to the online questionnaire, developed using Qualtrics software. Informed consent was obtained from all individual participants. The questionnaire consisted of demographic information, the FCRI-NL, and measures for validity assessment. To minimize patient burden, and at the same time have enough

different questionnaires to assess both convergent and divergent validity, we randomly selected two (out of six) measures for each participant. For exploring test-retest reliability, participants recruited until 4 October 2011 were invited to complete the FCRI-NL again after two weeks.

Statistical analyses

Descriptive statistics were calculated to describe the sample. Prior to data analysis, all relevant data was screened for normality by looking at skewness and kurtosis values. Z-scores (skewness and kurtosis values divided by standard error) were evaluated to test whether skewness and kurtosis were larger than expected by chance. Z-values of >2 or <-2 were considered a violation of the normality assumption.[22, 23] Furthermore, the data was screened for floor and ceiling effects, which are present if >15% of the respondents achieved the lowest or highest possible score.[24] Significance level was set at 5%.

In order to replicate the original 7-factor structure of the FCRI[8], CFA was performed. As already stated by Lebel et al.[7], the tested model is "a second-order CFA model with three levels: items (42), primary factors (7 subscales), and one secondary factor (FCR)". Goodness of fit was evaluated using the following fit indices: the adjusted goodness of fit index (AGFI); the normed fit index (NFI); the parsimonious normed fit index (PNFI); and the standardized root-mean-squared residual (SRMR).[25] The goodness of fit criteria for each fit index are: AGFI ≥ .90; NFI ≥ 0.95; SRMR ≤ .05.[25] The PNFI is difficult to interpret, because there are no threshold levels reported yet.[25–27] However, the use of a parsimony fit index (such as the PNFI) next to other goodness-of-fit measures is strongly recommended.[25] By default, AMOS uses maximum likelihood estimation to estimate model parameters. This method assumes multivariate normality of the item scores, yet this assumption is likely to be violated given the characteristics of our data. To handle any non-normal item score distributions, we used the scale-free least squares estimation method (also included in AMOS). Although this procedure is robust against violations of multivariate normality, it does not provide some well-known fit indices such as the root mean square error of approximation (RMSEA); the comparative fit index (CFI); and the non-normed fit index (NNFI). Furthermore, it was not possible to improve model fit by freeing parameters in the error covariance matrix, because modification indices were not given by the scale-free least squares estimation method.

Concerning reliability, Cronbach's coefficient alpha's (including confidence intervals) and test-retest reliability were calculated for the FCRI-NL and the subscales. An alpha of ≥.70 was considered acceptable and an alpha of ≥.80 was considered preferable.[28] For assessing test-retest reliability, intra-class correlations coefficients (ICC) were computed between the scores on two different occasions, separated by an interval of two weeks. High correlation coefficients of (ICC ≥.70) were considered sufficient.[29] Construct validity was evaluated by assessing convergent and divergent validity (Spearman's rank-order correlation coefficient). Convergent validity was examined by calculating Spearman's

correlations between the FCRI-NL and FCRI-SF-NL scores and related constructs: the tension subscale of the POMS; the ACQ; the neuroticism subscale of the BFI; and the state and trait anxiety subscales of the STAI-DY. Divergent validity was evaluated by calculating Spearman's correlations between the FCRI-NL and FCRI-SF-NL scores and the extraversion, openness, conscientiousness, and agreeableness subscales of the BFI. Moderate (r =.30-.49) and high (r ≥.50) correlations indicate convergent validity, while small correlations (r =.10-.29) indicate divergent validity.[30]

Analyses were conducted using IBM SPSS 23 for Windows.[31] CFA was conducted using IBM SPSS AMOS 22.[32]

Results

Patient characteristics

Patient characteristics are presented in Table 1. 546 potential participants clicked on the link to the questionnaire. Subsequently, 290 participants completed the FCRI-NL and two randomly assigned questionnaires at baseline (Time-1). Thirty-five participants (12%) reported a recurrence, leaving 255 (88%) participants eligible for analysis. To explore the test-retest reliability, the first 213 participants were invited to fill out the FCRI-NL again after an interval of two weeks (Time-2). Of them, 95 participants (45%) completed the questionnaire within 7-21 days and were eligible for test-retest analysis. Questionnaires that were filled out <7 or >21 days after baseline, were excluded for analysis. Mean time between Time-1 and Time 2 was 16.2 ± 2.0 days (range 13-21). Cancer characteristics were not collected.

Score distribution

Skewness and kurtosis values and z-scores, mean scores and standard deviations (for normally distributed subscales), medians and interquartile ranges (for non-normally distributed subscales), and floor and ceiling effects of the FCRI-NL and its subscales are shown in Table 2. The skewness and kurtosis values, z-scores, and floor and ceiling effects of the items are presented in Supplementary materials 2A. The assumption for normality was violated for 34 items and for the Psychological Distress, Functioning Impairments, Insight, Reassurance, and Coping Strategies subscales of the FCRI-NL. Floor scores were achieved by 45.9% of the participants on the Insight subscale and by 20.8% of the patients on the Reassurance subscale. More specifically, 45.9% of the participants answered "not at all" on all three items of the Insight subscale, indicating that their self-criticism towards FCR intensity is low.

Furthermore, 20.8% of the participants answered "never" on all three items of the Reassurance subscale, indicating that they do not seek reassurance through self-examination or repeated medical consultations. There were no ceiling scores larger than 15% for the subscales. Furthermore, floor scores were achieved by 21 items and

ceiling scores were achieved by 5 items (for details see Supplementary materials 2A). Correlations between the FCRI-NL subscales will not be discussed in the context of this paper, the correlation matrix will be attached for all who are interested (see Supplementary materials 2B).

Table 1. Patient characteristics at baseline a

	n = 255
Age (years)	51.0 ± 9.8
Age (min-max)	26-77
Gender (%)	
Female	226 (88.6)
Male	29 (11.4)
Education (%)	
Primary education	9 (3.5)
Lower General Secondary Education	29 (11.4)
High school, Higher General Secondary Education, pre-university education	21 (8.2)
Community College	75 (29.4)
College	92 (36.1)
University	28 (11.0)
Other	1 (0.4)

[a] Cancer characteristics were not collected.

Confirmatory Factor Analysis

The goodness of fit of the original second-order model was not convincingly confirmed. The model (χ^2 (812) = 1752.6, $p < .001$, χ^2/df = 2.16) showed an AGFI (.93) that meets the criteria for model fit. The NFI (.93) was smaller than the recommended criterion, and the SRMR index (.08) was greater than the recommended criterion, which indicates some misfit in the model. However, when applying older and less strict guidelines (i.e. NFI ≥ 0.90; SRMR ≤ .08), the criteria for model fit would be met.[25] The PNFI (.87) points towards an acceptable model fit. However, this goodness of fit index should be interpreted with caution because there are no strict guidelines reported.[26,27] Altogether, these mixed results suggest a reasonable yet suboptimal fit of the second-order model to the data.[1] The standardized parameter estimates (standardized regression weights and squared multiple correlations) associated with the model structure obtained with AMOS are presented in figure 1.

1 We were not able to improve model fit by freeing parameters in the error covariance matrix ourselves. However, because we were curious what would happen when we added some error covariances to the model, we also did confirmatory factor analysis using the exact models (including error covariances) of the French version (covariances between E2-E3, E9-E10, E15-E16, E22-E23, E39-E40) and the English version (covariances between E2-E3, E5-E6, E13-E14, E22-E23, E29-E30, E31-E32, E34-E35, E39-E40, E41-E42) [S. Simard, personal communication, 8 July 2010]. Results were very similar to the results of our model (French version: χ^2 (812) = 1634.9, AGFI = .94, NFI = .93, SRMR = .08, PNFI = .87; English version: χ^2 (812) = 1533.6, AGFI = .94, NFI = .94, SRMR = .08, PNFI = .87.

Table 2. Descriptive statistics, normality tests, and floor and ceiling scores [a]

FCRI-NL factors	Number of items	Score range	Normality test				Mean (SD) [c]		Median (IQR) [c]		Floor score [d]	Ceiling score [d]
				Time-1	Time-2	z-score [b]	Time-1	Time-2	Time-1	Time-2	Time-1 (%)	Time-1 (%)
Triggers	8	0-32	*Skewness*	-.112	.153	-.732	17.2 (6.3)	16.4 (6.4)	-	-	.4	.8
			Kurtosis	-.168	.304	-.553						
Severity / FCRI-SF-NL	9	0-36	*Skewness*	-.257	.153	-1.680	19.5 (6.3)	18.5 (6.7)	-	-	0	0
			Kurtosis	-.226	.304	-.743						
Psychological Distress	4	0-16	*Skewness*	.318	.153	2.078	-	-	7.0 (6.0)	7.0 (5.0)	1.2	2.7
			Kurtosis	-.560	.304	-1.842						
Functioning Impairments	6	0-24	*Skewness*	.989	.153	6.464	-	-	5.0 (7.0)	4.0 (7.0)	12.9	0
			Kurtosis	.437	.304	1.438						
Insight	3	0-12	*Skewness*	1.632	.153	10.667	-	-	1.0 (3.0)	0.0 (1.0)	45.9	.8
			Kurtosis	2.527	.304	8.313						
Reassurance	3	0-12	*Skewness*	1.153	.153	7.536	-	-	2.0 (3.0)	2.0 (2.0)	20.8	.4
			Kurtosis	.830	.304	2.730						
Coping Strategies	9	0-36	*Skewness*	-.420	.153	-2.745	-	-	18.0 (7.0)	18.0 (9)	1.2	0
			Kurtosis	.113	.304	.372						
Total score	42	0-168	*Skewness*	.070	.153	.458	71.6 (22.7)	67.7 (23.0)	-	-	0	0
			Kurtosis	-.045	.304	-.148						

[a] n = 255; [b] Z-scores of >2 or <-2 are considered a violation of the normality assumption; [c] Means and standard deviations (SD) were reported for normally distributed subscales, medians and interquartile ranges (IQR) were reported for not-normally distributed subscales; [d] Percentages of >15% indicate floor or ceiling effects.

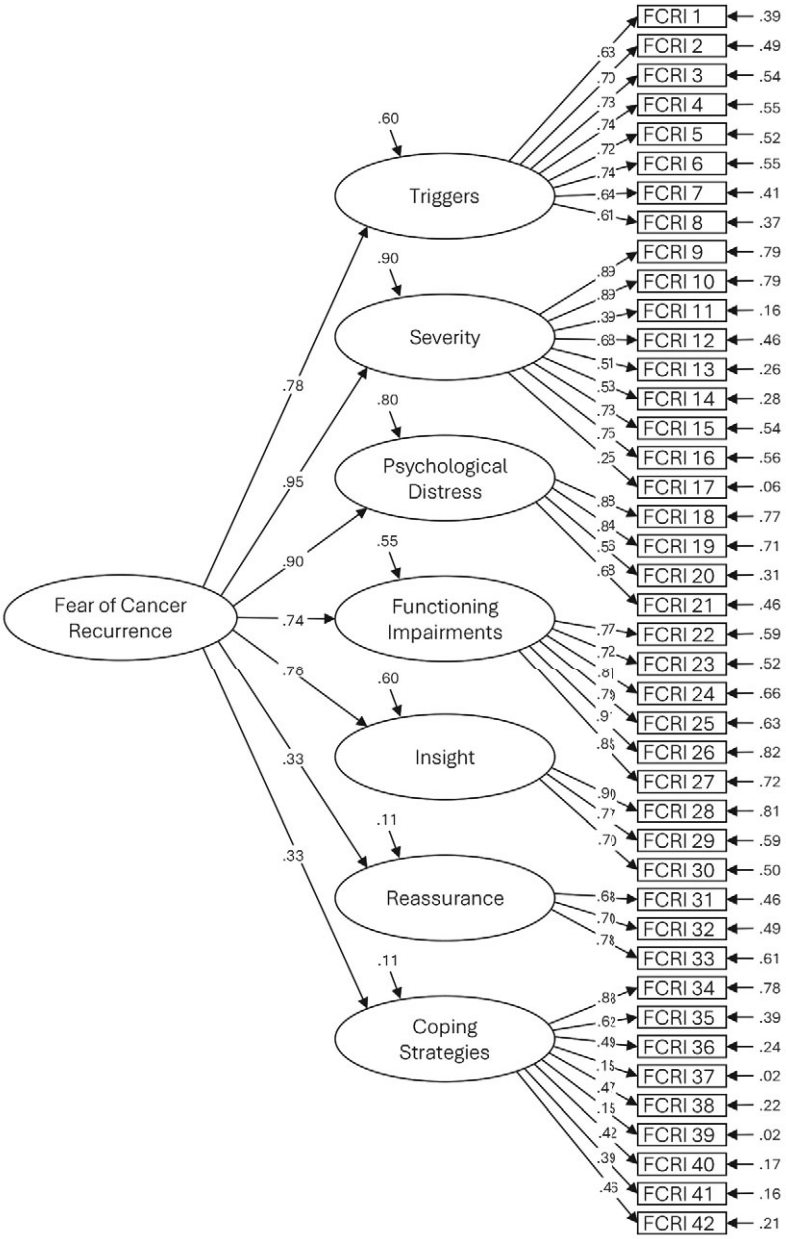

Figure 1. Path diagram with standardized parameter estimates of the tested model.

Reliability

The reliability (Cronbach's alpha) of both the FCRI-NL, the FCRI-SF-NL and most of the remaining FCRI-NL subscales exceeded .80 (except for Reassurance and Coping Strategies, internal consistency of these scales exceeded .70). The lower bound of the

Cronbach's alpha confidence intervals was >.70 for the FCRI-NL and all subscales, which indicates with certainty that reliability is sufficient. Test-retest reliability (ICC) of the FCRI-NL, the FCRI-SF-NL and most of the remaining FCRI-NL subscales exceeded .70 (except for Reassurance and Coping Strategies, test-retest reliability of these subscales exceeded .50). The ICC confidence intervals show that the FCRI-NL, the FCRI-SF-NL and most of the remaining FCRI-NL subscales have good test-retest reliability, except for Reassurance and Coping Strategies subscales. For these two subscales, test-retest reliability is weaker. Results are shown in Table 3.

Table 3. Reliability and test–retest reliability (including confidence intervals)

	Cronbach's alpha [a]		ICC [a]	
	Time-1	95% CI	(2 weeks)	95% CI
	n = 255		*n* = 95	
Triggers	.88	.86 - .90	.81*	.72 - .87
Severity / FCRI-SF-NL	.85	.82 - .88	.87*	.80 - .91
Psychological Distress	.84	.80 - .87	.74*	.63 - .82
Functioning Impairments	.92	.91 - .94	.78*	.68 - .84
Insight	.84	.80 - .87	.74*	.64 - .82
Reassurance	.76	.70 - .80	.56*	.40 - .68
Coping Strategies	.75	.71 - .80	.59*	.44 - .70
FCRI-NL	.93	.92 - .94	.84*	.77 - .89

[a] High correlation coefficients of ($r \geq .70$) were considered sufficient
*$p < .001$

Construct validity

Evidence of convergent validity was provided by high associations between the FCRI-NL and the tension subscale of the POMS, agoraphobic cognitions measured by the ACQ, the neuroticism subscale of the BFI, and the state and trait anxiety subscales of the STAI-DY. Convergent validity was also supported for the FCRI-SF, with a moderate association between the FCRI-SF-NL and the trait anxiety subscale of the STAI-DY, and by high associations between the FCRI-SF-NL and the tension subscale of the POMS, agoraphobic cognitions measured by the ACQ, the neuroticism subscale of the BFI, and the state anxiety subscale of the STAI-DY. Furthermore, weak associations were found between the FCRI-NL and the extraversion, openness, conscientiousness, and agreeableness subscales of the BFI, demonstrating divergent validity. The same was found for the FCRI-SF-NL. Results are shown in Table 4.

Table 4. Spearman's correlations obtained between the FCRI-NL, the FCRI-SF-NL and other measures

Measures	*N*	FCRI-NL	FCRI-SF-NL
		Spearman (rho)	*Spearman (rho)*
Convergent validity [a]			
Tension (POMS)	81	.66**	.50**
Agoraphobic cognitions (ACQ)	85	.65**	.57**
Neuroticism (BFI)	86	.53**	.50**
State anxiety (STAI-DY)	79	.63**	.53**
Trait anxiety (STAI-DY)	78	.63**	.48**
Divergent validity [b]			
Extraversion (BFI)	86	-.20	-.28**
Openness (BFI)	83	-.20	-.25*
Conscientiousness (BFI)	83	-.07	-.18
Agreeableness (BFI)	86	-.17	-.17

[a] Moderate and high correlations (r ≥ .30) indicate convergent validity; [b] Small correlations (r = .10- .29) indicate divergent validity; * $p < .05$; ** $p < .01$

Discussion

This is the first study that investigated the psychometric properties of the FCRI-NL and its subscales by performing a CFA to investigate whether the multidimensional 7-factor structure of the original FCRI could be confirmed in the FCRI-NL and by assessing reliability, test-retest reliability, and convergent and divergent validity.

Results indicate that the FCRI-NL has acceptable psychometric properties. The FCRI-NL, the FCRI-SF-NL, and the other subscales have sufficient to good reliability and test-retest reliability, except for a lower test-retest reliability on the Reassurance and Coping Strategies subscales. Convergent and divergent validity of both the FCRI-NL and FCRI-SF-NL are demonstrated in the current study. However, the hypothesized multi-dimensional structure of the FCRI-NL was not convincingly replicated in the present sample. CFA showed a reasonable yet suboptimal fit of the second-order model to the data. Because of this result, we strongly suggest that a FCRI-NL total score should not be used. It is unclear what a total score of the FCRI represents, but the individual items and some of the subscales scores capture important information and "may be useful indicators of when FCR levels are clinically significant".[13] We recommend to use the FCRI-SF-NL for research and screening purposes. For clinical practice the remaining subscales can be used and discussed by clinicians or clinical psychologists at item level for tailoring inventions to the patients' needs.

These results are largely comparable to the results of the validation studies of the original French and the English version, with the exception of the Insight, Reassurance, and Coping Strategies subscales that have lower scores on (test-retest) reliability.[7, 8] For a detailed comparison table see Supplementary materials 2C. These differences could be attributed to either the small number of items in some subscales, the translation, the sample, or cultural differences. Concerning the CFA, results are difficult to compare because it is unclear which estimation methods were used for the CFA of the French and English version. By all odds, the default estimation method (maximum likelihood) was used, and therefore different fit indices were reported, which makes it impossible to compare properly. However, their results also show some fit indices that only meet the criteria for model fit when older and less strict guidelines are applied, which could indicate some misfit in these models too.[25] One separate study on melanoma survivors in Australia reported a CFA in which they used the mean-adjusted and variance-adjusted weighted least squares estimation procedure, which is a more similar estimation technique compared to the scale-free least squares estimation method.[14] This study of Costa and colleagues showed a good model fit, which is better than the suboptimal fit we found in the current study.[14] Despite the difficulty with comparing results, we believe using the scale-free least squares estimation method, which handles any non-normal item score distributions, was the most appropriate way to perform the CFA.

When considering the findings of the current study, some limitations should be noted. First, the study sample may not be representative for the general population of cancer patients, because the online opt-in recruitment method may have resulted in response bias. For example, cancer patients with a high level of FCR may be preoccupied and may tend to participate in research on FCR. Also, this study sample consists of patients who are successfully treated for cancer, while in other studies patients with cancer recurrence or metastatic disease were included.[7, 8] However, compared to other studies, our study sample seems to be quite normal with respect to their FCRI scores. As already explained by Lebel and colleagues, the items of the FCRI were inspired by literature on anxiety disorders and DSM diagnostic criteria, and were included to discriminate between healthy levels of concerns about cancer recurrence and clinical levels of FCR, [6–8, 11]. Previous research showed that in most studies, FCR mean scores were below the mid-points of the FCR measures, indicating low to moderate levels of FCR.[6] Also, approximately 15% of cancer survivors report a high degree of FCR.[6, 7] This is largely in line with our results: our study sample is normally distributed and few participants have high scores on FCR. However, the mean score of the FCR Severity subscale is slightly higher than the subscale midpoint, which may indicate some response bias. A second limitation of this study is that the cancer characteristics were not assessed. This makes it difficult to compare between cancer types and to compare to earlier studies. However, in previous research no differences were found in FCR severity between different cancer types.[33] Since the results are largely comparable

to previous research, it is likely that these limitations of our study sample are not insurmountable. Moreover, these limitations of the sample have limited impact on validation studies. A further limitation is the small sample size for the CFA analysis. This may have resulted in unstable parameter estimates, especially because there are factors with fewer items.[34] Finally, translation of an already translated questionnaire might cause some problems, yet we have decided to use the English version for practical reasons (bilingual French-Dutch translators and experts are scarce in the Netherlands). More recently, this English translation also demonstrated good reliability and validity, therefore we do not foresee any problems.[7]

A strength of this study was the large amount of different measures that were used for validation, compared to previous validation studies of the FCRI. Also, this study adds to the knowledge on FCR measures in the Netherlands. The added value of the FCRI-NL compared to the only known other validated Dutch measure for FCR, the Cancer Worry Scale (CSW), is the extensiveness of the FCRI-NL, which gives a lot of important additional information compared to the CSW.[35]

Future studies are needed to replicate the results of the current study. When consensus about a golden standard for FCR is reached, a study assessing the screening potential of the FCRI-SF-NL for detecting clinical levels of FCR as assessed with the golden standard would be highly relevant. The clinical face-to-face interview (SIFCR) developed by Simard and colleagues, using specific criteria to define clinical levels of FCR, may serve as a starting point for discussion on the golden standard.[12] Moreover, future studies should further explore the factor structure of the FCRI-NL, preferably in larger samples. Also, in future research, the FCRI-NL should be studied using large heterogeneous inpatient and outpatient samples of cancer patients, to determine norm scores. Lastly, since there is a growing number of interventions for FCR in the Netherlands (for example a CBT-based online self-help training, and a combined online and face-to-face CBT), there is a need for future research that establishes the sensitivity to change of the FCRI-NL. [36, 37]

Conclusion

Overall, this study showed that the FCRI-NL has sufficient psychometric properties. However, the results of this study also show that caution is recommended with using and interpreting the FCRI-NL total score. Nevertheless, the FCRI-SF-NL may be a valuable screening tool for FCR severity in clinical care.

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03

Factor structure of the Fear of Cancer Recurrence Inventory (FCRI): comparison of international FCRI factor structure data and factor analysis of the Dutch FCRI-NL using three predominantly breast cancer samples

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Abstract

Objective

Factor structure results of Fear of Cancer Recurrence Inventory (FCRI) translations are inconclusive. Through investigating the factor structure, this study aimed to improve the FCRI and its usability. Therefore, we did a comprehensive comparison of the factor structure results of all translations, by exploring and improving the structure of the Dutch FCRI-NL, and by testing this new factor structure in two patient samples.

Methods

To compare factor structure results of FCRI translations, we did a literature search using PubMed and Google Scholar. We performed exploratory factor analysis (EFA) in a mixed cancer sample. The confirmatory factor analyses (CFAs) were secondary analyses performed in two randomized controlled trial samples: consecutive breast cancer patients and distressed, mainly breast cancer patients.

Results

All translations showed comparable and reasonable factor structure results, however, the FCRI factor structure can be improved. The EFA resulted in a four-factor solution: fear of cancer recurrence (FCR) severity, cognitive coping, impact of FCR on functioning, and behavioral coping. However, the 4-factor CFAs did not fit the sample 2 and 3 data well.

Conclusion

Further exploring the FCRI-NL factor structure did not result in a psychometrically stronger FCRI-NL. Therefore, we recommend retaining the 7-factor FCRI-NL.

Introduction

Fear of cancer recurrence (FCR) is one of the most reported concerns after surviving cancer and can continue for ten years or more after diagnosis.[1, 2] FCR is defined as "fear, worry, or concern about cancer returning or progressing" and is increasingly recognized as a multidimensional construct, including physical sensations, functioning impairments, psychological distress, intrusive thoughts, and coping strategies.[3–5] Across different cancer types, 39–97% of cancer survivors reported some level of FCR, 22–87% reported moderate to high levels of FCR, and 0–15% reported high levels of FCR.[6] It is important to identify high or clinical levels of FCR, so that psychological treatment can be offered. Therefore, good screening instruments are needed. Currently, at least 34 assessment instruments for FCR exist, including 11 subscales of larger measures, 19 brief questionnaires (2–10 items), and four longer (multidimensional) questionnaires (10+ items). Many of these scales are only available in one language, are cancer site specific, or have a limited availability of research and psychometric data.[6–8] The Fear of Cancer Recurrence Inventory (FCRI) is a multidimensional measure intended for use in all cancer patients, translated and validated in several languages, and currently one of the psychometrically strongest measures available.[8]

The FCRI is based on the definition of FCR, on DSM-IV diagnostic criteria of anxiety and somatoform disorders, and on a cognitive-behavioral conceptualization of FCR, and developed by a committee of experts in psycho-oncology.[5] The original French-Canadian version of the FCRI comprises 42 items measuring seven factors (Triggers, Severity, Psychological Distress, Coping Strategies, Functioning Impairments, Insight, and Reassurance).[5] The Severity subscale can be used as a short form of the FCRI (FCRI-SF) to screen for clinical levels of FCR, whereas the other subscales represent aspects related to FCR, such as antecedents (e.g., Triggers), modifiers (e.g., Coping Strategies), or consequences (e.g. Functioning Impairments).[9, 10] The original FCRI demonstrated good validity and reliability (internal consistency estimated by Cronbach's $\alpha = .95$; and test-retest reliability $r\,(287) = .89$, $p < .001$).[5] The psychometric properties of the English translation were similar ($\alpha = .96$; $r\,(135) = .88$, $p < .001$; intraclass correlation (ICC) = .94, $p < .001$), as were those of the recently published Dutch version (FCRI-NL; $\alpha = .93$; ICC (95) = .84, $p < .001$), the Mandarin version ($\alpha = .95$; ICC (109) = .86, $p < .001$), the Korean version (K-FCRI; $\alpha = .85$; ICC (62) = .90, $p < .001$), and the Danish version (ICC (49) = .84, p-value was not reported).[11–15] Results concerning the factor structure of the FCRI, measured by confirmatory factor analyses (CFAs), are inconclusive. Most research papers on the original 7-factor FCRI structure have reported a satisfactory model fit, while a reasonable, yet suboptimal fit was reported for the FCRI-NL.[11–14, 16–18] However, comparing CFAs of the different FCRI translations is hampered by the use of different CFA software, fit indices, and cut-off criteria.[12, 16]

There has been some discussion about the applicability of the FCRI in its current form. For example, Costa, Smith, and Fardell (2016) question the use of a combined FCRI total score.[9] They state that a total score represents an uninterpretable combination of concepts given the multidimensional nature of the FCRI.[9] Moreover, the Reassurance and Coping Strategies subscales show problematic features. For most translations, the internal consistency scores of the Reassurance and/or Coping Strategies subscales are slightly lower (but all above .70), and for some translations, the test-retest reliability was unsatisfactory.[19] Also, in analyses based on response theory (IRT), several items were found were respondents tended to use the *rarely* answer category less frequent than the other answer categories, including most items in the Reassurance and Coping Strategies subscales. Additionally, some items can better discriminate between respondents low or high on FCR than others.[20] These problems motivated research investigating an alternative multidimensional FCR model with 7 first order factors (instead of a second order model) or an alternative FCRI following exploratory factor analysis (EFA).[20, 21]

Given the inconsistencies in the body of research concerning the FCRI, this study aimed to (1) comprehensively compare all published research investigating the FCRI factor structure. Since the body of research on the FCRI shows there may be room for improvement concerning its factor structure, additional aims are to (2) further explore the factor structure of the FCRI-NL with EFA, in order to improve the FCRI-NL, and (3) to test the newly identified factor structure with CFAs in two new (predominantly breast cancer) patient samples (and to compare these samples).

Methods

Procedure and participants

To compare CFA results of all FCRI translations (first aim), all available articles reporting FCRI CFA results were collected using the electronic bibliographic database PubMed (search terms: ("fear of cancer recurrence inventory" [Title]) AND ("confirmatory factor analys*" [Title/Abstract])). Furthermore, we did an additional search on Google Scholar (search terms: "fear of cancer recurrence inventory" AND "confirmatory factor analysis"). Articles were eligible when they reported CFA results of (a translation of) the original 7-factor FCRI (not an adapted version).

To further explore the factor structure of the FCRI (second aim), we did a secondary analysis (by means of an EFA) on the data from *sample 1*. *Sample 1* is a mixed cancer patient sample (not selected on FCR level) recruited between 2011 and 2013 through patient organizations with an online opt-in recruitment method.[12] This sample was also used for the initial FCRI-NL validation.[12] Participants could fill out the online questionnaire (including demographic information and the FCRI-NL) through a link in an e-mail newsletter from their patient organizations in the Netherlands. Informed consent

was obtained from all individual participants. In total, 290 participants completed the FCRI-NL. Thirty-five participants were excluded because they reported disease recurrence, leaving 255 (87.9%) participants for analysis. The final sample included 255 mixed cancer patients (88.6% women, cancer types not assessed) with mean age 51.0 (±9.8) years.

To test the new factor structure (third aim), we did secondary analyses (by means of CFAs) on the data from *sample 2* and *sample 3*. Both data samples are from large randomized controlled trials and intervention studies.[22, 23] *Sample 2* consists of the baseline FCRI-NL scores of the CAREST study.[23] Oncology nurses in outpatient clinics consecutively recruited women with breast cancer in eight hospitals, both face-to-face and by sending comprehensive information letters. We obtained written informed consent on paper, and participants completed the FCRI and other self-report questionnaires on paper or online. In total, 516 participants returned informed consent. Sixty-two participants were excluded (36 did not complete any item of the FCRI-NL, 25 had missing values, and one had adopted a "0" response pattern for all items of the FCRI), leaving 454 (88.0%) participants for analysis. The final sample included 454 women with breast cancer with mean age 57.9 (±10.5) years.

Sample 3 consists of the baseline FCRI-NL scores of distressed cancer patients from the BeMind study.[22] The researchers recruited participants in participating outpatient clinics, and via offline and online media. Patients who were interested enrolled themselves on the study's website (www.bemind.info) and filled out the Hospital Anxiety and Depression Scale (HADS). To assess eligibility researchers phoned all survivors with ≥ 11 on the HADS. Written informed consent was obtained on paper, and participants completed the FCRI and other self-report questionnaires online prior to randomization. In total, 245 participants were eligible for the study and completed the FCRI-NL. Forty participants were excluded (39 had chronic or incurable cancer and one did not complete the FCRI), leaving 205 (83.7%) participants for analysis. The final sample included 205 mixed cancer patients (86.6% women) with mean age 50.9 (±10.4) years, including 67.5% women with breast cancer, 7.3% women with gynaecological cancer, 4.9% patients with colon cancer, 2.4% patients with non-Hodgkin, 5.4% patients with colon cancer, and 12.2% patients with other cancers.

Patient characteristics of all samples are presented in Table 1. On average, participants in *sample 2* were older than participants in *samples 1 and 3* (57.9 years vs. 51.0 and 50.9 years). Also, participants in *sample 2* had lower FCR levels than *samples 1 and 3* (mean FCR level on the FCRI-S 13.9 vs. 19.5 and 20.7). *Sample 2* consists of only female breast cancer patients, while *samples 1 and 3* are mixed samples including a majority of women (88.6% and 86.6%). Education differed between the samples: *samples 1 and 3* primarily consisted of highly educated patients (47.1% and 67.3%), while patients in *sample 2* most often had a medium level of education (50.0%).

Table 1. Demographic and medical characteristics of three samples

	Sample 1		Sample 2: CAREST		Sample 3: BeMind	
	(n=255)		(n=454)		(n=205)	
	n	%	*n*	%	*n*	%
Demographic characteristics						
Age †	n=255		n=450		n=205	
M (SD)	51.0	(9.8)	57.9	(10.5)	50.9	(10.4)
Range	26-77		26-85		26-77	
Gender	n=255		n=450		n=205	
Male	29	(11.4)	0	0.0	27	13.2
Female	226	(88.6)	454	100.0	178	86.6
Having a partner			n=380		n=205	
Yes	‡		315	82.9	171	83.4
No	‡		65	17.1	34	16.6
Education §	n=255		n=380		n=205	
Low (ISCED 0-1-2)	38	14.9	51	13.4	2	1.0
Medium (ISCED 3-4-5)	96	37.6	190	50.0	65	31.7
High (ISCED 6-7-8)	120	47.1	138	30.4	138	67.3
Unknown	1	0.4	1	0.3	0	0.0
Medical characteristics						
Time since diagnosis †	‡		n=450		n=205	
Median (IQR)	‡		2.4	(1.8)	1.6	(3.1)
Cancer diagnosis			n=454		n=205	
Breast cancer	‡		454	100.0	139	67.8
Gynaecological cancer	‡		0	0.0	15	7.3
Colon cancer	‡		0	0.0	10	4.9
Non-Hodgkin	‡		0	0.0	5	2.4
Prostate	‡		0	0.0	11	5.4
Other	‡		0	0.0	25	12.2
FCR Severity †	n=255		n=454		n=205	
M (SD)	**19.5**	**(6.3)**	13.9	(6.9)	20.7	(6.4)
Median (IQR)	20.0	(9.0)	**14.0**	**(9.0)**	**21.0**	**(10.0)**

Abbreviations: FCR = fear of cancer recurrence; IQR = interquartile ranges; ISCED = International Standard Classification of Education; M = mean; SD = standard deviation.
† Means and standard deviations (SD) were reported for normally distributed variables, medians and interquartile ranges (IQR) were reported for not-normally distributed variables (where both are reported, the bold numbers need to be looked at).
‡ These variables were not assessed in sample 1.
§ UNESCO Institute for Statistics (UIS). International Standard Classification of Education: ISCED 2011. Montreal, Quebec: UIS; 2012.

Material

The FCRI-NL consists of 42 items with a 5-point Likert scale ranging from 0 (*not at all* or *never*) to 4 (*a great deal* or *all the time*).[5, 12] See Supplementary materials 3A for the FCRI-NL. The FCRI comprises seven subscales: Triggers, Severity, Psychological Distress, Coping Strategies, Functioning Impairments, Insight, and Reassurance. Subscale scores can be calculated by summing the subscale item scores.[5] When summing all items, a total FCRI score can be calculated.[5] The Severity subscale (FCRI-SF) can be used to screen for clinical levels of FCR. The score of item 13 ''I believe that I am cured and the cancer will not come back'' must be reversed before summation.[5, 10] The reliability and validity of the original French, English, Dutch, Mandarin, Korean, and Danish versions of the FCRI total scale and most subscales are sufficient to good.[5, 11–15]

Statistical analysis

Analyses were conducted using IBM SPSS 23 for Windows.[24] Data was explored in the same way as the initial FCRI-NL validation study.[12] First, we checked normality of the FCRI item scores: *Z*-scores (skewness and kurtosis values divided by standard error) larger than 2 or smaller than -2 were considered a violation of normality. Then, we examined Quantile-quantile (Q-Q) plots and probability-probability (P-P) plots to screen for multivariate normality. In addition, we screened the data for floor and ceiling effects. Significance level was .05. We excluded participants when they had missing values on the FCRI-NL, because the scale-free least squares estimation method in IBM SPSS AMOS 22 (see below) could not handle missing values.[25] We also excluded participants when they had adopted the same response pattern (only 0, 1, 2, 3 or 4) for all items of the FCRI, including the reversed phrased item (item 13), because this indicates that they likely adopted an automatic response set.[26]

For comparing the FCRI translations (first aim), we used the following fit indices and cut-off criteria for evaluating good model fit: the root mean square error of approximation (RMSEA ≤ .10); comparative fit index (CFI ≥ .90); normed-fit index (NFI ≥ .95); standardized root mean square residual (SRMR ≤ .10); adjusted goodness-of-fit statistic (AGFI ≥ .90); Tucker Lewis index (TLI ≥ .95); non-normed fit index (NNFI ≥ .95), and the parsimonious normed fit index (PNFI).[27–29] Although the RSMEA, CFI, and SRMR cut-off criteria are less strict than sometimes recommended, they are considered adequate because the FCRI 7-factor model is a complex model (stricter cut-off values are preferred for simpler models).[29] Using a parsimony-corrected fit index next to other goodness-of-fit measures is strongly recommended, but it is difficult to interpret because there are no threshold levels recommended yet. However, it is possible to have acceptable models with parsimony-corrected fit index values in the .50s, and higher values indicate a better fit to the data.[27]

To further explore the factor structure of the FCRI (second aim), we performed an EFA on *sample 1*. First, we assessed the suitability of the data for conducting an

EFA, details are presented in Supplementary materials 3B. When the data met the criteria, factors were extracted with the principal components analysis (PCA) method. When the assumption of multivariate normality was violated, the principal axis factor (PAF) method was used. We used oblique (direct oblimin) factor rotation because we expected strong correlations between the factors.[30] We used multiple decision rules to determine the number of significant factors: (a) Kaiser's criterion (eigenvalue > 1 rule); (b) the Cattell's Scree test (eigenvalues above the elbow of the plot are retained as number of factors); and (c) Horn's parallel analysis.[31, 32] For Horn's parallel analysis, Monte Carlo PCA for Parallel Analysis (version 2.5) was used.[33] When the average communality was lower than .60, given sample size > 250, little value was attached to Kaiser's criterion and more value was attached to Cattell's Scree test and the more accurate parallel analysis.[31] Subsequently, we examined the pattern matrix according to the .40–.30–.20 rule. This rule implies that satisfactory items (a) load onto their primary factor above .40, (b) load onto alternative factors below .30, and (c) demonstrate a difference of .20 between their primary and alternative factor loading.[34] After removing the item that least met these criteria (first based on the factor loadings, then on the crossloadings), we repeated the PCA/PAF analysis in an iterative fashion until every remaining item met the criteria. After three experienced clinicians/researchers made a careful judgement on which solution was the best-fit and which of the factors extracted made the most conceptual sense, the best-fit solution was presented. Thereafter, they operationalized and labelled the factors.

To test the new factor structure (third aim), we tested the factor structure (identified with EFA) in CFAs on *samples 2 and 3*. We used the scale-free least squares estimation method in IBM SPSS AMOS 22, to handle any non-normal item score distributions.[25] We evaluated goodness of fit with AGFI, NFI, PNFI, and SRMR and the earlier described cut-off criteria.

Results

Comparison of the different FCRI translations (first aim)

We conducted a PubMed search on 23 April 2020, which resulted in six articles. All articles were reporting CFA results for FCRI translations and, therefore, eligible for comparison.[11–14, 16, 35] An additional search on Google Scholar resulted in 55 articles, of which two articles included CFA results for FCRI translations and were eligible for comparison.[18, 20] Table 2 shows the results of the comparison between the eight different studies. Since Simard et al. (2010) reported the CFA results very concise in their Methods section, extra information received from the first author was added to Table 2 (S. Simard, personal communication, 8 July 2010). It turned out that the psychometric properties were comparable across translations. For the total FCRI and most FCRI subscales, internal consistency was good (Cronbach's alpha ≥ .80). The reassurance and coping strategies subscales showed acceptable internal consistency

(estimated Cronbach's alpha .70 - .80) for 66.7% and 33.3% of the translations, respectively. Regarding test-retest reliability, the Insight, Reassurance, and Coping Strategies subscales showed suboptimal results. Internal consistency and test-retest reliability of these subscales differed between the translations.

There were differences between the included studies in for example the CFA software, the types and numbers of reported fit indices, and the cut-off criteria (see Table 2). Also, most studies reported both the original 7-factor CFA and an adjusted version in which residual covariance parameters were added to improve the model (7 studies). Yet, one study reported only the original 7-factor model, because the robust CFA method in IBM Amos did not allow adding residual covariance parameters.[12] When applying the same cut-off criteria to the reported fit indices of all studies, conclusions regarding model fit occasionally differed from those originally reported. For example, the original French CFA results were interpreted as a reasonably good fit with the original 7-factor structure, while based on the current criteria only one out of three fit indices was sufficient (S. Simard, personal communication, 8 July 2010).[18] Moreover, for the Dutch CFA, the results had been interpreted as a reasonable, yet suboptimal fit, while based on the current criteria three out of four fit indices were sufficient.[12] Also, there was some variation in the model fit between translations and within the CFAs conducted on the same translation. For example, both a good model fit and a more doubtful model fit were found for the English translation, with five out of five and one out of three acceptable fit criteria, respectively.[11, 16] These results illustrate that CFA results and interpretation are dependent on the used fit criteria. Comparing the different FCRI translations and applying the same cut-off criteria to all translations, results in acceptable factor analyses results. Results are fairly consistent across translations and do not seem to be dependent on the translations or cultural differences. However, there may be some room for improvement concerning the FCRI factor structure and items. For more details, see table 2.

Exploring the FCRI factor structure (second aim)

All criteria confirmed that the data is suitable for EFA (details are presented in Supplementary materials 3B). Because of the non-normally distributed item scores (see Supplementary materials 3C), we used the PAF method with oblique (direct oblimin) factor rotation to conduct an EFA on the 42 items of the FCRI. An initial PAF analysis showed nine components had eigenvalues larger than 1. The scree plot was slightly ambiguous and showed inflexions that would justify retaining nine or four components. Parallel analysis suggested four components. Since the average communality was lower than .60 (.47) and the sample size larger than 250 (255), Kaiser's criterion was not accurate, and we attached more value to the results of Cattell's Scree test and parallel analysis. We retained four factors for the final analysis.

Table 2. Comparison of the psychometric properties and factor structure (confirmatory factor analysis results) of the different FCRI translations

	French	English	English	Dutch	English/ Mandarin	Korean	English	Chinese
	(Simard et al., 2010)[18]	(Lebel, Simard, et al., 2016)[11]	(Costa, Dieng, et al., 2016)[20]	(van Helmondt et al., 2017)[12]	(Liu et al., 2017)[13]	(Shin et al., 2017)[14]	(Galica et al., 2018)[16]	(Lin et al., 2018)[35]
Sample	Mixed sample: Breast 49% Prostate 37% Colorectal 9% Lung 5%	Mixed sample: Breast 40% Prostate 42% Colorectal 12% Lung 6%	Melanoma sample (not metastatic)	Mixed sample (included cancer sites unknown)	Mixed sample: Breast 38% Gynaecological 27% Gastro-intestinal 14% Other 21%	Mixed sample: Stomach 39% Breast 25% Lung 9% Thyroid 8% Other 19%	Mixed sample: Breast 66% Other 34%	Head and neck cancer sample: Nasopharyngeal 45% Pharyngeal larynx 21% Oral cavity 29% Other 5%
Internal consistency								
	Cronbach's α	*Cronbach's α*	-	*Cronbach's α*	*Cronbach's α*	*Cronbach's α*	*Cronbach's α*	-
	n = 600	*n = 350*	-	*n = 255*	*n = 222*	*n = 444*	*n = 984*	-
Triggers	.90	.93	-	.88	.90	.80	.92	-
Severity	.89	.88	-	.85	.84	.77	.88	-
Psychological Distress	.86	.88	-	.84	.94	.83	.89	-
Functioning Impairments	.91	.94	-	.92	.95	.82	.94	-
Insight	.80	.85	-	.84	.89	.87	.89	-
Reassurance	.75	.71	-	.76	.82	.84	.77	-
Coping Strategies	.89	.91	-	.75	.91	.77	.89	-
Total FCRI	.95	.96	-	.93	.95	.84	-	-

Table 2. Comparison of the psychometric properties and factor structure (confirmatory factor analysis results) of the different FCRI translations (continued)

	French	English	English	Dutch	English/ Mandarin	Korean	English	Chinese
Test-retest reliability								
	Pearson's correlation (1 month)	*Pearson's correlation (1 month)*	-	*ICC (16 days)*	*ICC (unknown)*	*ICC (206 days)*	-	-
	n = 287	*n = 135*	-	*n = 95*	*n = 177*	*n = 62*	-	-
Triggers	.83	.78	-	.81	.80	.76	-	-
Severity	.80	.87	-	.87	.89	.84	-	-
Psychological Distress	.76	.79	-	.74	.87	.73	-	-
Functioning Impairments	.70	.71	-	.78	.83	.67	-	-
Insight	.58	.85	-	.74	.87	.80	-	-
Reassurance	.73	.56	-	.56	.84	.80	-	-
Coping Strategies	.75	.75	-	.59	.89	.54	-	-
Total FCRI	.89	.88	-	.84	.91	.90	-	-
Confirmatory Factor Analysis †								
	n = 1984	*n = 350*	*n = 228*	*n = 255*	*n = 222*	*n = 444*	*n = 984*	*n = 300*
Software	not reported	LISREL (v 9.1)	Mplus (v 6)	IBM Amos (v 22)	Mplus (v 6.12)	Mplus (v 6.1)	Mplus (v8)	not reported
Initial 7-factor model								
χ^2	7798	2602	1346	1597	2399	2710	4359	-
df	812	812	798	812	812	812	812	-
p	< .001	< .001	< .001	< .001	< .001	-	< .001	-
RMSEA	.066*	.079*	.055*	-	.077*	.073*	.067*	-

Table 2. Comparison of the psychometric properties and factor structure (confirmatory factor analysis results) of the different FCRI translations (continued)

	French	English	English	Dutch	English/ Mandarin	Korean	English	Chinese
RMSEA (90% CI)	-	-	.050-.060*	-	-	.070 - .076*	.065 - .069*	-
CFI	.870	.964*	.949*	-	.853	.853	.858	-
NFI	.860	.949	-	.927	-	-	-	-
SRMR	-	.088*	-	.083*	.085*	-	-	-
PNFI	-	.895*	-	.874*	-	-	-	-
TLI	-	-	.946	-	-	-	.849	-
AGFI	-	-	-	.935*	-	-	-	-
NNFI	-	-	-	-	-	.844	-	-
Final 7-factor model (model fit improved by freeing parameters in the residual covariance matrix)								
χ^2	5816	1963	1269	-	1804	2094	3460	-
df	807	803	796	-	801	803	807	-
p	< .001	< .001	< .001	-	< .001	-	< .001	-
RMSEA	.056*	.064*	.051*	-	.062*	.060*	.058*	.075*
RMSEA (90% CI)	-	-	.046-.056*	-	-	.057 - .063*	.056 - .060*	-
CFI	.910	.977*	.956*	-	.907	.900	.893	.948*
NFI	.900	.962*	-	-	-	-	-	.919
SRMR	-	.075*	-	-	.085*	-	-	.093*
PNFI	-	.897*	-	-	-	-	-	.867*
TLI	-	-	.953*	-	-	-	.886	-
AGFI	-	-	-	-	-	-	-	-
NNFI	-	-	-	-	-	.893	-	-

Abbreviations: *n* = sample size; Cronbach's α = Cronbach's alpha; ICC = intraclass correlation; χ^2 = Chi square; df = degrees of freedom, p = p-value; RSMEA = root mean square error of approximation; CI = confidence interval; CFI = comparative fit index, NFI = normed-fit index; SRMR = standardised root mean square residual; PNFI = parsimonious normed fit index; TLI = Tucker Lewis index; AGFI = adjusted goodness-of-fit statistic; NNFI = non-normed fit index.

† Cutoff criteria for fit indices: RMSEA ≤ .10; CFI ≥ .90; NFI ≥ .95; SRMR ≤ .10; for PNFI no thresholds have been recommended, although values between .50 and .90 are possible; TLI ≥ .95 acceptable and ≥ .97 good; AGFI ≥ .90; and NNFI ≥ .95.

Values that were not reported in the articles, were indicated with "-".

* acceptable model fit.

Following oblique (direct oblimin) rotation for a four-factor solution, factors 1 and 3 showed a moderate negative intercorrelation (r = -.50), the other factors showed small intercorrelations (r = -.05 - .18). Several items had factor loadings smaller than .40 or cross-loadings. Following the PAF analysis, we discarded 8 items in the following order: 36 – 38 – 17 – 21 – 20 (items that loaded below .40 on their primary factor), and 16 – 19 – 15 (items that loaded above .30 on their alternative factor and demonstrated a difference of < .20 between their primary and alternative factor loadings) (see Table 3). The remaining 34 items showed a clear four-factor solution (see Table 3), which explained 56.0% of the variance in the FCRI-NL item scores. Since we used an oblique rotation method, we interpreted the meaning of each factor using the pattern matrix, as these factor-item correlations are not confounded by the association of items with other factors. We labelled the factors FCR severity (factor 1; 14 items), cognitive coping (factor 2; 7 items), impact of FCR on functioning (factor 3; 10 items), and behavioral coping (factor 4; 3 items).

Table 3. Pattern matrix for final results of Principal Axis Factoring extraction with oblique (direct oblimin) rotation of a 4-factor solution for FCRI-NL items

	4-factor FCRI-NL items:	Factor 1: FCR severity	Factor 2: Cognitive coping	Factor 3: Impact of FCR on functioning	Factor 4: Behavioral coping
3.	**The following situations make me think about the possibility of cancer recurrence:** Medical examinations (e.g. annual check-up, blood tests, X-rays).	.800			
2.	**The following situations make me think about the possibility of cancer recurrence:** An appointment with my doctor or other health professional.	.797			
4.	**The following situations make me think about the possibility of cancer recurrence:** Conversations about cancer or illness in general.	.779			
5.	**The following situations make me think about the possibility of cancer recurrence:** Seeing or hearing about someone who is ill.	.732			
1.	**The following situations make me think about the possibility of cancer recurrence:** Television shows or newspaper articles about cancer or illness.	.692			
9.	I am worried or anxious about the possibility of cancer recurrence.	.669			
10.	I am afraid of cancer recurrence.	.668			
6.	**The following situations make me think about the possibility of cancer recurrence:** Going to a funeral or reading the obituary section of the paper.	.648			

Table 3. Pattern matrix for final results of Principal Axis Factoring extraction with oblique (direct oblimin) rotation of a 4-factor solution for FCRI-NL items (continued)

4-factor FCRI-NL items:		Factor 1: FCR severity	Factor 2: Cognitive coping	Factor 3: Impact of FCR on functioning	Factor 4: Behavioral coping
18.	**When I think about the possibility of cancer recurrence, I feel:** Worry, fear or anxiety.	.593			
11.	I believe it is normal to be worried or anxious about the possibility of cancer recurrence.	.572			
12.	When I think about the possibility of cancer recurrence, this triggers other unpleasant thoughts or images (such as death, suffering, the consequences for my family).	.558			
7.	**The following situations make me think about the possibility of cancer recurrence:** When I feel unwell physically or when I am sick.	.516			
13.	I believe that I am cured and that the cancer will not come back.	.482			
14.	In your opinion, are you at risk of having a cancer recurrence?	.448			
41.	**When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:** I try to replace this thought with a more pleasant one.		.746		
35.	**When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:** I try not to think about it. to get the idea out of my mind.		.669		
42.	**When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:** I tell myself “stop it”.		.605		
40.	**When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:** I try to find a solution.		.541		
34.	**When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:** I try to distract myself (e.g. do various activities, watch television, read, work).		.509		
37.	**When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:** I try to convince myself that everything will be fine or I think positively.		.470		

Table 3. Pattern matrix for final results of Principal Axis Factoring extraction with oblique (direct oblimin) rotation of a 4-factor solution for FCRI-NL items (continued)

4-factor FCRI-NL items:	Factor 1: FCR severity	Factor 2: Cognitive coping	Factor 3: Impact of FCR on functioning	Factor 4: Behavioral coping
39. **When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:** I try to understand what is happening and deal with it.		.434		
23. **My thoughts or fears about the possibility of cancer recurrence disrupt:** My work or everyday activities.			.890	
22. **My thoughts or fears about the possibility of cancer recurrence disrupt:** My social or leisure activities (e.g. outings, sports, travel).			.868	
27. **My thoughts or fears about the possibility of cancer recurrence disrupt:** My quality of life in general.			.775	
24. **My thoughts or fears about the possibility of cancer recurrence disrupt:** My relationships with my partner. my family. or those close to me.			.771	
26. **My thoughts or fears about the possibility of cancer recurrence disrupt:** My state of mind or my mood.			.763	
28. I feel that I worry excessively about the possibility of cancer recurrence.			.652	
25. **My thoughts or fears about the possibility of cancer recurrence disrupt:** My ability to make future plans or set life goals.			.637	
29. Other people think that I worry excessively about the possibility of cancer recurrence.			.579	
30. I think that I worry more about the possibility of cancer recurrence than other people who have been diagnosed with cancer.			.567	
8. **The following situations make me think about the possibility of cancer recurrence:** Generally, I avoid situations or things that make me think about the possibility of cancer recurrence.			.432	
31. **When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:** I call my doctor or other health professional.				.843

Table 3. Pattern matrix for final results of Principal Axis Factoring extraction with oblique (direct oblimin) rotation of a 4-factor solution for FCRI-NL items (continued)

	Factor 1:	Factor 2:	Factor 3:	Factor 4:
4-factor FCRI-NL items:	FCR severity	Cognitive coping	Impact of FCR on functioning	Behavioral coping
32. **When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:** I go to the hospital or clinic for an examination.				.816
33. **When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:** I examine myself to see if I have any physical signs of cancer.				.476
% of variance explained	32.0	9.1	8.5	6.4
Internal consistency (Cronbach's alpha)	.92	.76	.92	.76
Discarded items from original 42-item FCRI-NL:	FCR severity	Cognitive coping	Impact of FCR on functioning	Behavioural coping
36† **When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:** I pray, meditate or do relaxation.	.129	**.256**	.023	.275
38† **When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:** I talk to someone about it.	.131	**.248**	-.014	.278
17† How long have you been thinking about the possibility of cancer recurrence?	**.372**	.093	.041	-.004
21† **When I think about the possibility of cancer recurrence, I feel:** Helplessness or resignation.	.297	.022	**.384**	.103
20† **When I think about the possibility of cancer recurrence, I feel:** Frustration, anger or outrage.	.142	.092	**.370**	.106
16‡ How much time per day do you spend thinking about the possibility of cancer recurrence?	**.362**	-.013	**.443**	.089
19‡ **When I think about the possibility of cancer recurrence, I feel:** Sadness, discouragement or disappointment.	**.460**	.066	**.319**	.185
15‡ How often do you think about the possibility of cancer recurrence?	**.465**	.013	**.314**	.040

†Items that loaded <.40 onto their primary factor were discarded, according to the .40–.30–.20 rule.
‡Items with crossloadings that loaded >.30 onto their alternative factor and demonstrated a difference of < .20 between their primary and alternative factor loadings were discarded, according to the .40–.30–.20 rule.

Test the new factor structure (third aim)

CFA did not show good model fit of the 4-factor model for both *samples 2 and 3*. In *sample 2* (χ^2 (595) = 10750; $p < .001$; χ^2/df = 18.068), the AGFI (.750) and NFI (.695) were smaller than the recommended criterium, and the SRMR index (.147) was larger than the recommended criterion, all suggesting misfit (see Table 4). The PNFI of *sample 2* was .738. In *sample 3* (χ^2 (595) = 1195; $p < .001$; χ^2/df = 2.008), the AGFI (.920) and SRMR index (.109) met the criteria for adequate model fit and the NFI (.895) was smaller than the recommended criterion, indicating some misfit of the 4-factor model to the data of *sample 3* (see Table 4).The PNFI of *sample 3* was .949. At first sight, the 4-factor model seems to fit the data of *sample 3* better than the data of *sample 2*. However, these differences should be interpreted with care, as to the best of our knowledge there exists no statistical tests to assess whether the difference between fit indices of models fitted on different samples is statistically significant.

Table 4. Model fit of the 4-factor and the original 7-factor structure of the FCRI-NL in two patient samples

	4-factor structure		Original 7-factor structure	
	Sample 2: CAREST	Sample 3: BeMind	Sample 2: CAREST	Sample 3: BeMind
	n = 454	*n* = 205	*n* = 454	*n* = 205
χ^2	10750	1195	2326	1369
df	595	595	812	812
χ^2 / df	18.068	2.008	2.865	1.685
AGFI †	.750	.920	.958	.926
NFI †	.695	.895	.956	.917
PNFI †	.738	.949	.901	.864
SRMR †	.147	.109	.075	.086

Abbreviations: χ^2 = Chi square; df = degrees of freedom, AGFI = adjusted goodness of fit index; NFI = normed fit index; PNFI = parsimonious normed fit index; SRMR = standardized root-mean-squared residual.

† Goodness of fit criteria: AGFI ≥ .90; NFI ≥ .95; for PNFI no thresholds have been recommended, although values between .50 and .90 are possible; SRMR ≤ .10.

Based on these results, we additionally performed two non-prespecified CFAs to investigate the original 7-factor model in *samples 2 and 3*. In *sample 2* (χ^2 (812) = 2326; $p < .001$; χ^2/df = 2.865) , the AGFI (.958), NFI (.956), and SRMR index (.075) met the criteria for adequate model fit, indicating a good model fit of the 7-factor model to the data of *sample 2* (see Table 4). The PNFI of *sample 2* was .901. In *sample 3* (χ^2 (812) = 1369; p < .001; χ^2/df = 1.685), the AGFI (.926) and the SRMR index (.086) met the criteria for adequate model fit and the NFI (.917) was smaller than the recommended criterion, indicating some misfit of the 7-factor model to the data of *sample 3* (see Table 4). The PNFI of *sample 3* was .864. These results suggest an acceptable fit of the 7-factor model to the data of *samples 2 and 3*. At first sight, the 7-factor model seems to fit the

data of *sample 2* better than the data of *sample 3* (which is reversed compared to the 4-factor model). However, as mentioned before these differences should be interpreted with care. Additionally, internal consistency values for both the 4-factor and the 7-factor model in all samples are available in Supplementary materials 3D.

Discussion

This is the first study that has compared and evaluated all available information about the FCRI factor structure (first aim) and has tried to improve the factor structure of the FCRI-NL by testing a new factor structure (second and third aim).

The factor structure results of the different FCRI translations were comparable after applying the same cut-off criteria to all translations (first aim). The comparison of all published papers including FCRI factor structure results was hampered by the use of different fit indices. Results show that interpretation of the FCRI factor structure results for the different translations was dependent on the used fit criteria. Although we have interpreted the results of the 7-factor FCRI-NL as weaker than the results of other translations of the FCRI earlier, the results of the current comparison showed that they are in line with other translations.[12] Although the body of research shows a reasonable model fit, psychometric properties and the factor structure results show there still may be room for improvement.

Exploratory analysis resulted in a four-factor solution in which 34 items of the original FCRI-NL were retained (second aim). We labelled the factors FCR severity, cognitive coping, impact of FCR on functioning, and behavioral coping. However, this new multidimensional 4-factor structure of the FCRI-NL was not replicated in two new (predominantly breast cancer) patient samples (third aim). Non-prespecified CFAs of the original 7-factor structure of the FCRI-NL showed a reasonable fit of this model to the data of both samples. Because of these results, we suggest retaining the original 7-factor FCRI-NL, instead of the new 4-factor FCRI-NL. However, the comparison showed that psychometric properties of the Reassurance and Coping Strategies subscales of the FCRI were weaker. This confirms that caution is needed for using and interpreting the FCRI-NL total score.[12] Van Helmondt et al. (2017) recommended to use the FCRI-SF-NL for research and screening purposes.[12] The remaining subscales seem most valuable in clinical practice, to discuss at item level and for tailoring interventions to the patients' needs.

Although the factor structure of the FCRI may be suboptimal, there is increasing evidence for the multidimensional approach that underlies this questionnaire.[3, 5, 36–40] FCR is an intense, difficult and multidimensional experience according to patients.[41] Therefore, multidimensional measures for FCR should be preferred above unidimensional measures. Since multidimensional measures for FCR are scarce, and

often only available in one language, cancer site specific, or have limited availability of research and psychometric data, further refinement of the FCRI is recommended. To date, many FCRI translations have been made and the body of research concerning the FCRI is rapidly growing.[8] A first step for refinement of the FCRI was the development of the Turkish 5-factor FCRI, which fitted the data better than the original 7-factor model.[21] Also, a re-examination of the dimensionality of the FCRI was done by comparing different models of FCR. They found that a multidimensional model with seven first-order factors fitted the data better than the original second order model.[16] The current article adds to this body of research.

Limitations of this study are that *samples 2 and 3* consist of (mainly) female breast cancer patients and that the participants of *sample 3* registered themselves for an intervention study, which could have influenced the results. FCR is considered a multidimensional construct and there is a possibility that specific cancer types may involve different aspects of FCR.[3, 10, 38] Also, the results of the CFA may not be generalizable to all (breast) cancer patients, because patients willing to participate in an intervention study may experience more FCR than the general (breast) cancer population. Future research should study whether the FCRI factor structure and measurement model is invariant across different types of patient populations, using a test for measurement invariance.[42] A second limitation is the small sample size of *sample 3* for CFA. This may have resulted in unstable parameter estimates, especially because there are factors with few items.[43] A third limitation might be the use of an online version of the FCRI-NL for all samples. To the best of our knowledge, other studies have used a pen-and-paper version. However, several meta-analyses have shown that paper and electronic questionnaires can be considered psychometrically equivalent.[44, 45] Also, the current study found comparable factor structure results across all FCRI translations. This illustrates that the use of an online version of the FCRI-NL has most likely not influenced the results. A fourth limitation is that the scale-free least squares estimation method in AMOS (to handle any non-normal item score distributions) applies listwise deletion to handle missing values. Listwise deletion can be problematic as it can reduce the statistical power and may result in biased parameter estimates.[46] This approach resulted in exclusion of 25 participants with missing FCRI-NL item scores in *sample 2*. To find out if the use of the scale-free least squares estimation method was problematic for our results, we performed some additional analyses. We made a comparison of the current estimation approach (listwise deletion) and two missing data procedures that maximize the use of available data (pairwise deletion and multiple imputation) in Mplus. All approaches resulted in similar fit indices, indicating that our conclusions would not have been different when using other approaches to handle missing data. Therefore, we retained our analyses.

A strength of this study is that an accurate estimation method for CFA was used, which handled any non-normal item score distributions (i.e. scale-free least squares). The

CFAs of the French and English version of the FCRI, for example, do not mention which estimation method was used. Using the default maximum likelihood estimation on data that is not multivariate normally distributed, may lead to underestimated parameters and inflated standard errors.[47] A second strength of this study is the CFA for two different patient samples, with different levels of FCR. The model fit for the 7-factor model was better in *sample 2*, with a lower mean FCR Severity score (13.9). Although these results suggest that the FCRI-NL may be more suitable for a sample with a moderate level of FCR, more research on this topic is needed.

To conclude, although there may be room for improvement, comparing all available FCRI factor structure data showed that all translations had reasonable results. Finding a better fit by proposing a new 4-factor structure of the FCRI-NL did not succeed. Therefore, we recommend retaining the original 7-factor FCRI. Future research should focus on refinement of the weaker FCRI subscales in order to be able to assess the multidimensional nature of FCR.

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04

Study protocol of the CAREST-trial: A randomized controlled trial on the (cost-) effectiveness of a CBT-based online self-help training for fear of cancer recurrence in women with curatively treated breast cancer

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Abstract

Background

One of the most prevalent long-term consequences of surviving breast cancer is fear of cancer recurrence (FCR), which is associated with higher (mental) healthcare costs and lower surveillance rates. The majority of breast cancer survivors report a need for professional help in dealing with FCR. An easy-accessible and cost-effective evidence-based psychological intervention for reducing FCR is lacking. In the current study an online self-help training to reduce FCR will be evaluated. In addition, the secondary aim of this study is to identify factors that predict whether women can benefit from the online self-help training or not.

Methods/design

A multi-center, parallel-groups, randomized controlled trial will be conducted to evaluate the (cost-) effectiveness of the CAREST trial. A sample of 454 women with curatively treated breast cancer will be recruited from 8 hospitals in the Netherlands. Participants will be randomized to the intervention or usual care group (1:1). Self-report measures will be completed at baseline, 3 (post-intervention), 9, and 24 months. Primary outcome is FCR severity; secondary outcomes are healthcare costs, health status, and psychological distress. The online tailored self-help training "Less fear after cancer" is based on cognitive behavioral therapy and consists of 2 basic modules (psycho-education; basic principles of cognitive behavioral therapy) and 4 optional modules (rumination; action; relaxation; reassurance) to choose from. Each module consists of an informative part (texts, videos, audio files) and a practical part (exercises). For every patient, the intervention will be available for three months. Personal online support by an e-mail coach is available.

Discussion

Online self-help training may be an easy-accessible and cost-effective treatment to reduce the impact of FCR at an early stage in a large group of breast cancer survivors. A strength is the 24 months follow-up period in the health economic evaluation. The results of the study will provide information on the possible strengths and benefits of online self-help training for FCR in breast cancer survivors.

Background

Due to earlier diagnosis and improved medical treatments, the number of women living with breast cancer is rising. In the Netherlands, the prevalence of breast cancer has been estimated to rise from 100.000 in 2000 to 140.000 in 2020.[1] Similarly, in the USA, the 5-year relative survival rate of women with breast cancer improved from 75% in 1975 to 90% in 2009.[2] One of the most prevalent long-term consequences of surviving cancer is fear of cancer recurrence (FCR), which can be defined as the fear or worry of the possibility that the cancer will return or progress in the same organ or in another part of the body.[3] Although the majority (82%) of long-term breast cancer survivors reported low levels of FCR, a considerable amount of women (17%) reported moderate to high FCR.[4] In younger (age 18-45) early-stage breast cancer survivors, 70% of participants report moderate to high levels of FCR.[5] Younger age was also found to be associated with a higher intensity of FCR.[5, 6] Moderate to high levels of FCR have also been found in 29% of women with ductal carcinoma in situ or early invasive breast cancer two years after diagnosis.[7]

Findings on the long-term course of FCR are still unclear.[8] Thewes and colleagues found longer time associated with reduced FCR in younger cancer patients.[9] Several other studies found no significant relationship between time since diagnosis and FCR.[3, 10–15] Elevated levels of FCR represent a continuing problem in cancer patients, up to sixteen years after diagnosis.[3, 10–15] For example, long-term breast cancer survivors (5-12 years after diagnosis) report many factors that can trigger FCR, such as hearing about cancer, unclear bodily complaints, environmental triggers (e.g., on television, the internet, newspapers, and magazines; and visiting a doctor.[16] Women encounter these triggers about twice a month.[16]

Thus, FCR is a common and continuing problem in breast cancer survivors. Women cope with FCR in different ways. Elevated levels of FCR has been found to be associated with higher frequency of unscheduled visits to the general practitioner, larger number of outpatient and emergency room visits, and more use of health care services.[5, 16, 17] Higher levels of FCR may also lead to avoiding forms of cancer screening and medical control visits.[5, 16, 17] Moreover, FCR may lead to various types of (compulsive) self-examining.[5, 16, 17] Therefore, it is not surprising that preliminary evidence shows that FCR is associated with higher healthcare costs and lower surveillance rates, which may compromise health outcomes.[5]

Depending on the coping mechanisms used by breast cancer survivors to deal with their FCR, FCR also has a considerable impact on their lives. One of the most significant effects of FCR is the negative impact on quality of life.[4, 18, 19] Furthermore, FCR may have a correlation with distress, intrusive thoughts, avoidance, hyperarousal, psychological

disorders (e.g., depression, anxiety symptoms, posttraumatic stress disorder), and fatigue.[3, 4, 13, 14, 20] Subsequently, FCR is associated with higher mental health costs.[5, 19]

Cancer survivors frequently identify FCR as a major concern and 20 to 79% of them report to have a need for professional help coping with FCR.[19, 21] About 30% of cancer survivors have indicated that there is no support for them in dealing with FCR.[22] Reasons for this include lack of recognition, lack of trained mental health professionals, insurance coverage and cost issues, and geographical distance from providers.[22, 23] Considering the increasing prevalence of breast cancer, increasing healthcare costs, and the lack of professional help for FCR in a large group of cancer survivors, there is an urgent need for easy-accessible and cost-effective evidence-based psychological interventions for reducing FCR.[1, 2, 5]

Knowledge on treatment of FCR is limited. Simard and colleagues found only five face-to-face group interventions (cognitive behavior therapy, supportive-experiential therapy, mindfulness-based stress reduction, and emotion regulation) to reduce FCR[19]. Furthermore, Völker and colleagues suggest a stepped-care model for treating FCR.[24] Normalization, psycho-education and self-management are the first steps in this model.[24] Normalization helps patients to understand that fear is a normal reaction which can be helpful in some situations. Psycho-education is necessary, because cancer survivors experience many bodily symptoms (such as fatigue, new aches and pains, muscle tension, joint stiffness, feeling of weakness, indigestion, and other physical symptoms) that can easily be misinterpreted as symptoms of recurrence.[16] Anxiety itself also can cause several bodily symptoms (such as increased heart rate, shortness of breath, chest pressure, sweating, dry mouth, dizziness, feeling of weakness, muscle tension, and indigestion), which may increase other bodily symptoms and therefore reinforce FCR. In extreme cases, FCR has been associated with the development of anxiety disorders.[8] Misinterpretation of bodily symptoms can lead to negative thinking, which causes somatic amplification. Because of this somatic amplification, patients focus even more on their bodily symptoms, leading to a negative emotional spiral. With psycho-education, patients gain more knowledge about the bodily mechanisms of fear. This knowledge can help them to break the negative spiral. Ziner and colleagues found that breast cancer survivors with high self-efficacy in dealing with concerns related to breast cancer after treatment, had lower FCR and that self-efficacy may have a protective effect in these women.[25] Therefore, training in self-efficacy may reduce FCR.[24–26] If these first steps of treatment for FCR turn out to be insufficient, cognitive behavioral therapy (CBT) should be the next step in the treatment of FCR.[24, 27, 28] Furthermore, acceptance focused therapies, such as Mindfulness Based Stress Reduction (MBSR), Mindfulness Based Cognitive Therapy (MBCT) and Acceptance and Commitment Therapy (ACT) may be included in treatment for FCR.[24]

In order to reach the growing group of breast cancer survivors experiencing FCR, a CBT-based online self-help intervention (including normalization, psycho-education and self-management) may be an appropriate and accessible way to offer psychological treatment to patients for several reasons. First, self-help without support was the second most preferred type of supportive care by cancer patients (14-28%), after individual professional counseling.[21] Furthermore, there is a growing body of evidence that internet interventions can improve psychological well-being in cancer patients.[23] Online self-help interventions have several advantages, including convenience (such as working on the self-help training in the evening when there are no competing demands), ability to proceed at one's own pace to master the material, low cost, greater privacy and confidentiality, more comfort, the intervention content can be updated quickly, greater accessibility (for example for those living in rural areas), time- and cost-effective, and where waiting lists are long.[23, 29–31] Convenience and working in their own pace may be particularly attractive for young women, who often are still working and have young children.[5] Given the high prevalence of FCR in young breast cancer survivors, online self-help training may be an effective and attractive way to reach these young women[5] Moreover, an informational self-management intervention may reduce psychological distress (feelings of tension, anger and depression) in high risk patients who perceive little control and much illness uncertainty.[32] Thus, an online self-help intervention with psycho-education may empower patients. Disadvantages of online self-help interventions are internet access constraints, technical difficulties, high drop-out rates, poor adherence, safety issues, limited personal interaction, and not being able to detect more complicated issues and non-verbal or verbal clues in patients.[23, 31, 33, 34] Furthermore, online cognitive behavioral interventions for anxiety have been found to be effective for anxiety disorders and anxiety symptoms.[30, 35] Online cognitive behavioral self-help interventions for anxiety have been found to be at least as good as face-to-face treatment in several studies, but other studies found small effects favoring face-to-face treatment.[29, 34–37] Self-help interventions may be specifically effective, if based on a theoretical model such as CBT.[38] In conclusion, CBT-based online self-help interventions are promising and may provide effective, acceptable, and practical health care for those who may otherwise remain untreated. Because online self-help training may be both easily accessible and cost-effective, in the current study an online CBT-based self-help training to reduce FCR after breast cancer treatment will be evaluated.

Aims

The primary aim of the CAncer REcurrence Self-help Training [CAREST] randomized controlled trial is to evaluate the effectiveness and cost-effectiveness of the online CBT-based self-help training "Less fear after cancer" [in Dutch: "Minder angst bij kanker"] in reducing FCR in women with curatively treated breast cancer (breast cancer survivors), compared to usual care. Specific hypotheses are that:

1. FCR severity reduces more in the online self-help condition compared to the usual care condition between baseline and follow-up (3 months). This effect will sustain 9 and 24 months after baseline. Small effect sizes are expected.
2. Health care costs reduce more in the online self-help condition compared to the usual care condition between baseline and 24 months after baseline.
3. Psychological distress reduces more in the online self-help condition compared to the usual care condition between baseline and 3 months after baseline. These effects will sustain 9 and 24 months after baseline.

Online self-help for FCR is not expected to be effective for all participants. Several factors, such as level of FCR, psychological distress, coping strategies, and perceived self-efficacy may predict if women can benefit from the online self-help training. Therefore, the secondary aim is to identify factors that predict whether women can benefit from the online self-help training or not.

4. With regard to prediction of treatment effect we will explore the following hypotheses:
    a. *Baseline fear of recurrence severity*. In participants with low scores on FCR severity there is no need for psychological help, these participants are expected not to use the online self-help training or to drop-out. In participants with moderate scores on FCR severity a modest effect of the online self-help training is expected. In participants with high scores on FCR severity there will be a modest effect of the self-help training and additional need for psychological help or guidance by a therapist.
    b. *Psychological distress*. In participants with high scores on psychological distress extra psychological help will be needed, because psychological distress may interfere with self-management capacity. Participants with moderate scores on psychological distress will have enough motivation for self-help training. Participants with low scores on psychological distress are expected to have minimal motivation for self-help training and thus a low treatment effect.
    c. *Level of functioning impairment*. In participants with high scores on level of functioning impairment extra psychological help will be needed. Participants with moderate scores on level of functioning impairment will have motivation for self-help training. Participants with low scores on level of functioning impairment will have minimal motivation for self-help training.
    d. *Coping strategies*. The relation between coping and treatment effect will be explored.
    e. *Psychosocial problems and risk factors*. If participants score high in many problem domains extra help may be needed. Moreover, high scores on trait anxiety and low scores on social support indicate that extra psychosocial help may be needed.

f. *Perceived self-efficacy for online self-help*. Participants with low scores on perceived self-efficacy for online self-help may have poor self-management skills. The treatment effect for these participants will be minimal and extra support may be needed. For participants with moderate and high scores on perceived self-efficacy for online self-help, the training which is being investigated will be appropriate and will lead to moderate treatment effect.
g. *Socio-demographic variables* with respect to treatment effect will be explored. For example, for young women and women with a partner, online self-help training may be more effective than older participants or those without a partner. Also, for medium to highly educated women the self-help training may be more effective.
h. *Medical variables* with respect to treatment effect will be explored.

Methods/design

The CAREST-study design and intervention will be reported in accordance with the CONSORT statements for eHealth interventions and parallel group randomized trials, the SPIRIT 2013 statement, and in accordance with the recommendations and guidelines for internet intervention research in psycho-oncology. [23, 39–42]

Study design

The CAREST-study is a multi-center, randomized controlled trial, comparing online self-help training with care as usual in breast cancer survivors. A sample of 454 women with curatively treated breast cancer will be recruited from 8 hospitals scattered over the Netherlands. The participating hospitals are the Maasstad hospital in Rotterdam, St Antonius hospital in Utrecht, Admiraal de Ruyter hospital in Vlissingen, Reinier de Graaf hospital in Delft, Antonius hospital in Sneek, St. Elisabeth hospital in Tilburg, Catharina hospital in Eindhoven, and UMCG in Groningen (all situated in the Netherlands). After completion of the baseline measure, women will be randomized to either the online self-help or control group. Follow-up assessments are at 3 months (post-intervention), 9 months, and 24 months after baseline. Additionally, every 3 months participants will be asked to fill out a short measure about their healthcare use. Two reminders will be sent by e-mail one and two weeks after the first invitational e-mails. Eventually, participants who do not complete the questionnaires will receive a phone call from the researcher to remind them.

Participant eligibility

Women are eligible to participate if they had a diagnosis of breast cancer 1-5 years ago; have no signs of local or regional recurrence or metastatic disease; are capable of filling out questionnaires in Dutch; if their age at disease onset was 18 years or older; and if they have access to a computer with an internet connection. There are no exclusion criteria.

Recruitment settings and procedure

Patients will be recruited in two ways. First, four hospital sites are expected to recruit participants through oncology nurses, nurse practitioners, or oncologists, who will ask eligible patients to participate in the study. These patients will be informed about the study during their regular check-up at the outpatient clinic. When women show interest in participating in the study, they receive a comprehensive information letter. In three hospitals patients will be phoned by the researcher two weeks after receiving the information letter. They will be asked whether they have any questions and if they are interested in participating in the study. Second, the remaining four hospital sites are expected to recruit participants by a comprehensive information letter sent to them by mail. These patients will also be phoned by the researcher about two weeks after receiving the information letter to ask whether they are interested in participating in the study. When patients decide to participate, they are asked to return the included informed consent form with the reply-paid envelope within a week. Moreover, all participants will be informed about the possibility of psychological counseling nearby, so they know where to turn to in case they need (more) help.

Randomization

After completing the baseline measure, every patient will be randomly assigned to either the online self-help training or care as usual with an allocation ratio of 1:1. Block randomization (block size 10) will be carried out through a sealed envelope system, for each hospital separately. Both the participants and the researchers are blinded to the randomization process, but not for the randomization outcome. Statistical analysis will be done by a statistician blind for randomization outcome.

Intervention

After conducting a survey in patients from the Dutch association of cancer patients' organizations, the online self-help training "Less fear after cancer" was developed by the Helen Dowling Instituut, an institute for psycho-oncology in Bilthoven, the Netherlands.

"Less fear after cancer" is a tailored online self-help training based on cognitive behavioral therapy. Participants start the training by filling out the Fear of Cancer Recurrence Inventory (FCRI)[3], after which they get (automated) feedback about their scores and a suggestion about which modules to follow. The FCRI and all modules are visible on the worksheet of the intervention (see Figure 1). First, participants follow two basic modules: 1) Psycho-education about FCR, its symptoms and learning to recognize symptoms of fear; and 2) The basic principles of cognitive behavioral therapy (this module is divided in two parts). After these basic modules women can choose from the following four the modules that are relevant to their situation: 1) How to stop rumination, behavioral techniques to stop ruminating; 2) Action, making an action plan about what one can do when fear of recurrence pops up; 3) Relax, audio files with

relaxation practices; and 4) Reassurance, how and when to seek reassurance. Each module consists of an informative part and a practical part in which participants are motivated to do exercises or assignments in daily life. Participants are advised to take a week for each module they choose, so most participants will need four to six weeks depending on how many modules they do. It is explained that the more time they invest, the more effect they can expect from the training, but participants eventually choose themselves how much time is actually spent on the training. For every patient, the intervention will be available for three months.

The most important functionality of the online self-help training "Less fear after cancer" is the worksheet, because it gives an overview of the modules and access to the intervention. By clicking on a module, participants can access the information (texts, videos, audio files) and exercises of the self-help training. Other functionalities include a library with the information and forms in pdf format, videos, audio files, and a mailbox for technical assistance.

"Less fear after cancer" is fully automated and primarily non-guided and is delivered without professional support from a therapist. In this study, personal online support by an e-mail coach (the researcher) is available for the women that indicate a need for this. The e-mail coach can give technical assistance and eventually refer participants to their general practitioner or medical specialist when they indicate a need for professional help.

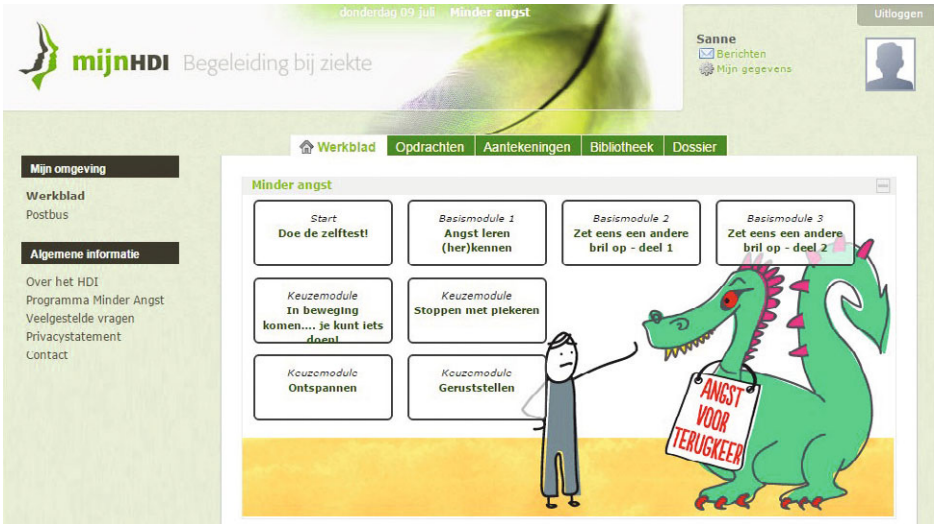

Figure 1. Screenshot of the "Less fear after cancer" online self-help training.

Usual care

The control group of this RCT has access to usual care. Care as usual may differ somewhat between hospitals and may include psychosocial care from within the hospital or elsewhere. In the Medical Consumption Questionnaire, the use of psychosocial care will be assessed. Care as usual will be available in both conditions, in the intervention condition the online self-help is extra.

Outcomes

All participant outcomes will be gathered using online self-report questionnaires hosted by SurveyMonkey.com. Participants will receive an invitational e-mail with a link to complete the questionnaires online. The questionnaires at baseline, 3 months, 9 months, and 24 months include questions on socio-demographic and medical variables.

Primary outcomes

Fear of cancer recurrence will be assessed using the 43-item Dutch version of the FCRI.[3] The FCRI consists of statements rated on a 5-point Likert scale ranging from 0 (not at all or never) to 4 (a great deal or all the time). The FCRI includes seven subscales: triggers, severity, psychological distress, coping strategies, functioning impairments, insight, and reassurance. The triggers-subscale evaluates the presence of potential stimuli activating FCR. Psychological consequences of FCR are evaluated by the subscales psychological distress and functioning impairments. The insight scale measures the level of self-criticism towards FCR intensity. The reassurance- and coping strategies-scales measure a variety of coping strategies that can be used to cope with FCR including denial, wishful thinking, cognitive avoidance, and reassurance. The severity subscale assesses the presence and severity of intrusive thoughts or images associated with FCR and this scale can be used separately as a brief screening instrument of FCR and as an outcome measure.[3] The severity subscale is the primary outcome measure. The coping strategies- and functioning impairments-scale scores at baseline will be used in the predictor analysis. The original 42-item French-Canadian version of the FCRI had a good internal consistency (Cronbach's α=0.95 for the total score and α=0.89 for the severity subscale) and stable over a 1-month interval (r=0.89, p<0.001).[3] The scale has a robust factor structure and the results support construct validity with other self-report scales assessing FCR (r's 0.68 to 0.78) or related constructs (r's 0.43 to 0.66) and quality of life (r's -0.20 to -0.36).[3] The Dutch version of the FCRI (FCRI-NL) is currently being validated.

Fear of cancer recurrence will also be assessed with the Dutch version of the Cancer Worry Scale (CWS).[43] The CWS assesses concerns about developing cancer or developing cancer again and the impact of these concerns on daily functioning. The Dutch version of the CWS consists of 8 items that are rated on a 4-point Likert scale ranging from 1 (never) to 4 (always). Higher scores indicate more frequent worries about

cancer. A cut-off score of 13 (low ≤13, high ≥14) turned out to be optimal for detecting severe levels of FCR.[43] Moreover, the CWS is a reliable questionnaire (Cronbach's α=0.87) and evidence has been found to support the construct validity.[43]

Secondary outcomes
Healthcare costs will be assessed with the Medical Consumption Questionnaire (MCQ), a questionnaire to assess non-disease specific healthcare costs.[44] More precisely, the volume of used healthcare will be assessed with the MCQ. Afterwards, the Dutch Manual on Cost Investigations will be used to calculate the healthcare costs.[45]

Furthermore, the Dutch translation of the EuroQol-5D (EQ-5D), a generic measure of health status, will be used for the economic evaluation.[46, 47] The EQ-5D comprises five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain consists of one question with three answer categories: (1) no problems, (2) some problems, and (3) extreme problems.[46] A health state can be derived by combining the scores from each dimension.[46] This results in a 5-digit number, for example state 12233. This health state indicates no problems with mobility, some problems with self-care and usual activities, and extreme problems with pain/discomfort and anxiety/depression.[46, 47] EQ-5D health states may be converted into a EQ-5D index by applying predetermined weights to the five domains.[48] The Dutch EQ-5D tariff will be used to value this EQ-5D index.[46] The EQ-5D index gives a societal-based global quantification of the patient's health status on a scale ranging from 0 (death) to 1 (perfect health).[49] For economic evaluation, the EQ-5D index scores will be used to determine quality-adjusted life years (QALYs).[49] Patients will also be asked to rate their overall health status on a visual analogue scale (EQ-5D VAS), a quantitative self-rating of health status in which patients are asked to rate their current health state on a 0 (worst imaginable health status) to 100 (best imaginable health status) scale.[47] The EQ-5D is a 'user-friendly' questionnaire, with acceptable reliability and validity for various populations.[50–52]

Psychological distress will be assessed with the corresponding subscale of the FCRI-NL.[3]

Process outcomes
In addition to the self-report questionnaires, technical data on the use of the intervention will be gathered in the intervention group. For example, frequency of logins, duration of logins, and website activity will be evaluated.

Other outcomes
The *use of extra (psychological) help* will be assessed with the Medical Consumption Questionnaire (MCQ).[45] Furthermore, help or referral by the e-mail coach will be registered and added to the MCQ score.

Psychosocial problems and risk factors will be assessed with the Psychosocial Distress Questionnaire-Breast Cancer (PDQ-BC).[53] The PDQ-BC is a multi-dimensional screening instrument specific for breast cancer patients. It consists of nine subscales using 35 items assessing psychological risk factors (i.e. trait anxiety and (lack of) social support) and state anxiety, depressive symptoms, social problems, physical problems, body image, financial problems, and sexual problems. All items are answered on a 4-point Likert scale, ranging from 1 (not at all) to 4 (very much).[53] For most subscales, high scores indicate more psychosocial problems, except for body image and social support for which higher scores indicate fewer problems.[54] The PDQ-BC appears to have a sufficient internal consistency, and good construct validity, test–retest reliability, and sensitivity to change. Furthermore, the PDQ-BC subscales state anxiety and depressive symptoms have a satisfactory sensitivity and specificity.[53–55]

Self-efficacy for online self-help will be assessed with a questionnaire which was especially assembled for the current study. Bandura argued that all-purpose measures of perceived self-efficacy usually have limited explanatory and predictive value because most of the items in an all-purpose test may have little or no relevance to the domain of functioning.[56] Scales of perceived self-efficacy should be tailored to the particular domain of functioning that is the object of interest. Therefore, we collected many potentially useful items from various self-efficacy questionnaires.[57–61] In consultation with both professionals and patients, we improved and reduced the items to a 15 item questionnaire tailored to assess self-efficacy for our online self-help training. The items are rated on a 5-point Likert scale, ranging from 1 (not like me) to 5 (totally like me). The items are divided into three domains: 1) general internet use (3 items); 2) health related coping strategies (7 items); and 3) patients' expectations on online self-help training for fear of cancer recurrence (5 items).

A subsample of patients (n=16) will be asked about their experience with the online self-help in a semi-structured interview, to evaluate the online self-help training and to detect possible ways to further improve the training. There are different profiles of FCR, which vary according to its severity and the type of coping strategies used. Patients will be selected based on their baseline score on the FCRI and will represent different FCR-profiles: mild FCR-severity and low coping, mild FCR-severity and high coping, moderate FCR-severity and high coping, moderate FCR-severity and low coping.[62] From the first 50 participants who finished the online self-help training, four participants from each FCR-profile group will be randomly picked. If women refuse to participate, another participant will be randomly picked from that group.

Sample size calculation

The sample size calculation is based on a clinically relevant improvement on the FCRI severity subscale at 3 months. With an effect size of *d* = 0.3, a minimum number of 2.28 points on the FCRI severity subscale could be detected. Based on our experience with the FCRI, this seems to be a clinically relevant difference. In total 454 patients need to be included (227 in each group) to statistically detect the minimum effect size of *d* = 0.3 between mean FCRI severity subscale scores of both groups with a power of 0.8 and a two-sided alpha of 0.05. The power analysis program G*Power 3.1.7 was used to calculate the effect sizes.[63] Since in previous online intervention studies amongst breast cancer patients about half of all invited patients expressed an interest in participating and another 35% was lost after randomization, the aim of this study is to ask a minimum of 900 patients to participate in the study.[64, 65]

Statistical analysis

Primary analyses

Baseline characteristics in both groups will be compared to check if randomization has resulted in an equal distribution of the baseline variables. Data will be analyzed according to the intention-to-treat (ITT) principle. In the primary analyses, post-training scores will be compared between the two groups, controlling for baseline symptom levels. Analyses will be performed using t-tests and linear mixed models including exploratory predictor analyses. An advantage of linear mixed models is the optimal use of available data. The primary analysis is aimed at comparing the online self-help with care as usual at 3 months on the FCRI severity subscale. Analysis of co-variance will be performed to test whether the outcome variables differed between the online self-help and care as usual, using baseline level as covariate. The stability of the results will be analyzed using the data from 9 months and 24 months after baseline, again using linear mixed models to control for the dependency caused by the repeated measurements. Time will be analyzed as a categorical predictor with four levels (baseline - 3 months - 9 months - 24 months). Linear mixed models with a specified covariance pattern model will be used to examine the course of FCR.[66] The fixed-effects parameters of the models will be estimated with maximum likelihood. Inspection of the Log likelihood ratio test, Akaike Information Criterion (AIC), and Bayesian Information Criterion (BIC) with restricted maximum likelihood (REML) will be used to find the most suitable covariance pattern model (e.g., compound symmetry, autoregressive, unstructured).

For the secondary analyses, significant predictors will be selected using exploratory predictor analyses. Then multivariate hierarchical regression analysis will be performed to assess predictors of effect. The predictors that are found statistically significant will be added as interaction terms with condition (online self-help versus care as usual). Dropouts (attrition) will be closely investigated, and predictors of dropouts will also be analyzed by multivariate regression analysis.

Cost-effectiveness analysis
The economic evaluation will consist of a cost-effectiveness analysis and a cost-utility analysis, both done from a societal perspective.[49] The cost-effectiveness ratio will represent the costs per significantly improved participant, while the cost-utility analysis will represent the costs per additional quality-adjusted life year (QALY). The time horizon will be lifetime. As the study period is limited in time, cost and effect will be modelled in time, using the assumption that the spontaneous recovery is 2 years. The effects of this assumption on the cost-effectiveness ratio will be tested by testing the scenarios of spontaneous recovery after 6 months, 1 year and 5 years.

Costs will be estimated from a societal perspective and will thus include the costs related to the intervention, all other healthcare costs and non-healthcare costs during the time horizon of the study. Healthcare consumption will be measured with the MCQ. Healthcare consumption includes all non-disease specific healthcare used in the previous 3 months, such as visiting the general practitioner or other healthcare providers, emergency room visits, hospitalization, and medication use. Then, the guidelines as descripted by the Dutch Manual on Cost Investigations will be used to calculate the healthcare costs.[45] For healthcare where no guidelines or standard prices are available, real cost prices will be determined or, when available, derived from the health care provider administration.

QALYs will be calculated from EQ-5D health states using the Dutch EQ-5D tariff.[46] Non-parametric bootstrap simulations will be used to estimate uncertainty intervals around the ICERs, in order to deal with the most likely skewed distributions of costs. Cost-effectiveness acceptability curves will be calculated to show the probability that the intervention is cost-effective in comparison with the control group, given varying thresholds for the willingness to pay for gaining one unit of effect, i.e. a QALY or a significantly improved participant. The robustness of the results will be explored using one-way sensitivity analyses in which the input variables for assessing both cost and effectiveness are varied.

Discussion

FCR is one of the most common long-term consequences of surviving cancer, with a major impact on personal, family, and professional life and is associated with considerable healthcare costs. In order to ensure the availability of affordable evidence-based psychological interventions for FCR in the future, research on cost-effective interventions for FCR is needed. This is especially relevant for psychological care in breast cancer survivors, as breast cancer is the most prevalent form of cancer in women and the prevalence is still increasing, together with the healthcare costs.[1] Online self-help training may be an efficient and cost-effective way to offer psychological treatment for this group. Moreover, online self-help may provide easy-accessible

treatment for the large group of breast cancer survivors with low to moderate FCR, diminishing the number women in need of face-to-face therapy. Therefore, the CAREST-study has been designed to evaluate the effectiveness and cost-effectiveness of an online self-help training for FCR.

Strengths and weaknesses

In the proposed study, an online CBT-based self-help training will be compared with care as usual. To the best of our knowledge, this is the first study to evaluate an online self-help training for FCR in breast cancer survivors. Using the internet, this intervention provides a novel and easy-accessible approach to reduce the impact of FCR at an early stage. In the long term this study may contribute to early prevention of FCR. Moreover, a health economic evaluation is included in the trial, to assess the cost-effectiveness of the online self-help training up to 24 months. The 24-month follow-up period strengthens the study, whereas many studies only include follow-up periods up to 12 months. The results of the study will provide information on the possible strengths and benefits of online self-help training for FCR in breast cancer survivors. However, since both the intervention and the control group are allowed to receive usual (psychological) care during the study, the expected effects are small. Inclusion of women with all levels of FCR, ranging from no FCR to considerable FCR, may also decrease the effectiveness of the online self-help training. Nevertheless, this design provides the opportunity to predict who benefits most from the intervention. Therefore, this trial will provide clinically relevant information. Considering the lack of intervention research for FCR in breast cancer patients, this study will contribute to the body of knowledge about how to best support this large and growing group. Research into alternative, long-term effective treatment options for this group will be of great clinical value. The eventual goal of the proposed study is to implement an easily accessible, evidence-based and cost-effective intervention for FCR in women who benefit most from these kind of online self-help interventions, within the follow-up care of breast cancer patients in the Netherlands.

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05

No effect of CBT-based online self-help training to reduce fear of cancer recurrence: First results of the CAREST multicenter randomized controlled trial

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Abstract

Objective

Fear of cancer recurrence (FCR) is a common consequence of surviving cancer; therefore an easily accessible self-help training could help many cancer survivors to deal with FCR at low costs. The CAncer REcurrence Self-help Training [CAREST] trial evaluates the effectiveness of an online tailored self-help training, based on evidence-based cognitive behavioral therapy principles in breast cancer survivors. Also, possible predictors for benefiting from the online self-help training were examined.

Methods

This multicenter randomized controlled trial included 262 female breast cancer survivors, randomly assigned to either online self-help training (n = 130) or care as usual (CAU; n = 132). Participants completed questionnaires at baseline (T0), three months (T1; after intervention), and nine months (T2). The primary outcome was FCR (Fear of Cancer Recurrence Inventory Severity subscale). Both effectiveness and predictors were analyzed with Latent Growth Curve Modeling (LGCM) according to the intention-to-treat principle.

Results

LGCM showed no differences between the average latent slope in both groups ($\chi^2(1) = 0.23$, $p = 0.63$), suggesting that the treatments did not differ in their change in FCR over time. Moreover, no differences were found in the effects of the predictors on the latent slope in both groups ($\chi^2(1) = 0.12$, $p = 0.73$), suggesting that no significant predictors were found for the effect of the intervention on FCR.

Conclusion

There was no effect of the CBT-based online self-help training "Less fear after cancer" in the current study. Therefore, we recommend adding professional support to online interventions for FCR.

Background

Fear of cancer recurrence (FCR) is defined as "fear, worry, or concern about cancer returning or progressing" and considered one of the most prevalent and stable long-term psychological consequences of surviving (breast) cancer.[1,2] FCR ranges from low or healthy levels in the majority of breast cancer survivors to clinical levels (moderate-high FCR) in 17% of breast cancer survivors.[2,3] In younger (age 18-45) early-stage breast cancer survivors, 70% experiences clinical levels of FCR.[4] High levels of FCR may negatively affect self-examining-, cancer screening-, and follow up behaviors, mood and quality of life, health outcomes, and may increase healthcare costs. [1,3–6]

There is a growing body of research on evidence-based interventions for FCR.[1,7,8] However, easy accessible and cost-effective interventions are still scarce. Online self-help interventions, although probably not suitable for every patient, have several advantages, including convenience, low costs, greater privacy, greater accessibility, and patients can work at their own pace.[9,10] Therefore, we started the CAncer REcurrence Self-help Training [CAREST] randomized controlled trial to test an online self-help training based on evidence-based cognitive behavioral therapy (CBT) to reduce FCR.[11]

In the trial, we evaluated the effectiveness of this online self-help training in reducing FCR compared to a care as usual (CAU) control group in women with curatively treated breast cancer (breast cancer survivors).[11] We hypothesized greater FCR reduction in the intervention group compared to CAU alone at three and nine months after ending the intervention. Moreover, since we expected that online self-help is not suitable for all patients, we were interested in predictors to identify the group for whom it may work.[11] Therefore, the following predictors were investigated: socio-demographic variables, medical variables, self-efficacy for online self-help, coping strategies, functioning impairments, psychological distress, and psychosocial problems and risk factors. Hypotheses concerning the predictors are described in detail in Supplementary materials 5A.

Methods

Setting and ethical issues

The study protocol of this RCT is published elsewhere.[11] Recruitment was carried out in eight hospitals in the Netherlands. Ethical approval was granted by the Medical Ethical Committee of the Maasstad hospital (TWOR) in Rotterdam (reference number 2013/41) and the local ethics committees of all participating hospitals. All participants signed an informed consent form before study participation. The CAREST trial has been registered in the Netherlands Trial Register (NTR4119). The study was conducted according to the principles of the Declaration of Helsinki.[12]

Recruitment procedures

Between April 2014 and May 2016, patients were recruited during their regular check-up at the outpatient clinic or by sending them a comprehensive information letter by mail (recruitment strategies differed because of pragmatic reasons). After 2 weeks, patients were reminded of the study by phone or they were sent a letter by the researcher. Patients who decided to participate returned the informed consent form within one week. On this form, they indicated whether they agreed to participate in the RCT or to complete the Dutch version of the Fear of Cancer Recurrence Inventory (FCRI-NL) once.

Participants

For growth models, a sample size of at least 100 is preferred.[13] Between April 2014 and July 2016, eligible patients were recruited consecutively from the eight participating hospitals. Women were eligible to participate if they had a diagnosis of breast cancer 1-5 years ago, had no signs of local or regional recurrence or metastatic disease (according to their oncologist or oncology nurse), were capable of completing questionnaires in Dutch, were 18 years or older at disease onset, and had access to a computer with an internet connection. There were no exclusion criteria.

Randomization

Block randomization (block size 10) was carried out through the sealed envelope system by an independent research assistant of the Helen Dowling Institute (HDI). The researchers did not have any influence on (and were blinded to) the randomization process. Participants were randomly assigned to either the online self-help training (intervention) or CAU with an allocation ratio of 1:1, stratified by hospital. Data was made anonymous by coding and separating personal data from the research data.

Intervention

A detailed description of the intervention is published elsewhere.[11] In short, the intervention *"Less fear after cancer"* is a tailored and CBT-based online self-help to reduce FCR, developed by researchers of the HDI. The program includes two basic modules containing psycho-education about FCR and the basic principles of CBT, and four additional modules: a) how to stop rumination, b) making an action plan for when FCR arises, c) audio files with relaxation practices, and d) how and when to seek reassurance. More details of the intervention are provided in Supplementary materials 5B. Participants in both the control and intervention groups received CAU: standard care (which may also include psychological or other support) in their own hospital.

Measures

Outcomes were collected through online self-report questionnaires at baseline (T0), three months (T1; after intervention), and nine months (T2). Participants received an invitational e-mail with a link to complete the questionnaires online. Socio-

demographic variables were assessed at baseline, medical variables at all time points, both were self-reported.

The primary outcome was FCR, assessed with the Severity subscale of the Dutch translation of the Fear of Cancer Recurrence Inventory (FCRI-SF-NL), which can be used to screen for clinical levels of FCR.[14–16] The FCRI-NL consists of 42 items on a 5-point Likert scale and comprises seven subscales: triggers, severity (FCRI-SF-NL; range 0-36), psychological distress, coping strategies, functioning impairments, insight, and reassurance.[15] A cutoff score of 13 or higher (FCRI-SF-NL) is considered optimal for detecting the presence of clinically significant FCR.[14] The FCRI-SF-NL demonstrated good reliability and validity.[16]

Coping strategies, functioning impairments, and psychological distress were assessed with the FCRI-NL (described above). Since there was no measure for self-efficacy for online self-help available, self-efficacy was assessed with a 15-item questionnaire developed for this RCT and described in the study protocol, which measured: 1) general internet use (3 items); 2) health-related behavior (7 items); and 3) patients' expectations of online self-help training for fear of cancer recurrence (5 items).[11] In this study, the estimated reliability of this questionnaire was good (Cronbach's α = 0.82 for the total scale and Cronbach's α = 0.72 - 0.93 for the subscales). Psychosocial problems and risk factors were assessed with the Psychosocial Distress Questionnaire-Breast Cancer (PDQ-BC).[17] The PDQ-BC is a 35-item multi-dimensional screening instrument specific for breast cancer patients. Its subscales measuring trait anxiety (10 items), (lack of) social support (1 item), depressive symptoms (7 items), and physical problems (4 items) were included in this study. Higher scores indicate more psychosocial problems, except for social support for which higher scores indicate fewer problems.[17, 18] The PDQ-BC showed good estimated reliability (Cronbach's α = 0.70 - 0.87) for the subscales used in this study, and satisfactory construct validity for the physical problems subscale (other subscales were not reported).[17–19]

Statistical analyses

Type of recruitment and reminder were compared with chi square tests and independent samples t-tests. Prior to data analysis, we assessed the multivariate normality assumption for the primary outcome variable FCRI-SF-NL, both with numerical tests (Shapiro, Mardia, Henze-Zirkler and Royston test for multivariate normality) and graphical tests (Q-Q plot).[20] Because this assumption was violated (see online Supplementary materials 5C), robust maximum likelihood (MLR) estimation was used to estimate the model parameters. The significance level was set at 5%. Little's MCAR test suggested that the data were likely missing completely at random, therefore we can use multiple imputation to handle missing data.[21–23] Data were analyzed according to the intention-to-treat (ITT) principle.[11]

In contrast with our study protocol, analyses were conducted with Latent Growth Curve Modeling (LGCM); a newer, more advanced and flexible technique than originally planned.[11, 24] LGCM is similar to linear mixed models (and repeated measures ANOVAs as a special case).[25] However, by using the repeated measurements to estimate a latent intercept and slope for each patient, LGCM allows for assessing change at the intra-individual level, as well as predicting what influences change at the inter-individual level. Moreover, the LGCM fit indices can be used to evaluate whether the hypothesized growth model adequately fits the observed data.[26] The new analysis was pre-registered at the Open Science Framework.[27]

A multi-group LGCM technique was used to examine effects on both group level (e.g., intervention versus CAU) and individual level (i.e., individual differences).[28] Within each group, individual changes in the FCR scores over time were used to estimate two latent growth factors (intercept and slope). These factors not only indicate whether the intervention and CAU on average resulted in a higher or lower FCR over time, but also how much the change in FCR varied across patients. Constraining the latent slope factors to be equal across the groups directly tests whether the intervention and CAU differ in their FCR change over time. However, to adjust this effect for the confounding influence of the predictors (presented in Figure 1), we first investigated whether the these predictors showed an equal effect on the latent slope factor in both groups, similar to the homogeneity of regression slopes assumption in ANCOVA models.[29] In LGCM, this assumption is met when the chi-square difference test indicates that the model including equal predictors effects across groups (homogeneous model) does not show significantly worse model fit than the model without those restrictions (unconditional model).

In general, model fit was assessed with the maximum-likelihood chi-square statistic (χ^2), the comparative fit index (CFI), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and the root mean squared error of approximation (RMSEA).[13, 30, 31] The goodness of fit criteria for the fit indices are: CFI ≥ 0.95 and RMSEA ≤ 0.06.[30, 31] The χ^2, AIC and BIC criteria were used to compare models, with higher χ^2, and lower values of AIC and BIC, indicating a better fit to the data.[30, 31]

Analyses were performed with IBM SPSS 23 for Windows and R statistical software (version 3.4.1), with software packages lavaan (for the LCGM, version 0.5-23.1097) and BaylorEdPsych (for checking missing data for random occurrences, version 0.5).

Results

Response rate and patient characteristics

Recruitment of patients by oncology nurses resulted in a higher response than recruitment by mail ($\chi^2 = 7.15$, $p = 0.03$), and reminders by phone resulted in a higher

response than reminders by mail (χ^2 = 16.37, p < 0.001). However, recruitment and reminder methods did not significantly differ in baseline FCR level (t (467) = -0.82, p = 0.42 and t (50) = 0.17, p = 0.87), age (t (1133) = -1.87, p = 0.06 and t (88.55) = 1.01, p = 0.32), and time since diagnosis (t (1130) = -1.75, p = 0.08 and t (232) = 1.57, p = 0.12). A total of 516 (44%) of the eligible patients gave their consent to participate (see Figure 2: flowchart). The patients who chose to complete the FCRI only once (n = 254; nonparticipants) were older (M = 61.05, SD = 10.55 vs. M = 55.55, SD = 9.89; p<.001) and had lower FCRI-SF-NL scores (M = 12.19, SD = 6.63 vs. M = 15.22, SD = 6.88; p<.001) than patients who signed up for the RCT (n=262, hereafter referred to as participants). Of the nonparticipants, patients who completed the questionnaire on paper were older (M = 64.81, SD = 10.60 vs. M = 60.24, SD = 10.33) and had higher FCRI-SF-NL scores (M = 13.55, SD = 6.23 vs. M = 11.23, SD = 6.69) than patients who completed the questionnaire online. In the RCT, all measures were completed online. Participants in the two RCT conditions did not differ from one another in terms of drop-out rate (χ^2 = 7.23, p = 0.06). Reasons for drop-out were personal circumstances (13), not experiencing FCR (six), questionnaires (six), technical difficulties (three), intervention (two), randomization outcome (two), cancer recurrence (two), or unknown (30). More details can be found in the flowchart (Figure 2). Table 1 shows the demographic and medical characteristics of the participants. Some participants reported recurrence or metastasis of cancer, while they were referred to this study as having “no signs of local or regional recurrence or metastatic disease” by their nurse practitioners. We decided to include all participants, because recurrences were reported > 1 year ago or were another primary cancer, most metastases reported were in the sentinel nodes (and probably curatively treated), and some cases were in fact no recurrence or metastasis.

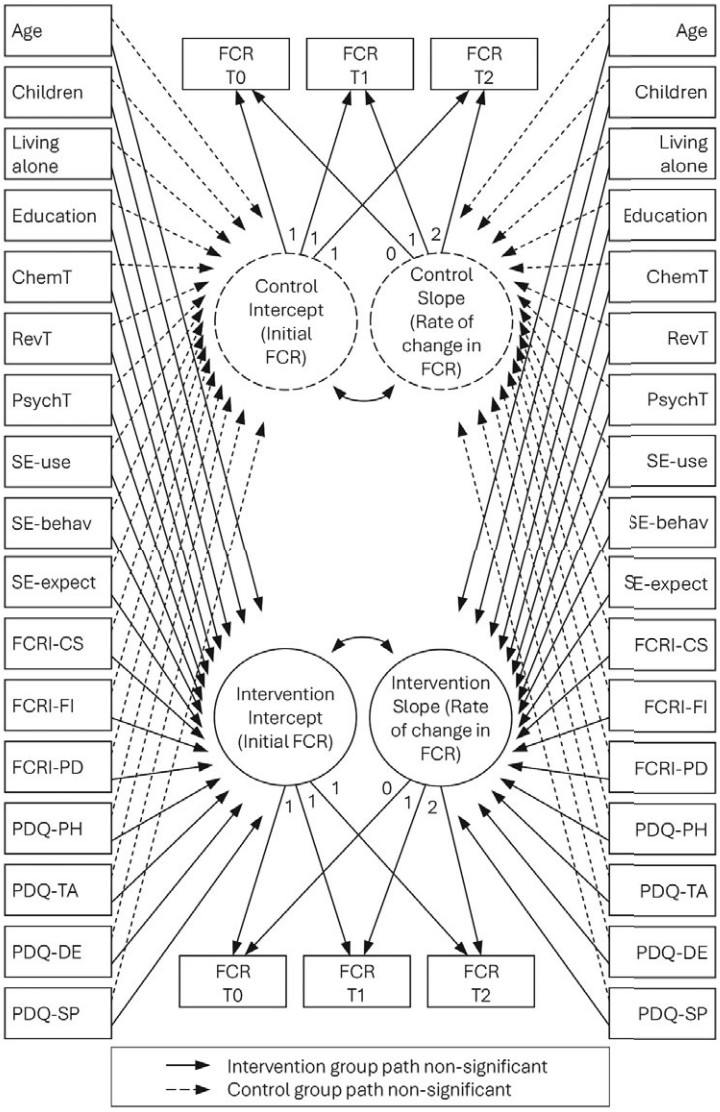

Figure 1. Multi-group latent growth curve model on the change in FCRI over time for both the intervention group and CAU control group.

The rectangles represent measured variables and the circles designate latent growth factors. The loadings on the latent intercept factors are fixed at 1, and on the latent slope factor are fixed at 0, 1 and 2, respectively for the three repeated FCR measurements. One-headed arrows represent regression paths; two-headed arrows represent correlations. Abbreviations: FCR = Fear of Cancer Recurrence; control = care as usual (CAU); intervention = online self-help for fear of cancer recurrence; T0 = time-0 (baseline); T1 = time-1 (three months); T2 = time-2 (nine months); ChemT = treatment chemotherapy; RevT = treatment revalidation; PsychT = treatment psychologist/psychiatrist; SE-use = self-efficacy for online self-help questionnaire, general internet use subscale; SE-behav = self-efficacy for online self-help questionnaire, health-related behavior subscale; SE-expect = self-efficacy for online self-help questionnaire, expectations of online self-help subscale; FCRI-CS = Fear of Cancer Recurrence Inventory, coping strategies subscale; FCRI-FI = Fear of Cancer Recurrence Inventory, functioning impairments subscale; FCRI-PD = Fear of Cancer Recurrence Inventory, psychological distress subscale; PDQ-PH = Psychosocial Distress Questionnaire, physical problems subscale; PDQ-TA = Psychosocial Distress Questionnaire, trait anxiety subscale; PDQ-DE = Psychosocial Distress Questionnaire, depressive symptoms subscale; PDQ-SP = Psychosocial Distress Questionnaire, social support subscale.

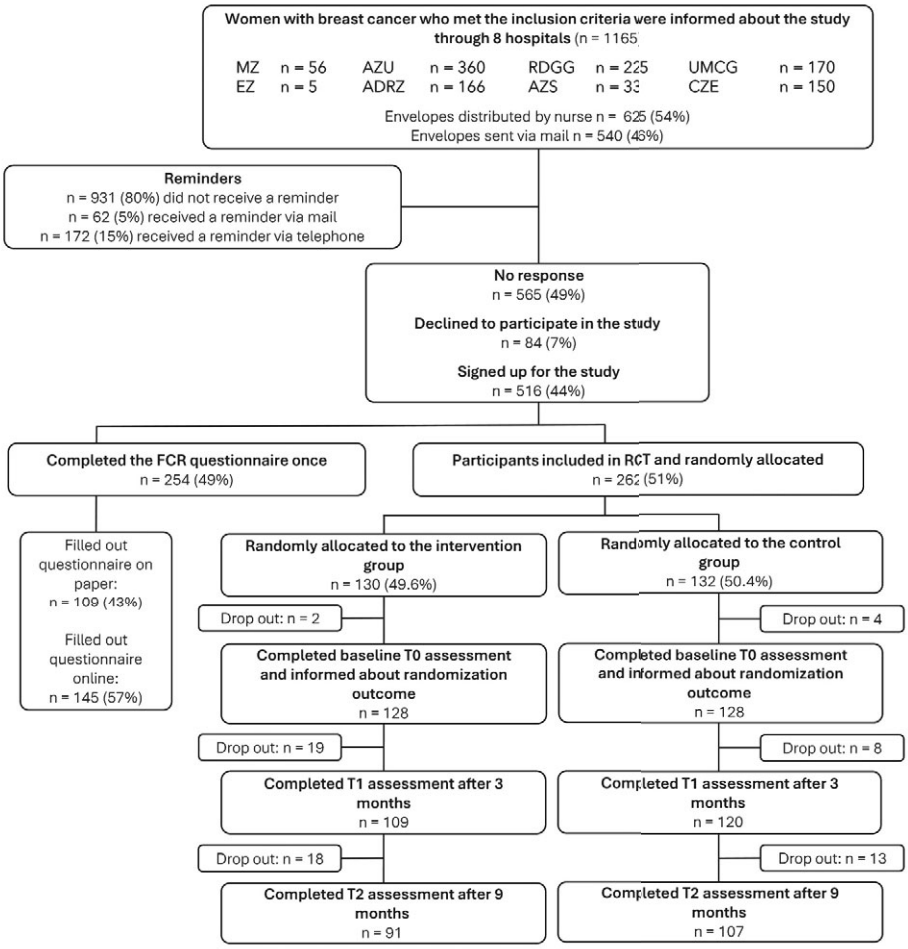

Figure 2. Flowchart for participant inclusion and retention in the randomized controlled trial.

Abbreviations: MZ = Maasstad hospital Rotterdam; EZ = Elisabeth hospital Tilburg; AZU = St Antonius hospital Utrecht; ADRZ = Admiraal de Ruyter hospital Vlissingen; RDGG = Reinier de Graaf hospital Delft; AZS = Antonius hospital Sneek; UMCG = The University Medical Center Groningen; CZ = Catharina hospital Eindhoven; control group = care as usual (CAU); intervention group = online self-help for fear of cancer recurrence; RCT = randomized controlled trial; T0 = baseline measure, before intervention; T1 = three months after inclusion, directly after intervention; T2 = nine months after inclusion, six months after intervention.

Table 1. Demographic and medical characteristics of the sample.

	Intervention (n=130)		Care as usual (n=132)		Total (n=262)	
	n	%	*n*	%	*n*	%
Demographic characteristics						
Age	n=126		n=128		n=254	
M (SD)	55.3	(10.1)	56.2	(9.8)	55.8	(9.9)
	n=128		n=128		n=256	
Having a partner	109	85.2	110	85.9	219	85.5
Having children under 12 years	18	14.1	13	10.2	31	12.1
Living situation	n=128		n=128		n=256	
Alone	14	10.9	15	11.7	29	11.3
With partner	41	32.0	52	40.6	93	36.3
With children	4	3.1	4	3.1	8	3.1
With partner and children	33	25.8	31	24.2	64	25.0
Alone, with (adult) children living on their own	0	0.0	1	0.8	1	0.4
With partner and (adult) children living on their own	19	14.8	16	12.5	35	13.4
With both children and (adult) children living on their own	2	1.6	1	0.8	3	1.1
With partner and both children and (adult) children living on their own	12	9.4	5	3.9	17	6.5
Other	3	2.3	3	2.3	6	2.3
Education[†]	n=128		n=128		n=256	
Low (ISCED 0-1-2)	17	13.3	15	11.7	32	12.5
Medium (ISCED 3-4-5)	60	46.9	62	48.4	122	47.7
High (ISCED 6-7-8)	50	39.1	51	39.8	101	39.5
Other	1	0.8	0	0	1	0.004
Employment	n=128		n=128		n=256	
Fulltime paid work	13	10.2	12	9.4	25	9.8
Less than full-time paid work	50	39.0	45	35.1	95	37.1
Self-employed entrepreneur	6	4.7	9	7.0	15	5.9
Housewife	19	14.8	16	12.5	35	13.7
Unemployed	3	2.3	4	3.1	7	2.7
Sick leave	3	2.3	5	3.9	8	3.1
Disability insurance act	8	6.3	6	4.7	14	5.5
Retired	17	13.3	21	16.4	38	14.8
Other	9	6.9	10	7.8	19	7.4
Medical characteristics						
Time since diagnosis	n=125		n=128		n=253	
M (SD)	2.5	(1.1)	2.6	(1.2)	2.6	(1.1)
	n=128		n=128		n=256	

Table 1. Demographic and medical characteristics of the sample. (continued)

	Intervention (n=130)		Care as usual (n=132)		Total (n=262)	
	n	%	*n*	%	*n*	%
Affected lymph nodes	48	39.3	50	40.3	98	39.8
	n=128		n=128		n=256	
Hereditary cancer	4	3.8	4	3.8	8	3.8
Treatment	n=128		n=128		n=256	
Mastectomy	54	42.2	65	50.8	119	46.5
Lumpectomy	77	60.2	70	54.7	147	57.4
Lymph node removal	49	38.3	46	35.9	95	37.1
Radiotherapy	94	73.4	79	61.7	173	67.6
Chemotherapy	83	64.8	78	60.9	161	62.9
Hormone therapy	76	59.4	69	53.9	145	56.6
Immunotherapy	20	15.6	22	17.2	42	16.4
Other	13	10.2	7	5.5	20	7.8
Disease status (self-reported)	n=128		n=128		n=256	
(No activity)	107	83.6	107	83.6	214	83.6
Recurrence	5	3.9	5	3.9	10	3.9
Metastasis	8	6.3	6	4.7	14	5.5
Previous serious illnesses	n=128		n=128		n=256	
	16	12.5	15	11.7	31	12.1
Previous rehabilitation program	n=126		n=127		n=253	
	39	31.0	53	41.7	92	36.4
Previous psychological care	n=128		n=128		n=256	
	39	30.5	44	34.4	83	32.4
FCR Severity (Baseline)	n = 128		n = 128		n = 256	
M (SD)	15.9	(7.2)	14.5	(6.6)	15.2	(6.9)

Abbreviations: M = mean, SD = standard deviation, ISCED = International Standard Classification of Education, FCR = fear of cancer recurrence.
† International Standard Classification of Education (ISCED) 2011

Latent growth curve models

In the LGCM, Model 1 indicated no differences between the average latent slope in the intervention versus CAU group, based on the chi-square difference test comparing submodels 1a and 1b (Table 2). Thus, constraining the latent slopes to be equal in both groups did not result in significantly worse model fit ($\chi^2(1) = 0.23$, $p = 0.63$). Furthermore, in both groups the mean latent slope did not significantly differ from zero. Thus, on average, participants in the intervention as well as the CAU group did not show lower FCR scores over time. This result can also be seen in Figure 3, which shows the individual growth curves of participants in each group. In both groups, the latent intercepts varied significantly across participants, indicating differences in FCR

levels at baseline. However, though patients also showed considerable variation in their change in FCRI, the average latent slopes did not significantly differ between both groups, suggesting that the absence of change in FCR over time was similar across participants.

Table 2. Latent growth models increasing in complexity for estimating change in fear of cancer recurrence severity.

Model		Parameters (df)	χ^2 (robust)[a]	χ^2 difference (robust)*	AIC[b]	BIC[b]	RMSEA[c] (95% CI)	CFI[d]
1a	Random intercept and random slope (unconditional)	16 (2)	5.56	-	4062.70	4119.42	.118 (.000 -.239)	0.99
1b	- with restricted equal latent slope mean across groups	15 (3)	5.81	0.23	4060.93	4114.11	.085 (.000 -.189)	0.99
2a	Model 1 with time-invariant predictors (unconditional)	84 (36)	56.91	-	20281.90	20580.02	.065 (.029 -.096)	0.97
2b	- with constrained equal group effects of the predictors on the latent slope (homogenous)	67 (53)	70.61	14.10	20261.58	20499.37	.049 (.000 -.078)	0.97
2c	- additional constrained mean of the latent slope to be equal in both groups	66 (54)	70.73	0.12	20259.68	20493.92	.048 (.000 -.076)	0.98

Abbreviations: df = degrees of freedom, χ^2 = Chi square, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, RMSEA = root mean squared error of approximation, CI = confidence interval, CFI = comparative fit index
* None of the χ^2 differences were significant;
[a] Higher χ^2 values indicate a better model;
[b] Lower AIC and BIC values indicate a better model;
[c] RMSEA ≤ 0.06 indicates good model fit;
[d] CFI ≥ 0.95 indicates good model fit.

Model 2 indicated no significant differences in the effects of the predictors on the latent slope between groups based on the chi-square difference test comparing submodels 2a and 2b (Table 2). Thus, constraining the effects of the predictors on the latent intercept and slope to be equal across groups did not result in significantly worse model fit ($\chi^2(17) = 14.10$, $p = 0.66$), suggesting that the predictors have similar effects in both groups on the latent FCR intercept and slope. The final chi-square difference test comparing submodels 2b and 2c indicates that after satisfying the assumption of equal predictor effects in the two groups, the average latent FCR slopes remain equal across groups ($\chi^2(1) = 0.12$, $p = 0.73$).

For all model comparisons, the results of the chi-square difference test are corroborated by the results of the model fit indices. Both AIC and BIC suggest better fit for the models including equal latent slopes across groups. Although the CFI indicated good fit for all models, the RMSEA only showed acceptable fit in Model 2 after constraining the predictor effects on the latent intercept and slope to be equal across groups (Table 2).

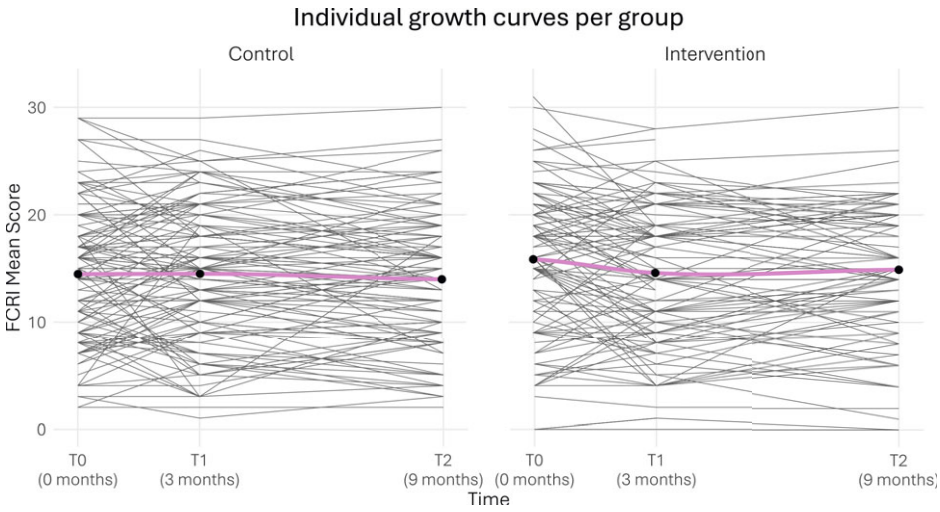

Figure 3. Growth curves for participants within each condition.

Control = care as usual (CAU); intervention = online self-help for fear of cancer recurrence. For each condition, the line between the dots represents the average FCRI score.

Table 3 shows the parameter estimates of the full linear growth curve model for predictors of the change in FCR following the intervention. In both the intervention and CAU, depressive symptoms are a significant predictor (intervention group: β = -0.37, B = -0.21, SE(B) = 0.07, $p < 0.01$; CAU: β = -0.30, B = -0.21 SE(B) = 0.07, $p < 0.01$). In other words, participants (in both groups) who score high on depressive symptoms show more decrease in FCR than participants with lower depressive symptoms scores. Because this effect occurred in both groups, depressive symptoms cannot be seen as a predictor of the intervention effect. In the intervention group, strong positive relations were found at baseline between FCR and education (β = 0.16, B = 0.61, SE(B) = 0.26, $p = 0.02$), between FCR and psychological distress (β = 0.44, B = 0.72, SE(B) = 0.15, $p < 0.01$), and between FCR and depressive symptoms (β = 0.20, B = 0.35, SE(B) = 0.15, $p = 0.02$). In CAU, strong positive relations were found at baseline between FCR and psychological distress (β = 0.35, B = 59, SE(B) = 0.23, $p < 0.01$) and between FCR and depressive symptoms (β = 0.28, B = 0.54, SE(B) = 0.24, $p = 0.02$). Figure 4 illustrates the LGCM including all parameter results.

Table 3. Parameter estimates and standard errors from the main effects of predictors on the fear of cancer recurrence latent intercept and slope factors.

	Intervention						*Care as usual*					
	Latent Intercept			Latent Slope			Latent Intercept			Latent Slope		
	B	SE (B)	β	B	SE (B)	β	B	SE (B)	β	B	SE (B)	β
Age	0.098	0.060	0.144	-0.018	0.022	-0.082	0.044	0.054	0.067	-0.018	0.022	-0.075
Children (< 12 years old)	-0.445	0.994	-0.032	-0.422	0.382	-0.097	0.883	0.918	0.064	-0.422	0.382	-0.086
Living alone	-0.190	1.202	-0.009	0.077	0.444	0.012	-0.255	1.141	-0.013	0.077	0.444	0.011
Education	*0.614	0.262	*0.160	-0.015	0.100	-0.013	0.387	0.262	0.104	-0.015	0.100	-0.012
Chemotherapy (ChemT)	1.493	1.133	0.105	-0.541	0.535	-0.121	0.210	0.888	0.016	-0.541	0.353	-0.115
Revalidation (RevT)	0.861	0.885	0.059	0.453	0.323	0.098	-0.114	0.746	-0.009	0.453	0.323	0.097
Psychological care (PsychT)	1.372	1.009	0.093	-0.402	0.355	-0.086	-1.325	0.901	-0.098	-0.402	0.355	-0.083
General internet use (SE-use)	0.182	0.132	0.084	-0.088	0.053	-0.129	0.126	0.125	0.069	-0.088	0.053	-0.136
Health-related behavior (SE-behav)	-0.067	0.086	-0.046	-0.025	0.039	-0.054	-0.098	0.090	-0.068	-0.025	0.039	-0.048
Expectations self-help (SE-expect)	0.166	0.101	0.106	-0.038	0.046	-0.078	0.084	0.119	0.054	-0.038	0.046	-0.068
Coping strategies (FCRI-CS)	0.059	0.070	0.059	0.016	0.021	0.050	0.084	0.059	0.103	0.016	0.021	0.054
Functioning impairments (FCRI-FI)	0.252	0.178	0.172	-0.006	0.051	-0.013	0.279	0.149	0.218	-0.006	0.051	-0.013
Psychological distress (FCRI-PD)	***0.721	0.146	***0.439	-0.025	0.054	-0.048	**0.593	0.225	**0.351	-0.025	0.054	-0.041
Physical problems (PDQ-PH)	-0.160	0.212	-0.040	0.170	0.099	0.136	-0.233	0.239	-0.066	0.170	0.099	0.135
Trait anxiety (PDQ-TA)	-0.250	0.149	-0.098	0.053	0.055	0.066	-0.052	0.121	-0.023	0.053	0.055	0.066
Depressive symptoms (PDQ-DE)	*0.352	0.148	*0.195	**-0.211	0.065	**-0.371	*0.544	0.235	*0.278	**-0.211	0.065	**-0.302
Social support (PDQ-SP)	-0.407	0.537	-0.050	-0.009	0.221	-0.003	0.471	0.557	0.052	-0.009	0.221	-0.003

Note: Results of the latent growth curve model. All estimated parameters are standardized. B = unstandardized parameter, covariance of intercept and slope; SE = standard error; β = standardized parameter, correlation.
Abbreviations: SE-use = self-efficacy for online self-help questionnaire, general internet use subscale; SE-behav = self-efficacy for online self-help questionnaire, health-related behavior subscale; SE=-expect = self-efficacy for online self-help questionnaire, expectations of online self-help subscale; FCRI-CS = Fear of Cancer Recurrence Inventory, coping strategies subscale; FCRI-FI = Fear of Cancer Recurrence Inventory, functioning impairments subscale; FCRI-PD = Fear of Cancer Recurrence Inventory, psychological distress subscale; PDQ-PH = Psychosocial Distress Questionnaire, physical problems subscale; PDQ-TA = Psychosocial Distress Questionnaire, trait anxiety subscale; PDQ-DE = Psychosocial Distress Questionnaire, depressive symptoms subscale; PDQ-SP = Psychosocial Distress Questionnaire, social support subscale.
Significance levels: *$p < .05$, **$p < .01$, ***$p < .001$

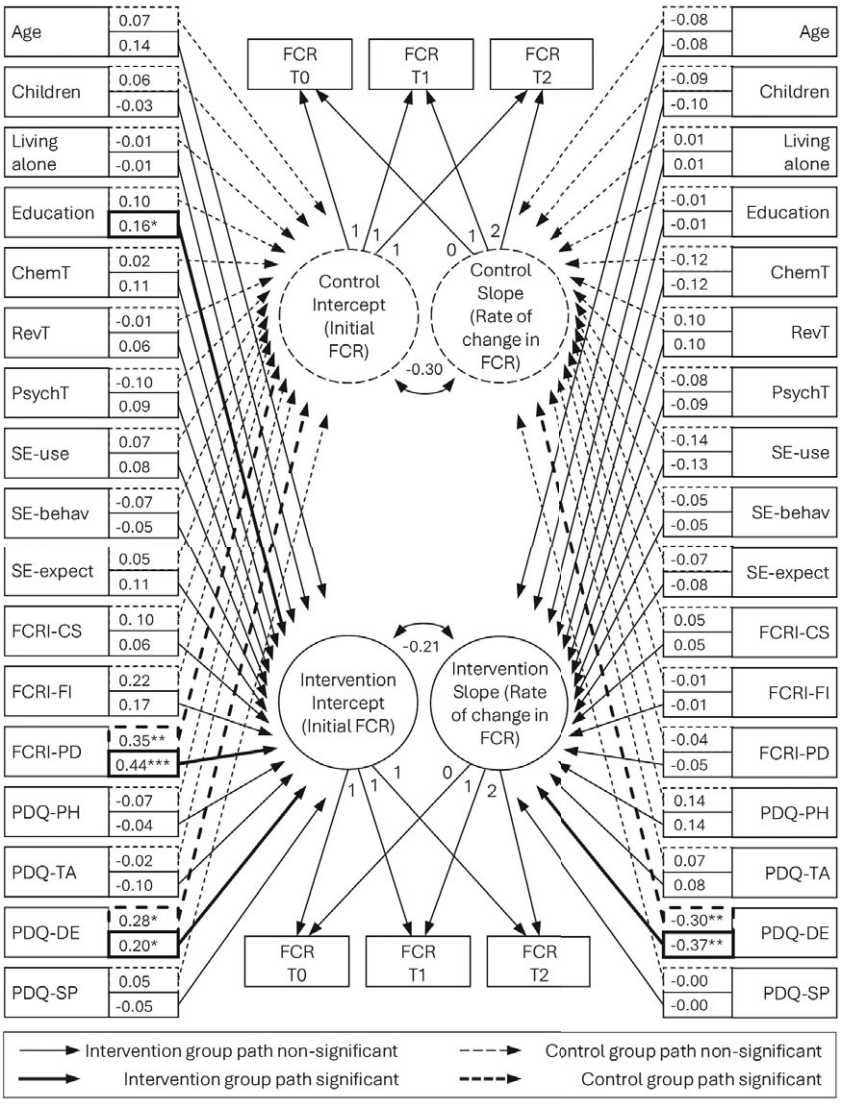

Figure 4. Final latent growth curve model.

All estimated parameters are standardized. The rectangles represent measured variables and the circles designate latent growth factors. The loadings on the latent intercept factors are fixed at 1, and on the latent slope factor are fixed at 0, 1 and 2, respectively for the three repeated FCR measurements. One-headed arrows represent regression paths; two-headed arrows represent correlations.
Abbreviations: FCR = Fear of Cancer Recurrence; control = care as usual (CAU); intervention = online self-help for fear of cancer recurrence; T0 = time-0 (baseline); T1 = time-1 (three months); T2 = time-2 (nine months); ChemT = treatment chemotherapy; RevT = treatment revalidation; PsychT = treatment psychologist/psychiatrist; SE-use = self-efficacy for online self-help questionnaire, general internet use subscale; SE-behav = self-efficacy for online self-help questionnaire, health-related behavior subscale; SE-expect = self-efficacy for online self-help questionnaire, expectations of online self-help subscale; FCRI-CS = Fear of Cancer Recurrence Inventory, coping strategies subscale; FCRI-FI = Fear of Cancer Recurrence Inventory, functioning impairments subscale; FCRI-PD = Fear of Cancer Recurrence Inventory, psychological distress subscale; PDQ-PH = Psychosocial Distress Questionnaire, physical problems subscale; PDQ-TA = Psychosocial Distress Questionnaire, trait anxiety subscale; PDQ-DE = Psychosocial Distress Questionnaire, depressive symptoms subscale; PDQ-SP = Psychosocial Distress Questionnaire, social support subscale. *p < .05, **p < .01, ***p < .001.

Discussion

This RCT demonstrates that there is no effect of CBT-based online self-help training to reduce FCR in breast cancer survivors, compared to CAU (after three and nine months). Moreover, no significant predictors were found for the effect of the intervention on FCR. Interestingly, depressive symptoms were found to be a predictor for decrease in FCR in both groups.

In line with the findings from Willems et al., we did not find an effect of our online self-help intervention for FCR.[32] Their web-based computer-tailored intervention to support cancer survivors with managing psychosocial issues was effective in reducing depression and other outcome measures, but no effects were found for anxiety.[32] Although this intervention was not specifically aimed to reduce FCR and included a mixed sample, this is an online self-help intervention for cancer patients and therefore more or less comparable to our online self-help training. Other studies showed that online interventions with (face-to-face or online) therapist support, standard email reminders, or studies that selected only patients with high FCR were effective.[33–35] The modest mean level of FCR and the high drop-out rate in our study could explain the absence of an effect of the intervention. Furthermore, the limited usage of the intervention may be an explanation for the lack of effect. Yet, the current study probably shows a realistic picture.

Study limitations

This study had several limitations. First, CAU slightly differed for participants, since they were recruited from different hospitals. This is a realistic picture, since participants of online self-help interventions will not receive the same CAU in each hospital. Moreover, to prevent a distorted picture, randomization was done "stratified by hospital" to create equally distributed groups. Second, despite randomization, significant baseline differences were found, which could have influenced the results. However, CONSORT guidelines recommend against significance tests of baseline differences in RCTs, because differences in baseline characteristics after proper random assignment are the result of chance rather than bias.[36] Third, some participants reported recurrence or metastasis of cancer, while the inclusion criterion was "no signs of local or regional recurrence or metastatic disease". Nevertheless, out of participants explanations we could extract that all participants could be included. Also, self-reported outcomes may be less reliable than the nurse practitioner's assessment.

Study strengths

Study strengths are the study design, which included a large consecutive sample, sufficient power, and state-of-the art analysis. Second, the ecological validity of the current study is high, because not screening on level of FCR, the use of CAU and self-help without extra help or e-mails reflects a realistic picture of online self-help interventions. Third, the study population of this RCT consisted of relatively young

women both compared to the other women in our patient cohort (56 years vs. 61 years) and to Dutch breast cancer survivors (80% >50 years)[37]. Given the high prevalence of FCR in young breast cancer survivors, and the fact that young women use the internet more often than older women for both searching for information and for personal development, we did reach the right target group with this RCT.[4, 38] Last, this RCT showed a large variation in the change in FCR scores within participants over time, which supports the importance of our choice to model individual differences in growth curves using a latent growth curve models. Many studies merely compare treatments on the average change in FCR over time, thereby obscuring the large variation between patients within a particular treatment group.

Clinical implications

This RCT showed a large variation in FCR scores within participants, which is important information when considering who needs treatment for FCR. Also, the mean level of FCR was lower than expected based on the literature, and the usage of the intervention was limited, which might indicate that we should offer treatment for FCR only to those patients who consistently score high on FCR. Since results from other RCTs showed that interventions with email reminders or some form of support were effective, we suggest implementing programs with professional support, for example from nurses or primary care workers. Future research should focus on the best form of support, while maintaining the advantages of online help.

Conclusion

In conclusion, overall there was no effect of the CBT-based online self-help training "Less fear after cancer" in the current study. Therefore, we recommend adding professional support, like e-mail contact or face-to-face assistance, to future online interventions for FCR.

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06

CBT-based online self-help training to reduce fear and distress after cancer (CAREST randomized trial): 24 months follow-up using latent growth models and latent class analysis

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Abstract

Background
Psychological distress (PD) and fear of cancer recurrence (FCR) are common consequences of surviving cancer. Online self-help training could help many cancer survivors deal with PD and FCR at low costs.

Purpose
To evaluate the long-term effectiveness of the CAncer REcurrence Self-help Training (CAREST trial) to reduce PD and FCR. Moreover, to evaluate the relation between FCR and PD across time and identify subgroups representing different change trajectories in FCR over time and their predictors.

Methods
This multicenter randomized controlled trial included 262 female breast cancer survivors, assigned to online self-help training or care as usual. Participants completed questionnaires at baseline and four times during the 24-month follow-up. The primary outcomes were PD and FCR (Fear of Cancer Recurrence Inventory). Latent growth curve modeling (LGCM) and repeated measures latent class analysis (RMLCA) were performed, both according to the intention-to-treat principle.

Results
LGCM showed no differences between the average latent slope in both groups for both PD and FCR. The correlation between FCR and PD at baseline was moderate for the intervention group and strong for the CAU group and did not significantly decrease over time in both groups. RMLCA revealed five latent classes and several predictors of class membership.

Conclusions
We did not find a long-term effect of the CBT-based online self-help training in reducing PD or FCR, nor in their relation. Therefore, we recommend adding professional support to online interventions for FCR. Information about FCR classes and predictors may contribute to improvement of FCR interventions.

Introduction

Advances in the diagnosis and treatment of (breast) cancer have resulted in increased survival rates. As a result, there is an increasing group of breast cancer survivors that have to cope with the long-term consequences of cancer. Fear of cancer recurrence (FCR) is one of the most common long-term psychological consequences of surviving breast cancer.[1, 2] FCR is defined as "fear, worry, or concern about cancer returning or progressing" and ranges from healthy levels in the majority of breast cancer survivors to clinical levels in 17% of breast cancer.[3–5] In younger (age 18-45) breast cancer survivors, this prevalence is much higher: 70% experiences clinical levels of FCR.[6] When FCR surpasses the healthy level, it becomes distressing. Psychological distress (PD) is another common consequence of the diagnosis of cancer and its treatment.[7, 8] Up to 50% of cancer survivors experience PD, ranging from normal feelings of vulnerability, feeling discouraged, sadness, and fears, to more disabling problems such as anxiety, panic and depression.[7–10] FCR and PD are associated constructs and FCR is reported to be a precursor of PD.[11–13] Otherwise, previous research also found that a reduction in PD may lead to a significant reduction in FCR.[14, 15] High levels of FCR are associated with higher frequency of breast self-examination and diminished quality of life.[5, 6, 11] Also, both serious PD and FCR are associated with nonadherence to cancer treatment or -screening and higher healthcare use and costs.[6, 16–20]

Given the burden of FCR and PD for cancer survivors, there is a need to develop (tailored) interventions to efficiently address FCR and also to reduce PD.[11, 21] Online interventions are promising, because they are easily accessible, have low costs, offer convenience and greater privacy, and patients can work at their own pace.[22, 23] Therefore, we developed "Less fear after cancer", an online tailored self-help training on the basis of evidence-based cognitive behavioral therapy (CBT).[24] This online self-help training was primarily developed to reduce FCR, but we also expected it to reduce PD because most of its components (e.g. the basic principles of cognitive behavioral therapy, behavioral techniques to stop ruminating, or relaxation practices) are more widely applicable than FCR alone.[24] This intervention was evaluated within the CAncer REcurrence Self-help Training (CAREST) randomized controlled trial (RCT), in which the intervention was compared to a care as usual (CAU) control group in women with curatively treated breast cancer (breast cancer survivors), with a follow-up period of 24 months.[24, 25] The evaluation of short-term effects at three and nine months showed no treatment effects of the self-help training for FCR.[25]

In the current paper, we will evaluate the long-term effectiveness (>15 months) of this online self-help training in reducing both FCR and PD and identify subgroups representing different change trajectories in FCR over time and their predictors. To meet this aim, we use three longitudinal latent variable models, each focusing on a different research question. First, in a multigroup latent growth model we will

evaluate change in FCR and PD (research question 1; RQ1). We hypothesize greater FCR and PD reduction in the intervention group compared to CAU at 15 and 24 months. Second, in a multivariate multigroup latent growth model we will evaluate the relation between FCR and PD at baseline and across time (research question 2; RQ2). We hypothesized a strong relation ($r \geq 0.50$) between FCR and PD at baseline and a significantly weaker relation after the intervention, because PD is expected to decrease more than FCR. In other words, we expected that patients who received the intervention perceive FCR less of a burden, because they have learned to cope with it better. Third, we will use repeated measures latent class analysis (RMLCA) to identify subgroups ("latent classes") representing different change trajectories in FCR over time (research question 3; RQ3). In our protocol paper we hypothesized that this intervention would not help all participants, but that there are subgroups to be found for whom this would be beneficial.[24] In the current study, we will investigate the predictors of subgroup membership to identify the characteristics of survivors that benefited most from the online self-help intervention. We will investigate the following potential predictors: socio-demographic and medical variables (age, living alone, rehabilitation, psychological care, chemotherapy, and education), self-efficacy for online self-help (general internet use, health-related behavior, and expectations for online self-help), and psychosocial problems and risk factors (physical problems, depressive symptoms, trait anxiety, and social support).

Materials and methods

The CAREST trial was registered in the Dutch Trial Register (NTR4119). The Medical Ethical Committee of the Maasstad hospital (TWOR) in Rotterdam approved this trial (reference number 2013/41) and all participating hospitals provided local ethics approval. The study protocol of this trial has been published.[24] Furthermore, this method section is largely published before in an earlier publication about the short-term treatment effects of this RCT, measures and statistical analyses are adapted for the current article.[25] We conducted this study in accordance with the principles of the Declaration of Helsinki and we reported this study in accordance to the CONSORT guidelines.[26 27]

Design

We conducted a multicenter randomized controlled trial (RCT) with two conditions. The intervention group received a CBT-based online self-help training to reduce FCR. Both the intervention group and the control group received care as usual (CAU), standard care in their own hospital.

The original sample size calculation mentioned in the study protocol does not apply for the statistical analyses in the current study.[24] In general, for growth models a sample size of at least 100 is preferred.[28] For this study, an alpha of .05 and df of 100 (in our

model, df = 123) results in an estimated power between .87 (for a sample size of 200) and .99 (for a sample size of 300), to reject the null hypothesis of RMSEA ≤ .05 if the true model only moderately fits the data (i.e. RMSEA = .08).[29] Therefore, the current sample of 262 is fit to perform Covariance Structure Modeling.

Participants were assessed through online self-report questionnaires at baseline (T0), three months (T1; after intervention), nine months (T2), 15 months (T3), and 24 months (T4). More details on the study design are described in the study protocol.[24]

Participants

Women were eligible to participate when they had a diagnosis of breast cancer 1-5 years ago, had no signs of local or regional recurrence or metastatic disease (according to their oncologist or oncology nurse), were capable of completing questionnaires in Dutch, were 18 years or older at disease onset, and had access to a computer with an internet connection.[24, 25]

Recruitment

Eligible patients were recruited consecutively during their regular check-up at the outpatient clinic of a hospital or by sending them a comprehensive information letter by mail (differed because of pragmatic reasons) between April 2014 and May 2016. Participating hospitals (all situated in the Netherlands) were the Maasstad hospital in Rotterdam, St Antonius hospital in Utrecht, Admiraal de Ruyter hospital in Vlissingen, Reinier de Graaf hospital in Delft, Antonius hospital in Sneek, ETZ in Tilburg, Catharina hospital in Eindhoven, and UMCG in Groningen. After 2 weeks, patients were reminded of the study by the researcher. Patients who decided to participate returned a signed informed consent form. On this form, they indicated whether they agreed to participate in the RCT or only to complete the Dutch version of the Fear of Cancer Recurrence Inventory (FCRI-NL) once.[25]

Randomization

Participants were randomly allocated to either the online self-help training (intervention) or CAU with an allocation ratio of 1:1, stratified by hospital. Block randomization (block size 10) was carried out through the sealed envelope system. Randomization was conducted by a researcher who was not otherwise involved in the study. The researchers had no influence on (and were blinded to) the randomization process. We used coding and separating personal data from the research data to anonymize the data.[24, 25]

Intervention

In short, the intervention is a CBT-based online self-help to reduce FCR. The program included two generic modules containing psycho-education about FCR and the basic principles of CBT, and four optional modules: a) Stop worrying; b) Positive actions; c)

Relax; and d) Reassurance.[25] More information about the intervention can be found in Supplementary materials 6A. All participants received CAU.

Measures

Socio-demographic and medical variables were self-reported and assessed at baseline and at all time points, respectively. The self-report questionnaires were assessed at all time points.

The primary outcomes FCR and PD were both assessed with the Dutch translation of the Fear of Cancer Recurrence Inventory (FCRI-NL).[30, 31] The FCRI-NL consists of 42 items on a 5-point Likert scale and comprises seven subscales.[30] PD was assessed with the psychological distress subscale (4 items; range 0-16) and FCR was assessed with the severity subscale or FCRI-SF-NL (9 items; range 0-36), which can be used to screen for clinical levels of FCR.[30–32] A cutoff score of 13 or higher on the severity subscale is considered optimal for detecting the presence of clinically significant FCR.[32] Both subscales demonstrated sufficient reliability and validity.[31]

Since there was no measure for self-efficacy for online self-help available, self-efficacy was assessed with a 15-item questionnaire developed for this RCT and described in the study protocol, which measured: 1) general internet use (3 items); 2) health-related behavior (7 items); and 3) patients' expectations of online self-help training for fear of cancer recurrence (5 items).[24, 25] In this patient sample, the estimated reliability of this questionnaire was good (Cronbach's α = .82 for the total scale and Cronbach's α = .72 - .93 for the subscales).[25]

Psychosocial problems and risk factors were assessed with the Psychosocial Distress Questionnaire-Breast Cancer (PDQ-BC), a 35-item multi-dimensional screening instrument specific for breast cancer patients.[33] We used the subscales measuring trait anxiety (10 items), (lack of) social support (1 item), depressive symptoms (7 items), and physical problems (4 items) in this study.[25] The PDQ-BC showed good estimated reliability (Cronbach's α = .70 - .87) for the subscales used in this study, and satisfactory construct validity for the physical problems subscale (other subscales were not reported).[25, 33–35]

Statistical analyses

Prior to data analysis, we checked the normality assumptions. When the assumption of multivariate normality was not met, we executed transformations of the dependent variable. When transformation did not lead to multivariate normality, we used robust maximum likelihood estimation (MLR) to fit the model. P-values smaller than 0.05 were considered statistically significant. Data were analyzed according to the intention-to-treat (ITT) principle, as mentioned in the study protocol.[24] Missing data were analyzed for random occurrence with Little's MCAR test for missing data.[36] Multiple imputation

was used for all variables to handle the missing data on item level when data was missing completely at random.[37, 38] We handled missing data due to attrition using the full information maximum likelihood procedures incorporated in the growth model function of the Lavaan R package. Differences in number of dropouts between both groups were compared with a cross table and chi-square test.

RQ1: Long-term effectiveness of online self-help training in reducing FCR and PD
To answer the first research question (i.e., do the intervention and CAU group differ in the change in FCR/PD over time), a multigroup second-order latent growth model was estimated. A second-order growth model estimates individual growth curves for each participant based on the individual FCR or PD item scores. A multigroup extension allows testing differences between interventions in the growth model parameters. The parameter of main interest was the average latent slope estimate in both the intervention and CAU groups and whether these differed between the groups. We estimated the model separately for FCR and PD, because the multivariate model for both FCR and PD did not converge (most likely, the model was too large for the data). Each of the FCR/PD models was built in five steps, first testing the assumption of longitudinal measurement invariance, followed by two models to test the null hypothesis that the difference between the groups in the latent slope is equal to zero. Growth model analyses were estimated with maximum likelihood estimation, using R statistical software (version 3.5.3), with software packages lavaan (R package for Structural Equation Modeling, version 0.6-9) and BaylorEdPsych (R-package used for checking missing data for random occurrences, version 0.5).[36, 39–41] The code used for the analyses in this study has been made openly available in the Open Science Framework (OSF) repository (https://osf.io/2sg6m/).

RQ2: Relation between FCR and PD over time
Answering the second research question (i.e., does the association between FCR and PD decrease over time), we started with a multivariate multigroup growth model including both FCR and PD scores over time. However, as this multivariate second order growth model did not converge, we used a first order growth model that models the growth parameters based on FCR and PD factor scores at each time point instead of on the questionnaire item scores. We first estimated the factor scores of the FCR and PD measurement models at each of the five time points, and subsequently used these factor scores in a multivariate multigroup first order growth model (Model 5) to investigate how change in FCR scores over time was related to change in PD scores over time and how these relations differed between the CAU and intervention group. To test whether the correlations between FCR and PD were equal over time, we added restrictions in Models 6 and 7 respectively to the intervention and CAU group. We assessed and interpreted the goodness-of-fit of the latent growth models as described above.

RQ3: Change trajectories in FCR over time and their predictors
For the last research question (i.e., can we distinguish characteristics of patients for whom the intervention worked), we modeled a repeated measures latent class analysis (RMLCA) within the intervention group. RMLCA analyses were performed with Latent Gold (version 5.0.0).[42] The first step of this analysis was to identify the optimal number of latent classes using the BIC, AIC and AIC3 fit indices, where each class represents a different pattern of change in FCR over time. When not all indices indicated the same number of latent classes, the model supported by most indices was chosen. The second step of the RMCLA was to investigate which predictor variables (as mentioned in the introduction) predict class membership, using Latent Gold's omnibus Wald test of differences between the latent classes on the predictor variables. Since we assessed multiple predictors, we adjusted the significance level using the Bonferroni-Holm correction.[43] For significant predictors, we used Z values >2 or <-2 to determine which class(es) significantly contributed to the predictor effects. Positive/negative values show that participants in that class show higher/lower than average scores on that predictor.

Supplementary materials 6B contains an extended and more detailed version of this paragraph.

Results

Response rate and sample characteristics
Details about enrolment, intervention allocation, follow-up, and drop-out can be found in the flowchart (Figure 1). In total 516 (44%) patients gave their consent to participate, of which 254 (49%) chose to complete the FCRI only once (nonparticipants) and 262 (51%) signed up for the RCT (participants). Reasons for drop-out were personal circumstances (16), not experiencing FCR (8), questionnaires were too burdensome (14), technical difficulties (5), intervention (1), randomization outcome (2), cancer recurrence and/or deceased (3), or unknown (66). Participants in the two RCT conditions did not differ from one another in number of dropouts ($c^2 = 8.33$, $p = .14$).

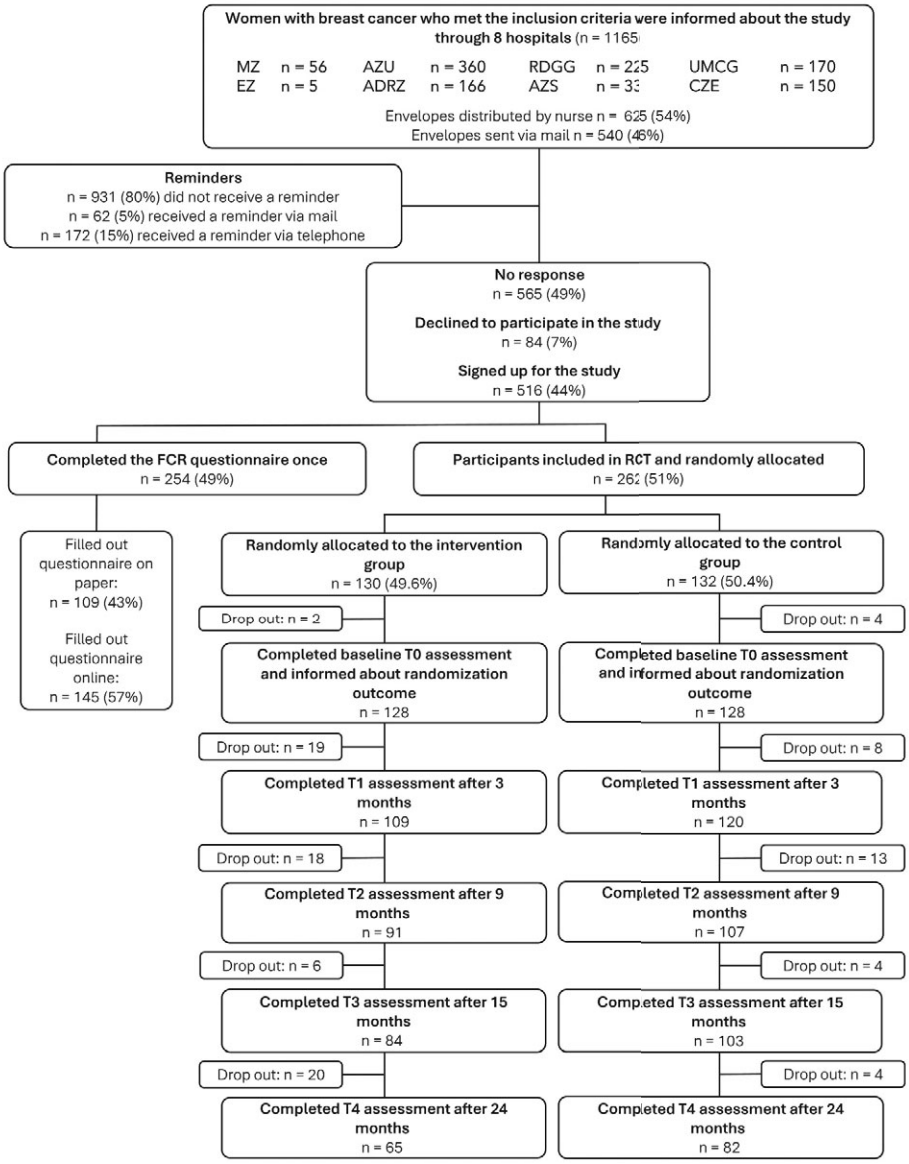

Figure 1. CONSORT diagram for participant inclusion and retention up to 24 months in the CAREST randomized controlled trial.

Abbreviations: MZ = Maasstad hospital Rotterdam; EZ = Elisabeth hospital Tilburg; AZU = St Antonius Hospital Utrecht; ADRZ = Admiraal de Ruyter Hospital Vlissingen; RDGG = Reinier de Graaf Hospital Delft; AZS = Antonius Hospital Sneek; UMCG = The University Medical Center Groningen; CZ = Catharina Hospital Eindhoven; control group = care as usual (CAU); intervention group = online self-help for fear of cancer recurrence; RCT = randomized controlled trial; T0 = baseline measure, before intervention; T1 = three months after inclusion, directly after intervention; T2 = nine months after inclusion; T3 = fifteen months after inclusion; T4 = twenty-four months after inclusion.

Women in the RCT had a mean age of 55.8 years (SD 9.9) and the majority was medium (48%) to highly (40%) educated. Data on participants' race/ethnicity were not collected. The majority (86%) had a partner, and a small number of women (12%) had children younger than 12 years old. Time since diagnosis was on average 2.6 years (SD 1.1) and 40% had affected lymph nodes. Most reported treatments for breast cancer were radiotherapy (68%), chemotherapy (63%), lumpectomy (57%), hormone therapy (56%), and mastectomy (47%). One third of the women reported to have followed a previous rehabilitation program (36%) or previous psychological care (32%). Baseline FCR was 15.2 (SD 6.9). More details about the response rate and the demographic and medical characteristics of the participants were described in an earlier publication.[25]

RQ1: Long-term effectiveness of online self-help training in reducing FCR and PD

When testing the assumption of longitudinal measurement invariance for FCR, the multigroup univariate second order latent growth model indicated no differences between the loadings of the five longitudinal factors across time, based on the chi-square difference test comparing submodels 0a and 1a (Table 1). Thus, constraining the loadings to be equal across time did not result in a significantly worse model fit ($c^2(63) = 59.38$, $p = .61$). Furthermore, the intercepts of individual items differed significantly across time, based on the chi-square difference test comparing submodels 1a and 2a (Table 1). Because constraining the intercepts of individual items across time did result in a significantly worse model fit ($c^2(80) = 111.87$, $p < .05$), we assumed invariant loadings across time, but we allowed the item intercepts to vary. To find out whether the intervention arms differ in their change in FCR across time, the chi-square difference test comparing submodels 3a and 4a indicates that the average latent FCR slopes remain equal across groups ($c^2(1) = 0.00$, $p = 1$). This means that FCR did not reduce more in the intervention group than in CAU across time.

For PD, the results were similar (Table 1). Constraining the loadings to be equal across time did not result in significantly worse model fit ($c^2(34) = 22.75$, $p = .93$). Yet, constraining the intercepts of individual items across time did result in significantly worse model fit ($c^2(36) = 65.64$, $p < .01$), so we assumed invariant loadings and varying item intercepts across time. To find out whether the interventions differ in their change in PD across time, the chi-square difference test comparing submodels 3b and 4b indicates that the average latent PD slopes remain equal across groups ($c^2(1) = 0.00$, $p = 1$), which means that PD did not reduce more in the intervention group than in the CAU group across time.

For FCR the RMSEA fit index was slightly higher than the recommended criterion of .06, and for PD the RMSEA fit index was around .06, suggesting an almost adequate fit of these models to the data. The CFI and TLI suggested a somewhat poor fit of the FCR models to the data. The TLI suggested an almost adequate fit and the CFI indicated a good fit for the PD models. Both AIC and BIC suggest a better fit for the

models including equal intercepts of individual items across time (2a and 2b) and for the models including equal latent slopes in the intervention and CAU group (4a and 4b). Answering the first research question (difference between the groups in effect of FCR and PD over time), this corroborates the findings mentioned above that long-term effects did not differ between the intervention group and the CAU group over time, for both FCR and PD models. In other words: the self-help was not effective in reducing FCR and PD in the intervention group long-term.

RQ2: Relation between FCR and PD over time

In line with the findings of the second order growth model, the results of the first order growth model indicate no significant change in FCR across time, for both the intervention (β = .041, p = .06) and CAU group (β = -.000, p = .98). Similarly, no significant change in PD across time was found, for both the intervention (β = .028, p = .13) and CAU group (β = .003, p = .83). At baseline, we found significant positive correlations between FCR and PD; a moderate correlation in the intervention group (r = .471) and a strong correlation in the CAU group (r = .708). The first order growth model indicated no change in the correlation between PD and FCR across time for both the intervention and CAU group, based on the chi-square difference test comparing submodels 5-6 and 6-7 (Table 1). Thus, constraining the correlation between PD and FCR to be equal at each time point did not result in significantly worse model fit in the intervention ($c^2(4) = 1.97$, $p = .74$) and CAU group ($c^2(4) = 6.02$, $p = .20$).

The results of these chi-square difference tests were confirmed by the model fit indices. Both AIC and BIC suggest a slightly better fit to the data for models 6 and 7 that constrained the correlations between FCR and PD to be equal at each time point. The CFI, TLI and RMSEA similarly indicated good fit for both models 6 and 7 to the data. In short, the model fit indices indicate that the relation between FCR and PD remains equal in both groups over time. Figure 2 illustrates (a) the correlation between FCR and PD, and the mean change in (b) FCR and (c) PD across time for both the intervention and the CAU group. Results show that the correlation between FCR and PD was moderate for the intervention group and strong for the CAU group at baseline and the correlation did not significantly decrease over time in both groups.

Table 1. Latent growth models supporting research questions 1 and 2, increasing in complexity.

Model		Parameters (df)	χ^{2} [a]	χ^{2} difference*	AIC[b]	BIC[b]	RMSEA[c] (95% CI)	CFI[d]	TLI[d]
RQ1a: Multigroup univariate second order latent growth model for fear of cancer recurrence (FCR)									
0a	Baseline model with five correlated longitudinal latent factors (one at each time-point)	500 (1660)	2520.7	-	20098	21871	.064 (.059 – .069)	.882	.859
1a	Model 0a + the loadings of the five longitudinal factors were constrained to be equal across time	437 (1723)	2580.1	59.38	20031	21581	.062 (.057 – .067)	.883	.865
2a	Model 1a + the intercepts of individual items were constrained to be equal across time	357 (1803)	2692.0	111.87*	19983	21249	.062 (.057 – .067)	.878	.866
3a	Model 1a + the latent growth factors (intercept and slope)	426 (1734)	2602.7	-	20032	21542	.063 (.058 – .067)	.881	.864
4a	Model 3a + the mean latent slope of the intervention and CAU groups was constrained to be equal	425 (1735)	2602.7	0.00	20030	21537	.063 (.058 – .067)	.881	.864
RQ1b: Multigroup univariate second order latent growth model for psychological distress (PD)									
0b	Baseline model with five correlated longitudinal latent factors (one at each time-point)	238 (222)	345.78	-	9172.1	10015.8	.066 (.052 – .079)	.962	.934
1b	Model 0b + the loadings of the five longitudinal factors were constrained to be equal across time	204 (256)	368.53	22.75	9126.8	9850.0	.059 (.045 – .072)	.965	.948
2b	Model 1b + the intercepts of individual items were constrained to be equal across time	168 (292)	434.16	65.64**	9120.5	9716.1	.062 (.049 – .074)	.956	.943
3b	Model 1b + the latent growth factors (intercept and slope)	192 (268)	384.72	-	9119.0	9799.7	.058 (.045 – .071)	.964	.949
4b	Model 3b + the mean latent slope of the intervention and CAU groups was constrained to be equal	191 (269)	384.72	0.00	9117.0	9794.1	.058 (.044 – .071)	.964	.949

Table 1. Latent growth models supporting research questions 1 and 2, increasing in complexity. (continued)

Model		Parameters (df)	χ^{2} [a]	χ^{2} difference*	AIC[b]	BIC[b]	RMSEA[c] (95% CI)	CFI[d]	TLI[d]
RQ2: First order growth model based on factor scores									
5	First order growth model	58 (72)	82.973	-	2338.9	2511.9	.046 (.000 – .085)	.992	.990
6	Model 5 + correlation between PD and FCR was constrained to be equal across time in the *intervention* group	54 (76)	84.941	1.97	2332.8	2494.0	.040 (.000 – .080)	.993	.992
7	Model 5 + correlation between PD and FCR was constrained to be equal across time in the *CAU* group	50 (80)	90.964	6.02	2330.9	2480.0	.043 (.000 – .081)	.992	.991

Abbreviations: df = degrees of freedom; χ^{2} = Chi square; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = root mean squared error of approximation; CI = confidence interval; CFI = comparative fit index; TLI = Tucker-Lewis index; RQ = research question, CAU = care as usual.
* $p < .05$; ** $p < .01$; *** $p < .001$; [a] Higher χ^{2} values indicate a better model; [b] Lower AIC and BIC values indicate a better model; [c] RMSEA ≤ .06 indicates good model fit; [d] CFI and TLI ≥ .95 indicates good model fit.

RQ3: Change trajectories in FCR over time and their predictors

First, we identified the optimal number of latent classes, where each class represents a distinct change pattern of FCRI for participants in the intervention group. BIC showed that a model with three different classes fitted the data best, while AIC and AIC3 suggested a model with five different classes. Because of the consensus between AIC and AIC3, we chose the model with five different classes. For each of those five classes, Figure 3 shows the mean FCR scores over time.

Second, we determined predictors of class membership. Table 2 shows the effect of various sociodemographic and clinical predictors on class membership. The omnibus test of differences showed that the latent classes differed significantly from each other on the following 5 predictors: living alone, physical problems, depressive symptoms, having followed rehabilitation, and trait anxiety. Figure 4 gives an overview of the characteristics of the members of the five latent classes based on the results in Table 2. Below, the classes will be described in the same order as Table 2 (largest to smallest class). Class 1 will be named “mild FCR and physical problems class”, because participants in this class have mild FCR (mean FCR severity of 13.5) and predominantly physical symptoms. Class 2 will be named “young, severe FCR and mental problems class”, because participants in this class have severe FCR (mean FCR severity of 24.2), predominantly mental symptoms and a notable lower mean age than all other classes (47.8 years vs. 56.3 to 58.3 years). Class 3 will be named “moderate FCR and mental problems class”, because participants in this class have moderate FCR (mean FCR severity of 18.0) and predominantly mental symptoms. Class 4 will be named “low FCR class”, because participants in this class have a very low FCR level (mean FCR severity of 5.0) and this class did not significantly contribute to the effect of any of the predictors identified through the omnibus tests. Class 5 will be named “moderate FCR and physical problems class”, because participants in this class have moderate FCR (mean FCR severity of 19.8) and predominantly physical symptoms.

Our results show quite stable FCR trajectories for four (out of five) latent classes over time (indicating stable severe, moderate, mild, and low FCR over time). At first sight, one of the classes shows a decrease of 5 points on the severity subscale of the FCRI over 24 months. Looking closer we see the decrease occurs after 9 months (6 months after the intervention); hence we do not expect this to be a treatment effect of our online self-help. In conclusion, RMLCA did not reveal classes who benefit from the intervention.

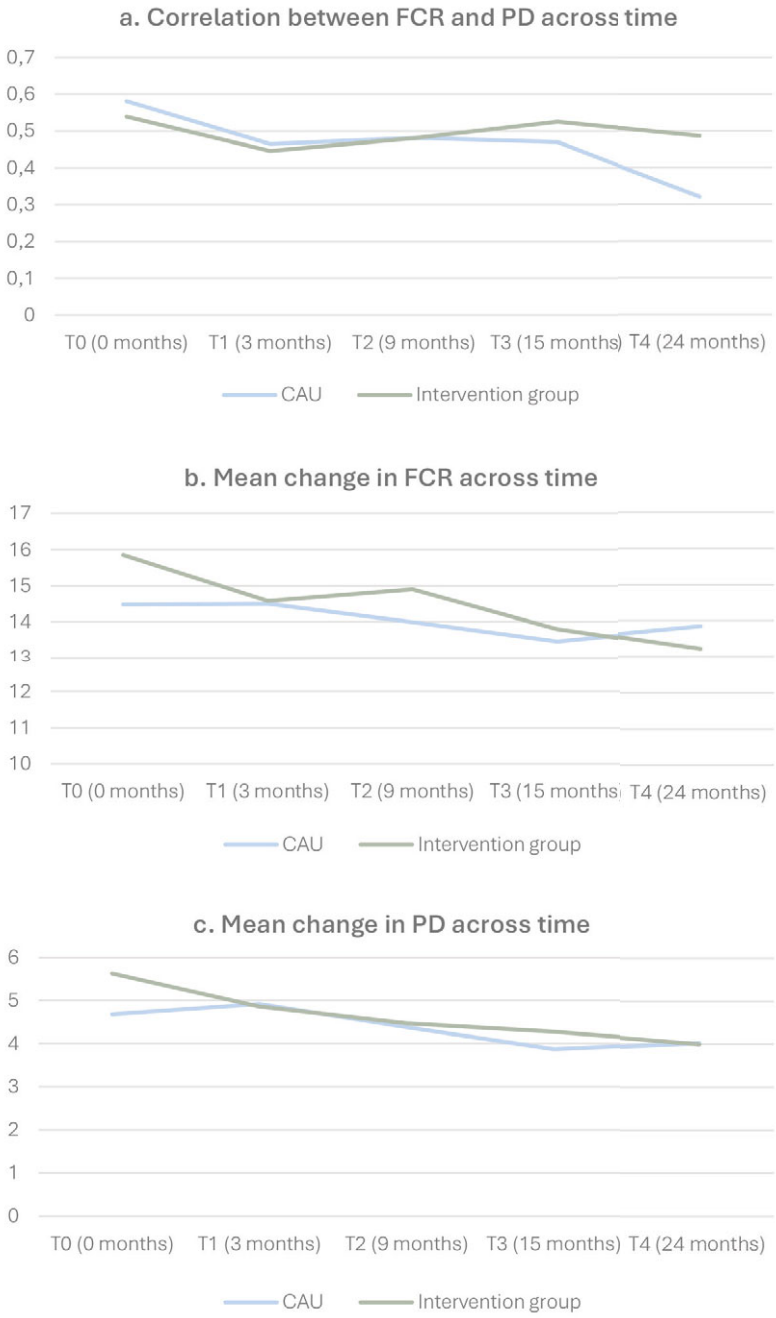

Figure 2. The correlation between fear of cancer recurrence and psychological distress (a), the mean change in fear of cancer recurrence (b) and psychological distress (c) across time for both the intervention and the care as usual (CAU) group.

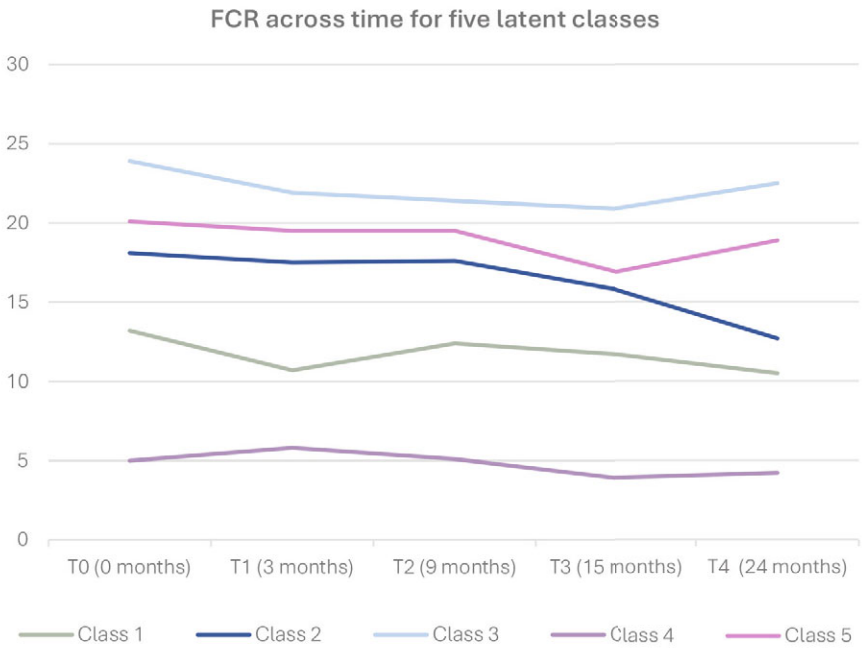

Figure 3. Fear of cancer recurrence (measured with the Fear of Cancer Recurrence Inventory-severity subscale; FCRI-S) across time for five latent classes.

Sensitivity analyses

More than one-third (37%) of the intervention group reported they did not actually follow the online self-help training, although they had access to the intervention. However, participants who followed the online self-help intervention and participants who did not follow the intervention did not differ from one another in class membership ($c^2 = 2.26$, $p = .69$). We have repeated our analysis of RQ1 excluding those participants who had indicated that they did not participate in the online self-help training. For FCR, the results of the sensitivity analyses show a latent slope of -.09 in the intervention group and -.05 in the control group, the difference in latent slopes of .04 was not statistically significant ($p = .175$). For PD the results of the sensitivity analyses show a latent slope of -.11 in the intervention group and -0.05 in the control group, the difference of .06 was almost statistically significant ($p = .052$). Thus, sensitivity analyses showed no significant treatment effect for the intervention group compared to CAU.

Table 2. Clinical and sociodemographic predictors of fear of cancer recurrence latent class membership (research question 3).

	Class 1	Class 2	Class 3	Class 4	Class 5	Wald test	p-value	Bonferroni-Holm adjusted significance level
	n = 39	*n = 25*	*n = 24*	*n = 22*	*n = 18*			
Living alone	**2.7677**	**-2.521**	**-3.697**	0.8813	**3.4848**	20.7346*	.00036	.00357
Physical problems (PDQ_PH)	**2.1964**	-1.189	**-3.695**	-1.892	**3.8359**	19.8868*	.00053	.00385
Depressive symptoms (PDQ_DE)	**-3.13**	**3.5567**	**3.7437**	-1.693	**-2.174**	18.9*	.00082	.00417
Rehabilitation	0.8723	**-2.234**	**-3.394**	-0.587	**3.4923**	17.515*	.0015	.00455
Trait anxiety (PDQ_AT)	**-2.14**	**2.5195**	**2.8991**	1.6154	**-3.528**	16.6462*	.0023	.005
Psychological care	-0.537	2.5382	-3.108	-1.293	2.0092	13.0318	.011	.00556
Expectations online self-help	-1.639	1.3169	-0.616	-3.017	1.8949	10.1127	.039	.00625
General internet use	-2.728	0.4759	1.2917	1.2778	-0.868	8.1693	.086	.00714
Social support (PDQ_SP)	-1.334	0.1144	0.5255	2.4202	-1.932	7.6463	.11	.00833
Children living at home	-1.66	-0.592	2.1218	1.2226	-1.344	7.0531	.13	.01
Health-related behavior	2.4824	-0.769	-1.474	-1.022	0.9706	7.157	.13	.0125
Age	-0.323	-2.42	-0.067	-0.057	1.8432	6.9047	.14	.01667
Chemotherapy	-0.567	2.3266	0.0262	-0.29	-1.521	5.739	.22	.025
Education	-0.133	0.1371	-0.061	-0.184	0.0775	27.7102	.69	.05

* Significant Wald test: p-value smaller than the Bonferroni-Holm adjusted significance level
Bold values: values of >2 or <-2 are used to determine which class(es) significantly contribute to the effect of the predictor. Positive values show that participants in that class show higher than average scores on that predictor; negative values show that participants in that class show lower than average scores on that predictor.

Discussion

The current study is one of the few studies that investigate the effect of an online self-help training for FCR with a follow-up of 24 months. Results indicate no change of both FCR and PD across time, for both the intervention and CAU group, nor any effect of the intervention on the relation between FCR and PD, nor did we find a class of participants that benefitted from our online self-help training. Although some p-values testing

whether a condition showed change over time were almost statistically significant, the expected change across time is very small and not clinically meaningful.

This result is largely in line with a recent literature review about online interventions aimed at reducing FCR and PD in cancer patients. They found partial support for reduction in PD, and limited evidence for reducing anxiety after online interventions.[44] The PD reductions were achieved by interventions in which patients were screened on PD before study inclusion, and interventions which included therapist support.[44] Since other studies showed that interventions with therapist support, standard e-mail reminders, or only including patients with high FCR were more effective, this may explain the differences in results with our study.[45–48] One of the papers from the literature review did not find an intervention-effect in the primary analysis, but secondary per-protocol analysis restricted to patients who accessed at least half of the intervention resulted in a greater decrease in psychological and cancer specific distress compared to a control group.[49] In the current study secondary analysis did not show an intervention effect for participants who followed the online self-help training, compared to CAU. In line with our study, another systematic review about self-guided interventions for managing PD in people with cancer found no effects in reducing PD in four online self-guided interventions.[50] With the current study, we consciously chose to evaluate the long-term effectiveness of our online self-help training in a realistic setting (how it was intended to use); without screening for high levels of FCR or PD, sending reminders, or therapist support. Such a purely online self-help training has several advantages, such as easy accessibility, low costs, greater privacy, and patients can work at their own pace.[22, 23] In conclusion, despite these advantages, online self-help interventions (without screening or support) may show limited effects. Moreover, in line with previous research, our results showed no significant natural decrease of both FCR and PD over time (in both groups), which may indicate that FCR and PD are stable over time.[1, 51, 52]

The baseline correlations between FCR and PD that we found in this study were in line with previous research.[15, 53] The difference between both groups on baseline correlation between FCR and PD is remarkable, since the groups were randomized. Presumably, this may be an incidental finding. A possible explanation for not finding a decrease in relation between FCR and PD could be the large variability in individual FCR and PD baseline levels.

Moreover, we identified five latent classes that capture different patterns in FCR across time. Our results showed quite stable FCR trajectories for four of the latent classes over time (stable severe, moderate, mild, and low FCR). One of the classes has moderate baseline FCR and starts to decrease 6 months after the intervention, but we do not expect this to be an effect of our online self-help training. Recently, some studies have been published about FCR classes and trajectories.[2, 54–61] However, comparison of

these studies is hampered by the use of different study designs, for example duration of the studies, outcome measures, and statistical methods. Therefore, the results of these studies about classes and trajectories in FCR are too disparate to compare them with our results. Likewise, five studies have reported predictors for FCR trajectory classes, but there is so much variability in study design, that we cannot compare results.[55, 57, 58, 61, 62]

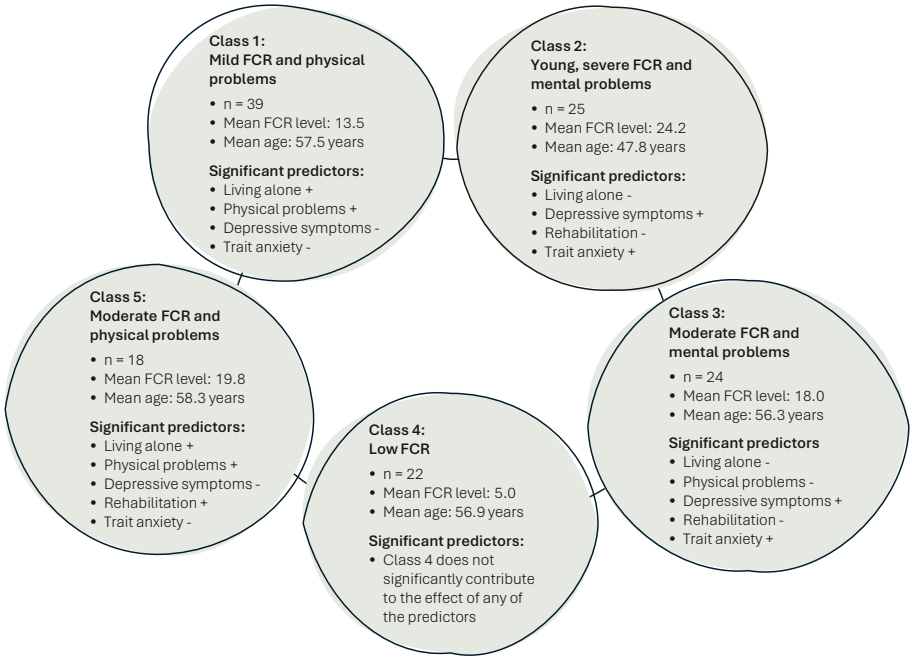

Figure 4. Significant predictors for the latent classes. - significantly less; + significantly more. FCR = fear of cancer recurrence.

Limitations and strengths

This study had several limitations. First, since R package lavaan gave a warning for all growth models using both MLR estimation and other robust estimators, ML estimation was used to fit the model. Presumably, the model with several hundred parameters was too large for our data. The ML estimator is not robust against deviations from normally distributed data, which can lead to biased model parameters. This should be considered when interpreting significant results. However, (full information) ML is a good estimator to handle missing data and to use as much data as possible in longitudinal analyses. Second, the high percentage of non-users may have distorted the results, although this shows probably a realistic picture of usage of online self-help interventions. Sensitivity analyses showed that the non-users did probably not influence the treatment effect of the intervention: when leaving the participants who did

not actually follow the online self-help training out of the analyses, also no significant treatment effect was found for the intervention group compared to CAU. Third, we used a subscale of the FCRI to measure PD, while most other studies used different questionnaires for psychological distress, such as the Hospital Anxiety and Depression Scale (HADS).[44] This may complicate comparison of the different studies.

An important strength of our study design is the long follow-up period of 24 months. The effect studies mentioned above, reported follow-up periods ranging from immediately after intervention to 12 months after baseline.[44, 46, 47, 49, 50] From the studies about FCR classes and trajectories in FCR, only two reported follow-up periods above 24 months: 5 years (a prospective cohort of women diagnosed with breast cancer at age ≤40 years) and 9 years (a national prospective longitudinal study from the American Cancer Society's Study of Cancer Survivors-I).[55, 61] This illustrates that the follow-up period of 24 months in our RCT is valuable and adds to the body of knowledge of FCR. Second, we used state-of-the-art analysis. When analyzing RCT data consisting of repeated measurements of a psychological construct, a latent growth model outperforms a traditional observed score model because the latter does not take into account the measurement error in the questionnaire item scores and therefore tends to produce biased treatment effects.[63] Also, as found in our earlier publication, the large variation in the change in FCR and PD scores within participants over time in this RCT supports the importance of our choice to model individual differences in growth curves using a latent growth curve models (instead of comparing the average change over time).[25] Third, as mentioned before, the ecological validity of the current study is high.[25] This study reflects a realistic picture of online self-help interventions, because we did not screen for high levels of FCR, CAU was allowed, and we offered purely self-help without extra help or emails. Other strengths (also mentioned in an earlier publication) were the use of a large consecutive sample and the fact that our study sample consisted of relatively young women.[25] Since young women use the internet more often than older women for both searching for information and for personal development, and the prevalence of FCR in young breast cancer survivors is high, we did reach the right target group with this RCT.[6, 64]

Clinical implications

Levels of FCR and PD seem to be stable over time (showed no significant natural decrease), which underlines the importance to develop interventions for both FCR and PD in breast cancer survivors. In the current study, we found no (long-term) effect of our online self-help training. To retain the benefits of online interventions, such as easy accessibility, low costs, and work at their own pace, we suggest to study whether online interventions with professional support, for example, from general practice mental health professionals (GP-MHPs) might be effective (as also suggested in our earlier publication).[25] This RCT showed five possible FCR subgroups representing different trajectories in FCR over time and their predictors, which is important information that

adds to the body of knowledge about FCR. Knowing more about the specific needs of each FCR group may contribute to the development of better interventions. More research is needed to confirm our results.

Conclusions

In conclusion, five latent classes and several predictors of class membership were found. Knowing more about the specific needs of FCR groups, may contribute to the improvement of interventions for FCR. Furthermore, there was no (long-term) effect of the CBT-based online self-help training "Less fear after cancer" in reducing both FCR and PD. Therefore, we recommend adding professional support, like email contact or face-to-face assistance, to future online interventions for FCR and PD.

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07

How online self-help training for fear of cancer recurrence was experienced: A thematic analysis of facilitators and barriers

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Submitted.

Abstract

Purpose

Breast cancer survivors often experience some level of fear of cancer recurrence. The aim of this study was to qualitatively explore the perceived barriers and facilitators in Dutch breast cancer survivors who were invited to use an online self-help for fear of cancer recurrence.

Methods

Semi-structured interviews were conducted with nine participants selected from the intervention group of the CAREST trial, using purposive sampling to avoid sampling bias. The interview material was analyzed using thematic analysis.

Results

Thematic analysis revealed facilitators and barriers to treatment, and elements that had been missed by participants. Participants appreciated the content and the benefits of online self-help training, despite some technical issues and ambiguities. For some participants, support would enhance online interventions, while for others professional or peer support is challenging. Therefore, we recommend developing tailored interventions.

Conclusions

Self-help internet interventions are acceptable to breast cancer survivors, but it is critical to provide tailoring and support to help overcome barriers and improve treatment adherence.

Introduction

Fear of cancer recurrence (FCR) is a stable and potentially long-term psychological consequence of surviving (breast) cancer, defined as "fear, worry, or concern about cancer returning or progressing".[1, 2] Most breast cancer survivors experience a low or healthy level of FCR, while around 22% experiences clinical (high) levels of FCR.[2–4] Clinical levels of FCR may negatively affect illness behavior, mood, quality of life, and increase healthcare costs.[1, 3, 5–7]

Given the burden of FCR, accessible interventions are needed.[1] Because online interventions may be promising due to their accessibility, low cost, convenience, privacy, and allowing patients to work at their own pace, we developed and evaluated an online tailored self-help training based on cognitive behavioral therapy (CBT) to reduce FCR.[8–11] Since we did not find our intervention to be effective, this qualitative study aimed to explore the perceived facilitators and barriers among Dutch breast cancer survivors invited to use online self-help for FCR. Participants were also asked what they felt was missing.

Material and methods

CAREST trial

This study was part of the CAREST randomized controlled trial (RCT), examining the effectiveness of an online self-help training to reduce FCR in (female) breast cancer survivors over a 24-month follow-up period. The design and quantitative results of the trial have been published elsewhere.[10–12] The trial was approved by the Medical Ethical Committee of the Maasstad hospital in Rotterdam (2013/41), registered in the Dutch Trial Register (NTR4119) and conducted in accordance with the principles of the Declaration of Helsinki.[13] Figure 1 provides an overview of the online self-help training, referred to as the "intervention".

Study population

Participants from the CAREST trial were contacted by phone and asked to participate in a post-intervention interview. We used purposive sampling to avoid sampling bias and to ensure a balanced representation, dividing participants into four groups based on their Fear of Cancer Recurrence Inventory scores (<13 low FCR; ≥ 13 moderate to high FCR) and whether they had completed the intervention. Informed consent was obtained from all participants.[10]

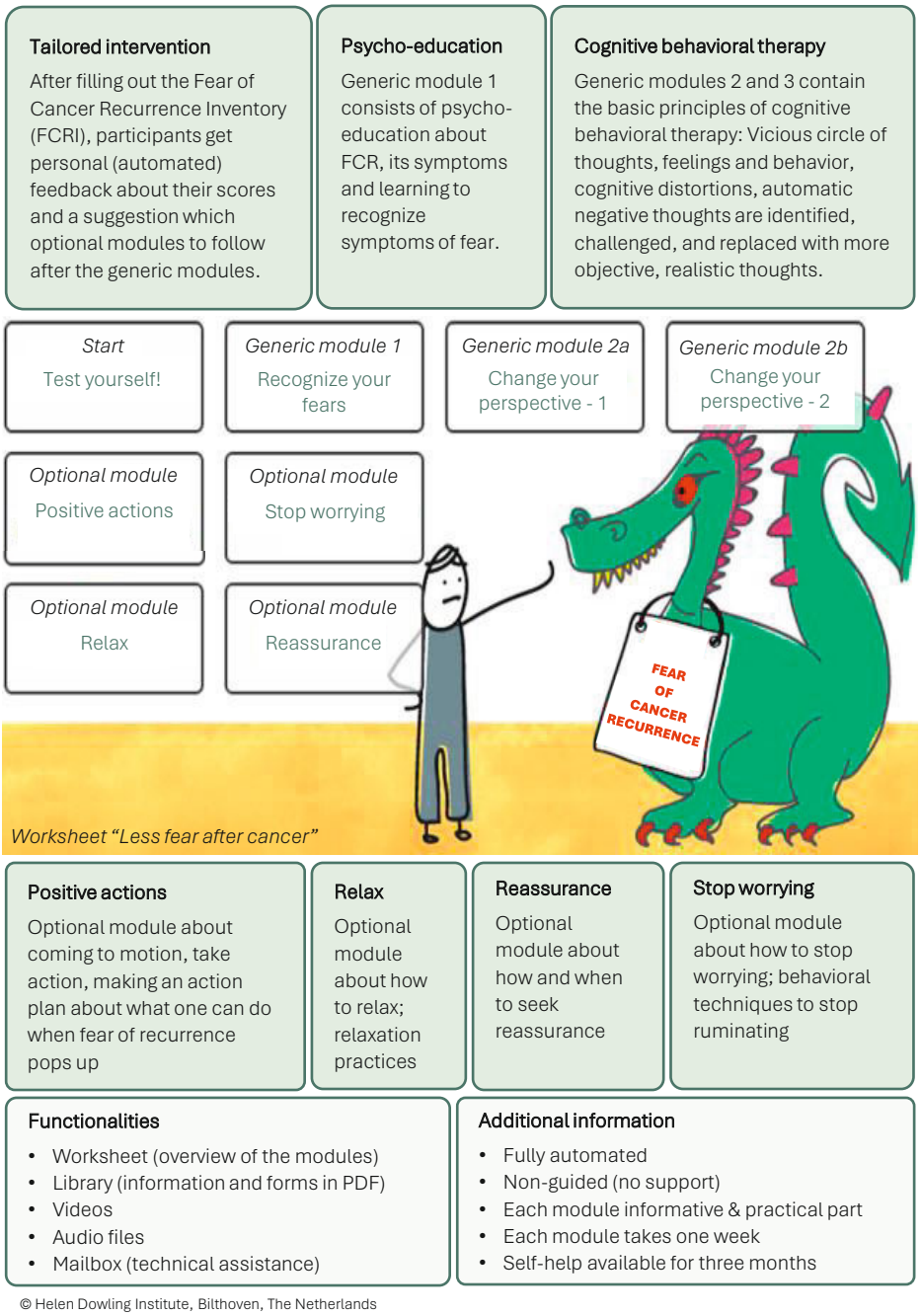

Figure 1. Content of the online self-help training "Less fear after cancer"

Data collection

Between March and August 2016, face-to-face interviews were conducted at participants' homes and audio-recorded using a digital voice recorder. The topic guide for the interviews is published on the Open Science Framework (in Dutch; https://osf.io/2sg6m/).

Design

To explore the perceived barriers and facilitators, we used a theoretical thematic analysis with a sematic and realist approach.[14] We used the Standards for Reporting Qualitative Research (SRQR) to ensure the robustness of the design.[15]

Data analysis

First, the interviews were transcribed verbatim using Express Scribe Transcription Software and reviewed for accuracy.[16] Subsequently, the data were analyzed thematically with line-by-line coding using ATLAS.ti software.[17] The first five transcripts were independently coded at the semantic level. Investigator triangulation was applied, involving several researchers in the coding and data analysis process.[18] Codes and interpretations were compared and discussed until consensus was reached. The remaining interviews were openly coded case-by-case in the same way. An analytical session with all authors was held to identify superordinate themes, discrepancies were discussed until consensus was reached.

Results

Nine participants were interviewed: six completed all modules (three low FCR; three moderate to high FCR), and three had partially completed the intervention (one low FCR; two moderate to high FCR). The interviews averaged 27 minutes (range 16-42), mean age was 57 (range 39-73) and mean Fear of Cancer Recurrence Inventory (FCRI) severity score at baseline was 14 (range 4-23).

Content-related experienced facilitators

Participants primarily mentioned facilitators when discussing the intervention's content; Table 1 provides an overview of the themes and subthemes.

Regarding the generic modules (GMs), participants valued the information on how fear operates in the brain, which helped them to put their fear into perspective. They also indicated that it helped them to give space to their anxiety, that it was okay for it to be there. Participants learned that their fear is perfectly normal, that they are not the only one. Moreover, the intervention helped them to view their anxiety with more distance, preventing them from becoming overwhelmed. It taught them not to exaggerate or downplay fears, offering a balanced perspective. Also, participants learned to reinterpret fear triggers, such as physical sensations or stories in their environment,

into more positive, constructive thoughts, leading to less fear-driven behavior. Lastly, the availability of the intervention was appreciated; it provides acknowledgement for their fear.

The optional modules (OMs) were less frequently mentioned; likely because not all participants completed them. Regarding the OMs, participants noted that they helped them to take action and actively engage with their fear. Additionally, participants reported that the OMs enabled them to shift their focus away from their fears, allowing them to feel more at ease. The intervention also helped them in breaking negative thought patterns and reducing overthinking. The "Relax" and "Reassurance" modules were barely mentioned, and no significant themes emerged from them.

Generally experienced facilitators and barriers

Participants mentioned various general facilitators and barriers, as outlined in Table 2. We identified two overarching themes: Treatment setting and Treatment format.

Treatment setting: Participants appreciated the convenience of self-help, as they could do it at home, at their own pace, despite occasional technical issues. Some preferred the self-help format over peer or therapist interactions, which they found confrontational and burdensome. Some faced difficulties while working on the intervention, due to cognitive issues (concentration and memory) and physical problems (eyes, arm). Some participants found the duration of access and instructions unclear.

Table 1. Experienced facilitators of the content on the intervention.

Themes	*Subthemes**
Generic modules	
Recognize fear	• Psycho-education is helpful (3)
	"What I really liked about it, was the fact that also the technical part about the brain and the substances produced in the brain and what effect they have, was discussed. Then I think, okay, that's how it works. That really helps me when I feel like that, that I can say to myself, wait a second. Just that type of approach" (patient 9, age 50, moderate to high FCR, completed all modules)
Give the fear right to exist	• Let the fear be (4)
	"Well, you don't want to feel the fear, but because you allow the fears to be there, something happens to you. Then it changes, and then it's just ok, whatever it is. You start looking at things differently. Then you don't panic as much anymore." (patient 1, age 39 , low FCR, completed all modules)
	• Acknowledge fear (3)
	"I really like that [the self-help] is there, it makes me happy, like, it's nice to make it available, because cancer affects many parts of your life. And fear [of cancer recurrence] is a large part of that, and that it's literally... [acknowledged]..., I think that's already worth a lot " (patient 1, age 39 , low FCR, completed all modules)

Table 1. Experienced facilitators of the content on the intervention. (continued)

Themes	*Subthemes**
	• Normalize fear (2) *"I think that when you know that you are not the only one, that it's very normal, I think that helps! Of course, that goes for everything, but I do believe you should not think that this only happens to you."* (patient 6, age 62, low FCR, completed 6 modules)
Look at things from a different perspective	• Look at your fear from a distance (5) *"At first, you get all kinds of scenarios in your head. You make yourself anxious because you think beyond the actual situation. So ehm, there is an alarm in your head and you literally want to get away from it. But it is the reality, and you have to deal with it. [....] It is there every day, and you have to handle it. And with the self-help you can literally start looking at it from a distance, instead of being sucked in, like in quicksand."* (patient 1, age 39 , low FCR, completed all modules) • See things in perspective (14) *"Sometimes there are triggers. Then I think, oh this better not be ... You know, when you have something or feel something, then you think, it better not be ... You think that, but then I immediately think - what helped me in your research - about seeing a snake in your garden and then finding it is a garden hose. That's what I think about then! Then I think, why would I, when you don't know beforehand ... ? I think about that often, ah a snake, but then I look at it better and I think, ah, it's a garden hose! So I think, is this something? but then I think, nah, it's not, come on!* (patient 6, age 62, low FCR, completed 6 modules)
Formulate helpful thoughts	• Learn to look at things differently (7) *"Taking a different perspective, also focusing on what is still possible, because of course a lot is. And sometimes you think that that's not the case, because a lot is gone, but yes, it is good to look at that."* (patient 1, age 39 , low FCR, completed all modules) • Positive thinking is helpful (2) *"So you really have to decide to let the negative go and to only look at the positive side. And when you do that, things will be alright!"* (patient 7, age 66, moderate to high FCR, completed 4 modules)
Optional modules	
Start moving mentally	• Get active (and stop avoiding) (4) *"Literally going into action. You can do something, and you are! And that's also nice."* (patient 1, age 39 , low FCR, completed all modules) • Become aware (3) *"Well also to be working on that. You have chosen to do that and so you are going to do it. You have a tool, it's also a tool. To really consciously start working on that. And also to process things, it all helps."* (patient 1, age 39 , low FCR, completed all modules)

Table 1. Experienced facilitators of the content on the intervention. (continued)

Themes	*Subthemes**
Stop ruminating	• Focus on something else (3) *"You had to put a rubber band [on your arm] and if you thought about something that was not really restful, or you had pain somewhere, like pain in your chest... then you had to pull on that rubber band and then concentrate your thoughts on the pain that you get because the rubber band shoots back on your wrist. Then you have pain in your wrist and not in your chest. And then of course you shift your thoughts to that. And I found that to be one of the things that really helped me, because I have great difficulty relaxing myself, so this allows me to shift my thoughts in a different way..."* (patient 4, age 73, moderate to high FCR, completed all modules) • Break through negative thoughts (1) *"It especially helps when you hear something, or when you feel something, and you think very far ahead: "See, it means I have this and that, and so I will get ill, and then what am I going to do? And how long do I have to live then? Maybe I will not be here in a year!" And then you say to yourself: "Hold on, stop! Back to ..." And then I really speak to myself, or otherwise my husband will speak to me. So ehm, that's how. So that really clarified it for me."* (patient 9, age 50, moderate to high FCR, completed all modules)

Abbreviations: FCR: fear of cancer recurrence.
*The number of quotes a subtheme is based on, is displayed between brackets after the subthemes.

Treatment format: Some participants found the videos relatable and helpful, while others did not. Moreover, some participants valued the ability to ask questions and access a professional therapist if needed, which was offered during the study for ethical reasons.

Missing elements

Participants noted several missing elements in the intervention (see Table 2). Overall, they mainly missed support. Some expressed a need for peer support, such as participating in a group or having a chat function to connect with peers. Also, participants mentioned a need for professional support, like having someone to talk to, ask questions, or express frustrations. Some participants found it difficult to seek help themselves, and one suggested that regular emails would enhance commitment. One participant repeatedly highlighted the lack of attention to patients' environment, noting that partners also endure significant challenges.

Table 2. Generally experienced facilitators and barriers: themes and subthemes illustrated with a quote.

Themes	*Subthemes – Facilitators**	*Subthemes – Barriers**	*Subthemes – Missing**
Treatment setting (the external conditions of the intervention)			
Home setting	• Work on it in my safe place (5)	• Save work is difficult (2)	
	"I liked doing it in my own house, in my own safety, to do it this way. To have the choice, yes." (patient 1, age 39 , low FCR, completed all modules)	*"I thought it was a bit unclear, how to use it, how to do it. Sometimes I thought: now I'm going to save my work, and then I thought: oh I lost it! Where is it? You know? I found that difficult." (patient 6, age 62, low FCR, completed 6 modules)*	
	• Have easy access (4)		
	"It is nice to do it in your own environment, because sometimes you are not in the situation that you can do much. Then you don't have to go to anyone, because that is also a barrier for me. So [doing it in your own environment] makes it accessible for me, to work on my fears." (patient 1, age 39 , low FCR, completed all modules)		
Individual treatment setting	• (Peer) support too burdensome (2)		• Need for peer support (4)
	"No contact with fellow sufferers, especially not. I think that is such a confrontation. I prefer to do my own things, in my own environment, with my own friends" (patient 8, age 57, moderate to high FCR, completed all modules)		*"[…] An online support group, I think that's very important. I think it helps to accept yourself. Like see, I am not the only one / alone!" (patient 6, age 62, low FCR, completed 6 modules)*
			• Need for support (8)
			"I got no feedback at all, like how did it go, did it go well, or did it not go well or something. Nothing! […] I think that you have to contact people after for example the first or second week, or the first or second module, to ask how it went, and if they like it or something. Then they have an opportunity to express their frustrations, for example. Now that is only possible afterwards." (patient 4, age 73, moderate to high FCR, completed all modules)
Time-ownership	• Work at own pace (5)		
	"I worked through it in three blocks, quite a lot at once. " (patient 2, age 57, low FCR, completed all modules)		

Table 2. Generally experienced facilitators and barriers: themes and subthemes illustrated with a quote. (continued)

Themes	*Subthemes – Facilitators**	*Subthemes – Barriers**	*Subthemes – Missing**
	• Work in own time (2) *"And that's the beauty of it, it is anonymous, and you can do it in your own time and in your own... It suits this era, yes." (patient 9, age 50, moderate to high FCR, completed all modules)* • Work when you feel the need (2) *"And that you can work on it at your own moment, in your own time, when you feel the need. And if that's during the day or during the night, you can work on it. I thought, when I feel better again, I don't need the self-help. [...] If I don't need it, I shouldn't evoke it either." (patient 9, age 50, moderate to high FCR, completed all modules)*		
Illness barriers		• Computer work too demanding (5) *"I wasn't clear in my head, because I was still worried about it so much. And I still suffer from that. Also from concentration and memory problems, I just have lost a lot. So its every time...reading is difficult for me, I have to read with concentration to understand what is written." (patient 3, age 58, low FCR, completed all modules)*	
Lack of information		• Unclear what to do (4) *"But what I found annoying was that I sometimes found it quite complicated. Not the questions, but how I should do it." (patient 6, age 62, low FCR, completed 6 modules)* • Unclear how long the intervention is accessible (6) *"And I thought I actually had much longer. Until a certain date and suddenly it was over! [...] I found that a bit unclear. How to use it, how to do it." (patient 6, age 62, low FCR, completed 6 modules)*	

Table 2. Generally experienced facilitators and barriers: themes and subthemes illustrated with a quote. (continued)

Themes	*Subthemes – Facilitators**	*Subthemes – Barriers**	*Subthemes – Missing**
Treatment format (how the intervention was internally organized and delivered)			
Content	• Recognition in videos (2)	• No recognition in videos and exercises (3)	
	"And I also really liked that with those videos. That you hear people from experience, gosh, I've experienced this and that. And ehh... Who just describe that from their own experience." (patient 9, age 50, moderate to high FCR, completed all modules)	*"I react very differently than the person in the video. That's just the way it is and you can't compare it. That's difficult, you know." (patient 7, age 66, moderate to high FCR, completed 4 modules)*	
Support	• Possibility to ask for support (2)		• Need for feedback by e-mail (4)
	"But well, you said if you get anxious you can call in a therapist. I think that is very important." (patient 6, age 62, low FCR, completed 6 modules)		*"Well at some point... at the times that you mailed, you participated! So if you mailed a little more frequently, you participate a little more! So that's another tip." (patient 2, age 57, low FCR, completed all modules)*
Target group			• Need for more attention for partners and environment (3)
			"So when you're talking about a care program for the fear of cancer recurrence, I think a program for the environment is just as important." (patient 9, age 50, moderate to high FCR, completed all modules)

*The number of quotes a subtheme is based on, is displayed between brackets after the subthemes.

Discussion

This is the first paper to qualitatively examine an online self-help training for fear of cancer recurrence by exploring its facilitators, barriers, and gaps. Participants mainly mentioned facilitators regarding the treatment's content. Our online self-help is a tailored intervention; these results confirm that the suggestion for which optional modules to follow after completing the FCRI was appreciated.

Participants generally valued the advantages of the online self-help training, despite some technical difficulties and ambiguities. Some participants desired additional support. Our RCT did not find a treatment effect, potentially due to the lack of support. The BLANKET study, which evaluated this online training for fear of cancer recurrence with support from mental health workers in a primary care setting, found the intervention effective in reducing FCR.[19] Additionally, two systematic reviews

showed that online interventions with support are more effective.[20, 21] However, we found that for some participants professional or peer support can be confrontational or burdensome. Another qualitative study noted that self-help addresses issues patients might be too embarrassed to discuss face-to-face.[22] Therefore, we recommend offering support as an optional component of the tailored intervention.

Some participants experienced technical issues and ambiguities as a barrier, which was also reported for another online self-help intervention for cancer patients.[22] For instance, in our study participants were unsure about the duration of access or the steps to follow. Despite our efforts to provide clear instructions (e.g., the welcome email stated the intervention was accessible for three months), these insights highlight the need for improvement. If participants progress slower than expected, extending the access period or providing clearer guidance may be necessary.

Limitations and strengths

A limitation was that some participants completed the intervention a while ago, possibly leading to recall bias. Additionally, fewer interviews were conducted than planned due to limited participant availability, raising uncertainty about data saturation. Although saturation seemed reached after eight interviews, the ninth revealed additional subthemes, highlighting the challenge of determining when to stop data collection. Therefore, results may not be generalizable to all Dutch female cancer survivors. A strength was the inclusion of participants with varying levels of intervention exposure, reflecting real-world use.

Clinical implications

This study adds to the body of knowledge on online self-help interventions. Despite their many benefits, the effectiveness of these treatments can be disappointing. Our findings may help enhance future online self-help interventions, making them better suited to the needs and preferences of patients.

Conclusions

In conclusion, the intervention's content and the benefits of online self-help training were appreciated, despite some technical issues and ambiguities. However, support would enhance online interventions especially for fear of cancer recurrence. As some participants find professional or peer support challenging, we recommend developing tailored interventions.

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08

General discussion

This chapter provides a summary and general discussion of the main findings of the studies in this thesis. Furthermore, the limitations and strengths of the studies as well as recommendations for clinical practice and future research are discussed.

Assessment of fear of cancer recurrence

As explained in the introduction, good, concise, reliable, and valid measures to assess FCR are needed. When we started this study, only the 8-item unidimensional Cancer Worry Scale was available in Dutch.[1] Therefore, in **chapter 2**, we decided to translate and validate the Fear of Cancer Recurrence Inventory (FCRI), the best multidimensional measure available at that time, already available in French-Canadian and English. The FCRI-NL was examined by assessing internal consistency, test-retest reliability, and convergent and divergent validity of the FCRI-NL and its subscales. In addition, a confirmatory factor analysis (CFA) was done to investigate whether the seven-factor structure of the original FCRI could be confirmed. We found that the FCRI-NL has acceptable psychometric properties. The FCRI-NL and its subscales have sufficient to good reliability and test-retest reliability, except for a lower test-retest reliability on the Reassurance and Coping Strategies subscales. Convergent and divergent validity are demonstrated for the FCRI-NL, and its Severity subscale (FCRI-SF-NL). However, the multidimensional structure of the original FCRI was not convincingly replicated for the FCRI-NL in the present sample. The CFA showed a reasonable but suboptimal fit of the second order model to the data, which is slightly weaker than the other translations.

Therefore, we aimed to improve the FCRI-NL further in **chapter 3**. We explored the factor structure of the FCRI-NL using exploratory factor analysis (EFA) and tested the new factor structure with CFAs in two new patient samples. The EFA revealed a 4-factor solution with 34 items from the original FCRI-NL. However, this new 4-factor structure was not replicated in the two new (mainly breast cancer) patient samples. Additional non-prespecified CFAs of the original 7-factor structure showed a reasonable fit to the data in both samples. Based on these results, we suggested retaining the original 7-factor FCRI-NL instead of the new 4-factor version. Given the inconsistencies in the body of research concerning the FCRI, we also comprehensively compared its factor structure across all published psychometric studies in **chapter 3**. The comparison was complicated by the fact that the studies used different fit indices, cut-off scores, and software. However, after applying the same criteria to all FCRI translations, the factor structure results were largely comparable. When taking the results of **chapters 2 and 3** together, we can conclude that the factor structure results of the FCRI-NL align with other translations.

Although FCR is increasingly acknowledged as a multidimensional construct, a FCRI total score is still commonly used in empirical research, raising the question whether a total score of a multidimensional questionnaire data, such as the FCRI, accurately

represents the multidimensional construct. [2–4] Combining the subscale scores of the FCRI to derive a total score may hamper interpretation of the questionnaire, because a total score combines level of fear with its antecedents and consequences.[5–7] Thus, a total score represents an uninterpretable combination of concepts.[7] Many possible combinations of subscale scores can give identical total scores. So, when we sum up the subscale scores, we lose a lot of important clinical information. Moreover, when measuring multiple time points, using a total score may obscure changes in the subscale scores that may be clinically meaningful. Therefore, concerning the FCRI total score, we strongly recommend against its use, because it is unclear what it represents. However, individual items and some subscale scores provide important information and may be useful indicators of when FCR levels are clinically significant.[7] Therefore, the FCRI subscales are valuable in clinical practice for discussing item level details and tailoring interventions to patients' needs.

There have been several attempts to improve the FCRI. One study reexamined the dimensionality of the FCRI; they found that a multidimensional model with seven first-order factors fitted the data better than the original second-order model, and another study performed an EFA and presented an alternative 5-factor FCRI which fitted the data better than the original 7-factor model.[8,9] In **chapter 3**, we also contributed to the body of research on improving the FCRI, by performing an EFA and presenting and testing an alternative FCRI.

To avoid using the FCRI total score, we can use the Severity subscale (FCRI-SF), as we did in the CAREST trial (**chapters 5 and 6**). Although the FCRI-SF is not representative for the complete FCRI, it is appropriate for screening purposes.[5] However, the FCRI-SF may also have issues because some items disproportionately contribute to a positive screen for clinical FCR.[5] For instance, the item "How long have you been thinking about the possibility of cancer recurrence?" is influenced by the time since diagnosis. Long-term cancer survivors may score higher and be more likely to be identified as probable clinical FCR cases, even if these thoughts do not cause significant distress or functional impairment.[5] Since the CAREST trial included breast cancer survivors who were diagnosed 1 to 5 years ago (and time since diagnosis is on average 2.6 years in our sample), this issue is not a problem for our findings.

In conclusion, the two psychometric FCRI studies in this thesis (**chapter 2** and **chapter 3**) contributed to the body of knowledge on measuring FCR in the Netherlands. The FCRI-NL is the first comprehensive multidimensional questionnaire that has been translated into Dutch. It has acceptable psychometric properties, although the multidimensional structure of the FCRI-NL was not convincingly replicated in our sample. However, we showed that all FCRI translations have acceptable and largely comparable factor structure results after applying the same fit indices and cut-off criteria. Although there may still be room for improvement concerning the FCRI factor structure, we failed to

improve the FCRI-NL factor structure by testing a new 4-factor structure, and therefore, we suggest retaining the original 7-factor FCRI-NL. Even though we recommend against using the FCRI total score, using a multidimensional questionnaire to measure FCR still has added value because the subscales and individual items are valuable in clinical practice and for tailoring interventions to patients' needs.

Managing fear of cancer recurrence in breast cancer survivors

Due to the significant impact that high levels of FCR can have on the lives of (breast) cancer survivors, including reduced quality of life, poorer health outcomes, and increased healthcare costs, it is essential to develop cost-effective interventions to alleviate FCR.[10–12] Therefore, after administering a questionnaire to patients of the Dutch association of cancer patients, the CBT-based online self-help training "Less fear after cancer" was developed by the Helen Dowling Institute, an institute for psycho-oncology. **Chapter 4** describes the study protocol of our randomized controlled trial (RCT) investigating the effectiveness of our online self-help training for FCR in Dutch women with curatively treated breast cancer (breast cancer survivors), hereafter named the CAREST (CAncer Recurrence Self-help Training) trial. Originally, we aimed to investigate the effectiveness and cost-effectiveness of the online self-help training. Because we did not expect online self-help to be effective for all participants, we also aimed to identify factors that predict which women benefited most from the online self-help.

The short-term and long-term effectiveness of our online self-help training to reduce FCR are described and discussed in **chapters 5 and 6**. The CAREST randomized controlled trial showed that there was no evidence for an effect of the online self-help training in reducing FCR compared to care as usual, after 3, 9 and 24 months follow-up. Also, we did not find a long-term effect of the intervention in reducing psychological distress (PD), nor on the strength of the relation between FCR and PD. Furthermore, we evaluated the relation between FCR and PD across time, because we expected a strong correlation at baseline and a significantly weaker correlation after the intervention, as we expected PD to decrease more than FCR. However, we found a moderate baseline correlation between FCR and PD for the intervention group, and a strong correlation for the CAU group, but the correlation did not significantly decrease over time in both groups. Moreover, no significant predictors were found for the effect of the intervention on FCR. We did identify five latent classes that represent a distinct change pattern of FCR over time (and their predictors). Four classes showed stable trajectories over time (stable severe, moderate, mild, and low FCR over time), and one class shows a decrease of FCR over time. However, because the decrease occurred after nine months (six months after the intervention), we do not expect this to be a treatment effect. In conclusion, we did not identify classes who benefit from the intervention.

The CAREST trial was conducted differently in some aspects than initially described in our study protocol (chapter 4). First, we planned to analyze effectiveness of the online self-help using linear mixed models. However, due to progressive insight, after collecting the data we have decided to use more state-of-the-art analysis, i.e., a latent growth model. As described in chapter 6: "When analyzing RCT data consisting of repeated measurements of a psychological construct, a latent growth model outperforms a traditional observed score model because the latter does not take into account the measurement error in the questionnaire item scores and therefore tends to produce biased treatment effects".[13] Moreover, the large variation in the change in FCR and PD scores within participants over time that we found in chapter 5 supports the importance of our choice to model individual differences in growth curves using a latent growth curve model (instead of comparing the average change over time).[14] Second, as we did not find an effect of the online self-help training in reducing FCR, we were not able to perform cost-effectiveness analyses. Although we did perform preliminary analyses, as expected, we did not find any differences in healthcare use between the groups.

In chapter 7 we qualitatively described the experiences of Dutch breast cancer survivors with the online self-help training for FCR, by means of a thematic analysis of facilitators and barriers. Thematic analysis revealed that participants appreciated the content and the benefits of online self-help training, despite some technical issues and ambiguities. For some participants, support would enhance online interventions, while for others professional or peer support is challenging. Therefore, we recommend developing tailored interventions.

Although we did not find an effect of our online self-help, it may still be suitable for some patients. In chapter 7 we found that our online self-help is acceptable to and appreciated by breast cancer survivors. Moreover, online self-help fits well within the first two steps of the stepped-care approach we discussed in the introduction.[15, 16] The stepped-care approach may help to prevent sub-clinical FCR from deteriorating into a clinical level of FCR, and at the same time also to reduce costs.[16] Also, despite not finding an effect, the ecological validity of the study was high. It reflects a realistic picture of online self-help interventions, because we did not screen for high levels of FCR, CAU was allowed, and we offered purely self-help without extra help or emails. In summary, even though we did not find a significant reduction of FCR, it is appreciated by participants and may help cancer survivors cope with mild FCR, without lowering the FCR. Moreover, the intervention can be used as a first step for patients who find interventions with support too challenging.

A recent online Delphi consensus study stated that development and evaluation of intervention models was considered the most important focus for FCR research, and development and evaluation of more accessible models of care (e.g., low cost,

online, blended care) was identified as the highest research priority.[17] As stated in the introduction, despite the growth in the use of eHealth in recent years, there is still much uncertainty about the effectiveness of online interventions for cancer patients.[18] To my knowledge, no systematic reviews or meta-analyses concerning the effectiveness of internet-delivered interventions for reducing FCR in breast cancer patients have been published yet. Cincidda and colleagues (2022) conclude in their scoping review that almost all CBT-based psychological interventions can be efficacious in managing FCR in cancer patients, especially at posttreatment, regardless of whether it is delivered face to face, on the web, or using a blended approach.[19] However, the number of studies about online or blended therapy with actual results in this review is very limited, and a vast minority of these studies are RCTs. Nevertheless, some studies have been published, which we briefly review below (although the following overview may not be complete). A feasibility and acceptability study found that an online (guided) mindfulness-based intervention shows promise for Chinese breast cancer survivors, facilitating a reduction in FCR.[20] In the SWORD trial (RCT), blended cognitive behavior therapy has a statistically and clinically significant effect on the severity of FCR in a mixed sample of cancer survivors, both posttreatment and on the long-term (15 months).[21, 22] In the FoRtitude trial (RCT), a targeted eHealth intervention using cognitive behavioral skills training and telecoaching reduces FCR postintervention, and telecoaching improves adherence and retention.[23] However, the results are comparable between CBT and attention controls.[23] Given that both traditional and contemporary face-to-face CBT approaches have been proven effective, they may have failed to translate effectively into the online context.[24] The only study with a self-management intervention is a feasibility study that found that iConquerFear, a five-module self-guided digital FCR intervention, is a feasible and potentially efficacious intervention for reducing FCR in breast cancer survivors.[25] In summary, there are a few studies concerning the effectiveness of internet-delivered interventions for reducing FCR in (breast) cancer patients. Not all studies are RCTs, and most of the studies report about guided or blended interventions. There are hardly any studies published about the effectiveness of unguided online self-management interventions for reducing FCR in breast cancer patients. Concluding, we can say that despite attempts to investigate the effectiveness of online self-management interventions for reducing FCR, the current literature offers little additional insight into effective online self-management interventions than it did at the start of the CAREST trial. Possibly there is a publication bias, where research may have been conducted but not published if, like in the CAREST trial, no effect was found.

When considering the effectiveness of online self-help interventions from a broader perspective, we can find multiple meta-analyses and systematic reviews that found effective online self-help interventions targeting, for example, adult problem drinking, mental problems (depression, anxiety and stress) among adolescents and college students, and adults with depression, anxiety disorders or insomnia.[26–30] Treatment

effects seem higher for depression than for anxiety, which may give us an indication of why we did not find an effect of online self-help for FCR.[27] Another possibility may be that patients with FCR show avoidance behavior, although inconsistent evidence was found for an association between avoidance and FCR.[11, 31–35]

Although online self-help interventions have many advantages, such as low costs, easy accessibility, convenience and greater privacy, and patients can work at their own pace, there is still no convincing evidence for the effectiveness of online self-help interventions for FCR.[36, 37] Therefore, it is important that we improve our intervention, to make it more effective. In **chapter 7**, we found that solving technical issues or making instructions clearer, adding email-reminders, and adding support (e.g., peer support or professional support) may improve the effectiveness of our intervention. However, professional or peer support was experienced as confrontational or burdensome by some patients, and by adding professional support the intervention becomes a different type of intervention, i.e., a guided online intervention. When looking at the literature, a qualitative study that explored barriers and facilitators of adherence to an online psychological intervention for cancer-related distress, found facilitators like intervention factors, psychological factors, computer/technology factors, and personal factors.[38] Intervention factors like email/phone reminders, program satisfaction, ease of use, and program content were mostly mentioned.[38] Several participants stated finding email or phone reminders motivating.[38] A more general systematic review about predictors of adherence to online psychological interventions found that female gender, higher treatment expectancy, sufficient time, and personalized intervention content predicted higher adherence.[39] As a follow-up to the CAREST trial described in **chapters 5 to 7** of this dissertation, the BLANKET study evaluated our online training for fear of cancer recurrence with support from mental health workers in a primary care setting.[40] They found "Less fear after cancer" effective in reducing FCR.[40] A possible reason for the treatment effect found in the BLANKET study is the fact that they evaluated the online training with support from mental health workers. Support can, among other things, lower the threshold for cancer survivors to start with the intervention. Another possible reason is the high mean baseline FCRI severity score of 22.6, which is much higher than the mean baseline FCRI severity score of 15.2 in the CAREST trial. The high baseline score in the BLANKET study may be a result of the convenience sampling they performed, while we used consecutive sampling in the CAREST trial. Cancer survivors with severe FCR may be more likely to participate in an intervention, and a high FCR score can also more easily decrease. Some degree of FCR often remains present. Lastly, another possible reason is the fact that they used a mixed cancer sample (almost half of the participants had breast cancer), while the CAREST trial used a breast cancer sample.

In conclusion, to improve our online self-help "Less fear after cancer", we should solve any technical issues, make our instructions clearer, and add (automated) e-mail

reminders to ensure that participants are more actively involved. Moreover, given the results of the BLANKET study, professional support for some (but not all) participants (for example from mental health workers in a primary care setting) would be a valuable addition to the tailored intervention, which fits well within the third step of the above mentioned stepped-care approach. Support can be provided in traditional ways, such as face-to-face, telephone, video calls, or email. Recently, there has been increasing attention to the use of AI chatbots for providing guidance in online interventions in mental health care. A recent mixed-methods review found that AI-delivered self-guided interventions demonstrated medium to large effects on managing mental health symptoms.[41] AI helped enhancing treatment response and adherence, drop-out rates were comparable to non-AI interventions. However, the quality of the available evidence was low to very low, so additional robust and high-powered studies in this emerging field are needed.

We can ask ourselves whether FCR is the best construct to measure effectiveness of FCR interventions. As stated above, FCR ranges from "normal" to "clinical" and some level of FCR can even be helpful by promoting treatment compliance and healthy lifestyle adaptations.[42, 43] The goal of an intervention should therefore not be to eliminate FCR, but rather to focus on helping cancer survivors cope with FCR. This raises the question of how to measure effectiveness of a FCR intervention. A recent suggestion is to measure the impact of FCR on daily life, for which the FCRI Functioning Impairments subscale (FCRI-FI) might be useful.[4, 35] For example, a Delphi study reported impairment in functioning and maladaptive coping strategies (amongst others) as potential characteristic of clinical FCR.[4] Moreover, a recent network analysis reported that worry and bodily triggers appear to be core components of FCR that are experienced as impairing in daily life.[35] They suggest that in addition to FCR severity, assessing functional impairment, worry, and bodily triggers could be valuable when screening for clinical levels of FCR.[35] To conclude, we think that cancer survivors need help when FCR interferes with daily life. For this, we can look at how much survivors suffer from FCR, but also at the impact of FCR on their daily lives. The FCRI Functioning Impairments subscale (FCRI-FI) might be useful for this.

Overall, the CAREST trial contributed to the body of knowledge on online self-help interventions for FCR. We did not find evidence that our online self-help to reduce FCR in a realistic setting "Less fear after cancer" was effective in reducing this fear neither on the short-term nor the long-term. We did not find predictors for the intervention effect, nor classes that could predict which women would benefit from the intervention. What we found were 5 classes with stable trajectories over time, which confirms that FCR is stable over time. Knowing more about the specific needs of FCR groups may contribute to the improvement of interventions for FCR. Our qualitative study shows that participants appreciate the content of our intervention "Less fear after cancer"

and the benefits of online self-help training in general, and many participants (but not all) would appreciate some form of guidance.

Limitations and strengths

The most significant limitations of the FCRI studies concerned the study samples. First, study samples 1 and 3 were small for CFA analysis. Because there are factors with fewer items, this may have resulted in unstable parameter estimates.[44] Moreover, in sample 1 the cancer characteristics were not assessed, which hampers the comparison between cancer types and comparison with earlier studies. Also, samples 2 and 3 consist of (mainly) female breast cancer patients. FCR is considered a multidimensional construct, and there is a possibility that specific cancer types may involve different aspects of FCR.[3, 45, 46] However, since no differences were found in FCR severity between different cancer types and our results are largely comparable to previous research, the impact of using mainly breast cancer samples may be limited.[47]

With respect to the CAREST trial, several limitations should be mentioned. First, significant baseline differences were found despite randomization. This could have influenced the results. However, differences in baseline characteristics after proper random assignment are the result of chance rather than bias, and the CONSORT guidelines even recommend against significance tests of baseline differences in RCTs.[48] Because we used a proper randomization method, we can assume that there is no selection bias in our trial group assignment. Second, the control group received care as usual, which slightly differed between participants since they were recruited from different hospitals. This provides a realistic perspective, as participants in online self-help interventions do not receive uniform care across all hospitals. To avoid a distorted representation, randomization was performed using a "stratified by hospital" approach to ensure balanced group distribution. Moreover, 37% of the intervention group reported that they did not actually engage with the online self-help training, despite having access to it. This high percentage of non-users may have distorted the results. However, it probably reflects a realistic picture of how online self-help interventions are used. Sensitivity analyses (as described in **chapter 6**) indicated that the non-users probably did not affect the treatment effect of the intervention. When excluding participants who did not follow the online self-help training from the analysis, no significant treatment effect was observed for the intervention group compared to the usual care group.

A general limitation of our studies is the limited generalizability of the findings to all cancer patients, as the studies were conducted for the Dutch context. We examined the Dutch translation of the FCRI and a Dutch online self-help training for FCR using Dutch samples, meaning our results are only applicable to Dutch breast cancer survivors.

A strength of our studies is that they were the first study in which a multidimensional FCR measure was translated into Dutch and the first study that developed and investigated an online self-help intervention for FCR in the Netherlands. Therefore, these studies add to the knowledge on measuring and managing FCR in the Netherlands. Strengths concerning the FCRI study were the large number of different measures that were used for validation, compared to previous validation studies of the FCRI, and that an accurate estimation method for CFA was used. Concerning the CAREST trial, an important strength is the long follow-up period of 24 months. Other effect studies reported follow-up periods ranging from immediately after intervention to 12 months after baseline.[21, 49–52] This illustrates that the follow-up period of 24 months in our RCT is valuable and adds to the body of knowledge of FCR. Second, we used state-of-the-art analyses. We found a large variation in the change in FCR and PD scores within participants over time in chapters 5 and 6, which supports the importance of our choice to model individual differences in growth curves using latent growth curve models. Many studies merely compare treatments on the average change in FCR over time, thereby obscuring the large variation between patients within a particular group. Third, the ecological validity of the current study is high.[14] This CAREST trial reflects a realistic picture of online self-help interventions, because we did not screen for high levels of FCR, CAU was allowed, and we offered purely self-help without extra help or emails.

Clinical implications

The FCRI-NL is the first comprehensive multidimensional measure for FCR available in the Netherlands. Besides research purposes, the questionnaire can also be valuable in clinical practice. It provides a lot more information than short unidimensional FCR measures, such as the Cancer Worry Scale. For instance, FCRI-SF and FCRI-FI can be used for screening purposes in clinical practice, the FCRI-FI can be used to evaluate an intervention, and all the FCRI subscales for tailoring interventions for FCR. Furthermore, although some of the subscales are of lesser quality, they do provide valuable information for clinical practice. The individual questions can serve as a starting point for engaging in conversation with a patient. Naturally, the FCRI-NL is useful within psycho-oncology, but it can also be valuable for, among others, doctors and nurses working in oncology practice, and general practitioners and mental health workers who work in general practice.

FCR is a multidimensional construct, and there is some evidence for an association with, e.g., depression and fatigue (although inconsistent).[11, 31, 32, 34, 53, 54] The Dutch foundation for interdisciplinary knowledge sharing and development in oncological care (SONCOS) recommends in its latest guidelines (version 13, 2025) that structural screening of physical, cognitive and behavioral impairments should take place during the treatment and follow-up.[55] In the Netherlands, the Distress Thermometer (in Dutch: Lastmeter) is recommended to detect distress symptoms and the need for

help. When symptoms of anxiety, depression or fatigue are detected, the FCRI may be a suitable measure to further investigate the symptoms and serve as a starting point for a conversation.[56] Given the overlap of psychological and physical symptoms, we should also ask ourselves which symptoms we should treat first. We can look at what patients struggle with the most in their daily functioning. The FCRI-FI can be of value here. But ultimately, we leave it up to the patients themselves to decide which complaints we treat first. Also, we need to consider whether patients or survivors actually want (professional) help. A recent survey study showed that although nearly all cancer patients and survivors with anxiety express a need for help, only 40% actually seek psychological support or coaching.[57]

In the CAREST trial we found stable mean levels of FCR and PD over time, it showed no significant natural decrease. As described in the introduction, relatively stable trajectories of FCR are in line with previous research, although results were inconclusive. When we look on an individual level, for the majority of (breast) cancer survivors, FCR fluctuates over time, as we also described in **chapter 5**.[58] As mentioned in the introduction, FCR can be triggered by several internal or external triggers, including physical symptoms, treatment side effects, doctor appointments, hearing about someone else having cancer, and annual mammograms.[11, 32, 59, 60] This may (partly) explain fluctuating levels of FCR. As mentioned above, we can question whether we should aim for a low level of FCR when investigating the effectiveness of FCR interventions. Perhaps this is not achievable, given the constant triggers that (breast) cancer survivors are confronted with. Also, in **chapter 6**, we demonstrated that FCR remains relatively stable over time for many women, highlighting the importance of investigating predictors of baseline FCR. Personality traits, such as trait anxiety and neuroticism, may help explain individual differences in baseline levels of FCR. In **chapter 2**, we reported moderate and high associations of trait anxiety and neuroticism with FCR. Schellekens at al. found in their recent network analysis that people who worry more (as in trait anxiety) and are more hypervigilant to bodily triggers, experience more severe FCR as well as more impairment in their daily functioning.[35] Therefore, instead of aiming for a low level of FCR, we might be better off focusing on learning to cope with FCR. When we look at the BLANKET study, for example, although they find a significant effect of the intervention, participants still have a high level of FCR of around 20 on the FCRI-SF after the intervention (in the CAREST trial, the mean FCRI-SF score was approximately 15).[40] They conclude that although many participants still experience FCR after the intervention, the fear is more manageable and its burden on their mental well-being has decreased.[40] So although levels of FCR may be stable high or fluctuating, development of effective interventions for both FCR and PD is still important to learn (breast) cancer survivors cope with FCR. The CAREST trial showed five possible FCR subgroups representing different (mostly stable) trajectories in FCR over time and their predictors, which is important information that adds to the body of knowledge about FCR. Knowing more about individual trajectories of FCR is important

information when considering who needs treatment for FCR and to tailor interventions to the patients' needs.

Since results from other RCTs showed that interventions with email reminders or some form of support were effective, we suggest implementing programs with the possibility to use professional support, for example, from nurses or primary care workers. As mentioned above, the follow-up study of the CAREST trial, the BLANKET study, found a positive effect of our intervention "Less fear after cancer" when support from mental health workers in a primary care setting was offered.[40] As a result of our research, "Less fear after cancer" is now available through the Onco Appstore, a website with interventions for cancer patients in the Netherlands, both with and without support from a therapist.

Recommendations for future research

This thesis shows that there may be room for improvement concerning the FCRI factor structure. However, since there are some issues using the FCRI total score, for research purposes we recommend using the FCRI-SF (i.e., the Severity subscale of the FCRI) for measuring FCR. The FCRI-SF is less burdensome for patients since it is much shorter (9 vs. 42 items). For clinical practice and intervention studies, we recommend using the FCRI-FI (i.e., the Functioning Impairments subscale of the FCRI). Further investigation of this subscale is still warranted. Using the remaining FCRI subscales is still valuable for future intervention studies, for example they can be used for tailoring interventions for FCR. Tailoring interventions is important to provide patients with an intervention that meets their needs.

In the CAREST trial, we found no effect of our online self-help training "Less fear after cancer". Studies about the effectiveness of online self-management interventions for reducing FCR in breast cancer patients in the last ten years are very limited. However, because some (feasibility) studies show promising results, more studies (preferably RCTs) are warranted. Also, since there may be publication bias in this field of research, it is important to publish trials regardless of their findings. As mentioned above, instead of measuring the level of FCR in intervention studies, it may be useful to look at the impact of FCR on the daily lives of cancer survivors, for example with the FCRI-FI. Further research is warranted to determine whether the FCRI-FI is a suitable measure for evaluating interventions. Moreover, we suggest studying if online interventions with professional support are effective. Future research should focus on the best form of support, while maintaining the benefits of online interventions, such as low costs, easy accessibility, and work at their own pace. Support can consist of face-to-face conversations, or conversations via phone or email with a therapist, and automated emails to remind patients to work on self-help can also promote usage.

As explained above, we tailored "Less fear after cancer" to the patients' needs, by using the FCRI subscales. Future research could improve tailoring interventions to the needs of patients by utilizing personalized psychological treatment, which "aims to optimize treatment outcome for the individual patient by tailoring treatment to unique or specific needs, preferences or other characteristics of an individual patient and includes a systematic adaptation of treatment or a differentiation between treatment strategies".[61] In other words, with personalized psychological treatment you can tailor an intervention to the patients' needs, as we did, to the preferences of patients, or to other characteristics, such as which symptom is currently most prominent. A recent systematic review and meta-analysis indicates that personalization in psychological therapy is an effective strategy to improve outcomes from psychological therapy.[62] To my knowledge, currently the first RCT investigating personalized versus standard cognitive behavioral therapy for fear of cancer recurrence and other symptoms in cancer survivors is being conducted.[63]

Despite not being able to conduct cost-effectiveness analyses in the CAREST trial, cost-effectiveness remains very important for future research. Since FCR is associated with increased use of healthcare and higher healthcare costs, it is important that FCR treatments not only reduce the individual burden, but also the strain on the healthcare system.[10, 64] The stepped care approach may help increasing the probability of cost-effectiveness, for example by using self-help or blended interventions for patients with a low or moderate level of FCR and face-to-face interventions for patients with severe FCR.[10]

In the CAREST trial, we investigated the long-term effects of "Less fear after cancer" over 24 months. As mentioned above, most effect studies reported follow-up periods up to 12 months after baseline. However, longer follow-up periods can show us whether intervention effects are lasting. Therefore, future RCTs about online self-management interventions for reducing FCR (or other interventions) should include longer follow-up periods.

Lastly, there is an increasing body of research showing that caregivers experience as much FCR as cancer survivors themselves.[65, 66] Two recent systematic reviews found that about half of the caregivers reported clinically significant levels of FCR, often equal to or greater than the level of FCR of cancer survivors.[65, 66] The FCR level of caregivers is associated with poorer quality of life in both caregivers and survivors.[66] Therefore, more caregiver-specific research is urgently needed. For example, FCR measures for caregivers need to be developed and validated, and interventions need to be developed or adapted to reduce FCR in caregivers.[65] Some steps have been made concerning FCR measures for caregivers. Recently, the CARE-FCR, a psychometrically robust caregiver-specific measure of fear of cancer recurrence and progression, was presented (English).[67] Also, the FCRI-SF has been found valid for measuring FCR

in family caregivers of patients with head and neck cancer (Chinese).[68] However, more research concerning measuring FCR in caregivers is needed. Research about interventions to reduce FCR in caregivers is still very limited. Recently, one research protocol about an online version of a cognitive-existential fear of recurrence therapy, adapted for caregivers (FC-FORT) was published.[69] More research concerning interventions to reduce FCR in caregivers is needed. As mentioned above, adaptations of existing interventions for cancer survivors could be a good option. Other options could be a caregiver specific module within an intervention for cancer survivors, or a newly developed intervention for caregivers of cancer survivors.

Conclusion

Considering that almost half of all breast cancer survivors experience some FCR, which may negatively affect their mood, quality of life, health outcomes, and may increase healthcare use and costs, it is important to develop measures for FCR and interventions to learn them to cope with FCR.[10–12, 43, 60, 64, 70] This thesis contributed to the body of knowledge on assessing and managing FCR in the Netherlands. We provided the first comprehensive multidimensional questionnaire for measuring FCR in Dutch, the FCRI-NL, which performs largely the same as other FCRI translations. We found that the Severity subscale should be used for measuring FCR, while the other subscales are valuable in clinical practice or tailoring interventions.

Online self-help has potential to reduce FCR in a cost-effective way. However, the CAREST trial showed no evidence for an effect of our online self-help training "Less fear after cancer", although participants appreciate the content of our online self-help and the benefits of online self-help training in general. Since there is still hardly any research about online self-help for FCR, we recommend further research into online self-help interventions for FCR, such as personalized interventions or interventions for both cancer survivors and their loved ones. Also, since there is some evidence for effective interventions with therapist support, we recommend further research into online interventions that are available both with and without therapist support. Since the number of cancer survivors continues to grow, developing cost-effective interventions for FCR that fit within a stepped-care approach remains an important topic.[71]

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09

Summary
Samenvatting

Summary

The number of cancer survivors is increasing, because of earlier detection and improved treatments. As a result, there is a large and increasing group of breast cancer survivors that have to cope with the long-term consequences of cancer. Fear of cancer recurrence (FCR) is one of the most common long-term psychological consequences of surviving cancer. FCR is defined as "fear, worry, or concern about cancer returning or progressing". The threat of cancer recurrence is often metaphorically referred to as the "Sword of Damocles", which hangs over the head of cancer survivors and their families for the rest of their lives. FCR is a normal reaction to the cancer experience which at a certain point becomes problematic or pathological. **Chapter 1** provides an overview of the current state of knowledge on FCR, including its prevalence, theoretical frameworks explaining FCR, the duration and course of FCR, factors associated with FCR, assessment methods for FCR, and interventions for managing FCR. The main objectives of the studies presented in this thesis were (1) to translate the Fear of Cancer Recurrence Inventory (FCRI) and investigate its psychometric properties, and (2) to investigate the effectiveness of a CBT-based online self-help training to reduce FCR, compared to care as usual. Therefore, this dissertation consists of two parts.

Assessment of fear of cancer recurrence

At the start of this project, Dutch FCR measures were scarce. Therefore, in **chapter 2**, we decided to translate and validate the FCRI, the best multidimensional measure available at that time, in a mixed cancer sample. The Dutch version of the FCRI (FCRI-NL) was examined by assessing internal consistency, test-retest reliability, and convergent and divergent validity of the FCRI-NL and its subscales. In addition, a confirmatory factor analysis (CFA) was done to investigate whether the 7-factor structure of the original FCRI could be confirmed. We found that the FCRI-NL has acceptable psychometric properties. The FCRI-NL and its subscales have sufficient to good reliability and test-retest reliability, except for a lower test-retest reliability on the Reassurance and Coping Strategies subscales. Convergent and divergent validity was demonstrated for the FCRI-NL, and its Severity subscale (FCRI-SF-NL). However, the multidimensional structure of the original FCRI was not convincingly replicated for the FCRI-NL in the present sample. The CFA showed a reasonable but suboptimal fit of the model to the data, which is slightly weaker than the other translations.

Therefore, we aimed to improve the FCRI-NL further in **chapter 3**. We explored the factor structure of the FCRI-NL using exploratory factor analysis (EFA) and tested the new factor structure with CFAs in two new patient samples. The EFA revealed a 4-factor solution with 34 items from the original FCRI-NL. However, this new 4-factor structure was not replicated in the two new (mainly breast cancer) patient samples. Additional non-prespecified CFAs of the original 7-factor structure showed a reasonable fit to the data in both samples. Based on these results, we suggested retaining the original

7-factor FCRI-NL instead of the new 4-factor version. Given the inconsistencies in the body of research concerning the FCRI, we also comprehensively compared its factor structure across all published psychometric studies in **chapter 3**. The comparison was complicated by the fact that the studies used different fit indices, cut-off scores, and software. However, after applying the same criteria to all FCRI translations, the factor structure results were largely comparable. When taking the results of **chapters 2 and 3** together, we can conclude that the factor structure results of the FCRI-NL align with other translations.

Managing fear of cancer recurrence in breast cancer survivors

Due to the significant impact that high levels of FCR can have on the lives of (breast) cancer survivors, including reduced quality of life, poorer health outcomes, and increased healthcare costs, it is essential to develop cost-effective interventions to alleviate FCR. Therefore, the CBT-based online self-help training "Less fear after cancer" was developed by the Helen Dowling Institute, an institute for psycho-oncology. **Chapter 4** describes the study protocol of our randomized controlled trial (RCT) investigating the effectiveness of our online self-help training for FCR in Dutch women with curatively treated breast cancer (breast cancer survivors), hereafter named the CAREST (CAncer Recurrence Self-help Training) trial. Originally, we aimed to investigate the effectiveness and cost-effectiveness of the online self-help training. Because we did not expect online self-help to be effective for all participants, we also aimed to identify factors that predict which women benefited most from the online self-help.

The short-term and long-term effectiveness of our online self-help training to reduce FCR are described and discussed in **chapters 5 and 6**. The CAREST randomized controlled trial showed that there was no evidence for an effect of the online self-help training in reducing FCR compared to care as usual, after 3, 9 and 24 months follow-up. Also, we did not find a long-term effect of the intervention in reducing psychological distress (PD), nor on the strength of the relation between FCR and PD. Furthermore, we evaluated the relation between FCR and PD across time, because we expected a strong correlation at baseline and a significantly weaker correlation after the intervention, as we expected PD to decrease more than FCR. However, we found a moderate baseline correlation between FCR and PD for the intervention group, and a strong correlation for the CAU group, but the correlation did not significantly decrease over time in both groups. Moreover, no significant predictors were found for the effect of the intervention on FCR. We did identify five latent classes that represent a distinct change pattern of FCR over time). Four classes showed stable trajectories over time (stable severe, moderate, mild, and low FCR over time), and one class shows a decrease of FCR over time. However, because the decrease occurred after nine months (six months after the intervention), we do not expect this to be a treatment effect. In conclusion, we did not identify classes who benefit from the intervention.

In **chapter 7** we qualitatively described the experiences of Dutch breast cancer survivors with the online self-help training for FCR, by means of a thematic analysis of facilitators and barriers. Thematic analysis revealed that participants appreciated the content and the benefits of online self-help training, despite some technical issues and ambiguities. For some participants, support would enhance online interventions, while for others professional or peer support is challenging. Therefore, we recommend developing tailored interventions. Although we did not find a significant reduction of FCR in our online self-help, it is appreciated by participants and may help cancer survivors cope with mild FCR, without lowering the FCR. Moreover, the intervention can be used as a first step for patients who find interventions with support too challenging.

In the general discussion in **chapter 8**, our findings were placed in a broader perspective and relevant topics were discussed. For example, concerning the FCRI-NL, we discussed that although FCR is increasingly acknowledged as a multidimensional construct, a total FCR score is still commonly used in empirical research, raising the question whether a total score of the FCRI accurately represents the multidimensional construct. Combining the subscale scores of the FCRI to derive a total score may hamper interpretation of the questionnaire data, because a total score combines level of fear with its antecedents and consequences. Thus, a total score represents an uninterpretable combination of concepts. Also, since many possible combinations of subscale scores can give identical total scores, we lose a lot of important clinical information when we sum the subscale scores. Therefore, we strongly recommend against using the FCRI total score, because it is unclear what it represents. Nevertheless, using a multidimensional questionnaire to measure FCR still has added value because the subscales and individual items are valuable in clinical practice and for tailoring interventions to patients' needs. Furthermore, we discussed whether FCR is the best construct to measure effectiveness of FCR interventions. As stated above, FCR ranges from "normal" to "clinical" and some level of FCR can even be helpful by promoting treatment compliance and healthy lifestyle adaptations. The goal of an intervention should therefore not be to eliminate FCR, but rather to focus on helping cancer survivors cope with FCR. This raises the question of how to measure effectiveness of a FCR intervention. A recent suggestion is to measure the impact of FCR on daily life, for which the FCRI Functioning Impairments subscale (FCRI-FI) might be useful. To conclude, we think that cancer survivors need help when FCR interferes with daily life. This requires considering not only how much survivors suffer from FCR, but also its impact on their daily lives.

In conclusion, considering that almost half of all breast cancer survivors experience some FCR, it is important to develop measures for FCR and interventions to learn them to cope with FCR. This thesis contributed to the body of knowledge on assessing and managing FCR in the Netherlands. We provided the first comprehensive multidimensional questionnaire for measuring FCR in Dutch, the FCRI-NL, which

performs largely the same as other FCRI translations. We found that the Severity subscale should be used for measuring FCR, while the other subscales are valuable in clinical practice or tailoring interventions. Online self-help has potential to reduce FCR in a cost-effective way. However, the CAREST trial showed no evidence for an effect of our online self-help training "Less fear after cancer", although participants appreciate the content of our online self-help and the benefits of online self-help training in general. Since there is still hardly any research about online self-help for FCR, we recommend further research into online self-help interventions for FCR, such as personalized interventions or interventions for both cancer survivors and their loved ones. Also, since there is some evidence for effective interventions with therapist support, we recommend further research into online interventions that are available both with and without therapist support. Since the number of cancer survivors continues to grow, developing cost-effective interventions for FCR that fit within a stepped-care approach remains an important topic.

Samenvatting

Er zijn steeds meer mensen die kanker overleven, doordat het eerder wordt ontdekt en doordat behandelingen zijn verbeterd. Daardoor is er een steeds groter wordende groep vrouwen die borstkanker heeft overleefd en moet leven met de langetermijngevolgen van kanker. Angst voor terugkeer van kanker (in het Engels "fear of cancer recurrence", afgekort FCR) is één van de meest voorkomende psychologische langetermijngevolgen van kanker. FCR wordt omschreven als "angst, zorgen of bezorgdheid dat de kanker terugkeert of zich verder uitbreidt". De dreiging van terugkeer van kanker wordt vaak metaforisch het "Zwaard van Damocles" genoemd. FCR is eigenlijk een normale reactie op het ervaren van kanker, wat op een bepaald punt problematisch of pathologisch wordt. Hoofdstuk 1 geeft een overzicht van de huidige stand van kennis over FCR, waaronder de prevalentie, theoretische kaders, duur en verloop van FCR, factoren die samenhangen met FCR, meetmethoden voor het meten van FCR en interventies voor het omgaan met FCR. De belangrijkste doelstellingen van de studies in dit proefschrift waren (1) het vertalen van de "Vragenlijst voor angst voor terugkeer van kanker" (in het Engels "Fear of Cancer Recurrence Inventory", afgekort FCRI) en het onderzoeken van de psychometrische eigenschappen ervan, en (2) het onderzoeken van de effectiviteit van een op CGT gebaseerde online zelfhulptraining om FCR te verminderen, vergeleken met de gebruikelijke zorg. Dit proefschrift bestaat uit twee delen.

Meten van angst voor terugkeer van kanker

Aan het begin van dit project waren er weinig Nederlandse meetinstrumenten om FCR te meten beschikbaar. Daarom hebben we in hoofdstuk 2 de FCRI, destijds het beste beschikbare multidimensionale meetinstrument, vertaald en gevalideerd in een gemengde patiëntengroep. De Nederlandse versie van de FCRI (FCRI-NL) werd onderzocht door de volgende psychometrische eigenschappen te beoordelen: interne consistentie, test-hertestbetrouwbaarheid en convergente en divergente validiteit van de FCRI-NL en haar subschalen. Daarnaast werd een confirmatieve factoranalyse (CFA) uitgevoerd om te onderzoeken of de 7-factorstructuur van de originele FCRI kon worden bevestigd. We vonden dat de FCRI-NL acceptabele psychometrische eigenschappen heeft. De FCRI-NL en haar subschalen vertonen voldoende tot goede betrouwbaarheid en test-hertestbetrouwbaarheid, met uitzondering van een lagere test-hertestbetrouwbaarheid op de subschalen "Geruststelling" (In het Engels: Reassurance) en "Coping Strategieën (in het Engels: Coping Strategies). Convergente en divergente validiteit zijn aangetoond voor de FCRI-NL en de "Ernst"-subschaal (in het Engels: Severity subscale; afgekort FCRI-SF-NL). De multidimensionale structuur van de originele FCRI werd in deze steekproef niet overtuigend gerepliceerd voor de FCRI-NL. De CFA toonde een redelijke maar suboptimale fit van het model met de data, wat iets zwakker is dan bij andere vertalingen.

Daarom hebben we in **hoofdstuk 3** geprobeerd om de FCRI-NL te verbeteren. We onderzochten de factorstructuur van de FCRI-NL met behulp van een exploratieve factoranalyse (EFA) en testten de nieuwe factorstructuur met CFA's in twee nieuwe patiëntgroepen. De EFA resulteerde in een 4-factorstructuur met 34 items uit de oorspronkelijke FCRI-NL. Deze nieuwe 4-factorstructuur werd echter niet gerepliceerd in de twee nieuwe patiëntgroepen (voornamelijk borstkankerpatiënten). Aanvullende, niet vooraf gespecificeerde CFA's van de oorspronkelijke 7-factorstructuur toonden een redelijke fit met de data in beide patiëntgroepen. Op basis van deze resultaten stelden we voor om de oorspronkelijke 7-factorstructuur van de FCRI-NL te behouden in plaats van de nieuwe 4-factorversie. Gezien de inconsistenties in de literatuur over de FCRI, hebben we in **hoofdstuk 3** ook een uitgebreide vergelijking gemaakt van de factorstructuren in alle gepubliceerde studies. Deze vergelijking werd bemoeilijkt doordat de studies gebruik maakten van verschillende fitmaten (Engels: fit-indices), afkapwaarden en software. Echter, na het toepassen van dezelfde criteria op alle FCRI-vertalingen, bleken de resultaten grotendeels vergelijkbaar. Uit de resultaten van **hoofdstukken 2 en 3** kunnen we concluderen dat de factorstructuur van de FCRI-NL overeenkomt met die van andere vertalingen.

Omgaan met de angst voor terugkeer van kanker bij borstkankeroverlevers

Vanwege de grote impact die een hoge mate van FCR kan hebben op het leven van (borst)kankeroverlevers, waaronder een verminderde kwaliteit van leven, slechtere gezondheidsuitkomsten en hogere zorgkosten, is het essentieel om kosteneffectieve interventies te ontwikkelen om FCR te verminderen. Daarom werd de op cognitieve gedragstherapie (CGT) gebaseerde online zelfhulptraining "Minder angst na kanker" ontwikkeld door het Helen Dowling Instituut, een instituut voor psycho-oncologie. **Hoofdstuk 4** beschrijft het studieprotocol van onze gerandomiseerde gecontroleerde trial (RCT) waarin de effectiviteit van onze online zelfhulptraining voor FCR wordt onderzocht bij Nederlandse vrouwen die curatief behandeld zijn voor borstkanker (borstkankeroverlevers), hierna aangeduid als de CAREST-studie (CAncer Recurrence Self-help Training). Oorspronkelijk was het doel om de effectiviteit en kosteneffectiviteit van de online zelfhulptraining te onderzoeken. Omdat we verwachtten dat online zelfhulp niet voor alle deelnemers effectief zou zijn, wilden we ook factoren identificeren die voorspellend zijn voor de mate waarmee vrouwen baat hebben bij de online zelfhulp. De korte- en langetermijneffectiviteit van onze online zelfhulptraining om FCR te verminderen worden beschreven en besproken in **hoofdstukken 5 en 6**. Uit de CAREST trial bleek dat er geen bewijs was voor een effect van de online zelfhulptraining op het verminderen van FCR in vergelijking met de gebruikelijke zorg, na 3, 9 en 24 maanden follow-up. Ook vonden we geen langetermijneffect van de interventie op het verminderen van psychologische stress (in het Engels: psychological distress; afgekort PD) en op de grootte van de relatie tussen FCR en PD. Daarnaast onderzochten we de relatie tussen FCR en PD in de tijd, omdat we een sterke correlatie verwachtten bij aanvang en een significant zwakkere correlatie na de interventie, aangezien we

verwachtten dat PD sterker zou afnemen dan FCR. We vonden echter een matige correlatie bij aanvang tussen FCR en PD in de interventiegroep, en een sterke correlatie in de groep die gebruikelijke zorg ontving, maar de correlatie nam in beide groepen niet significant af over de tijd. Bovendien werden er geen significante voorspellers gevonden voor het effect van de interventie op FCR. Wel identificeerden we vijf latente klassen die een verschillend veranderingspatroon van FCR over tijd vertegenwoordigen). Vier klassen vertoonden stabiele trajecten over tijd (stabiele ernstige, matige, milde en lage FCR), en één klasse liet een afname van FCR over tijd zien. Aangezien deze afname pas na negen maanden plaatsvond (zes maanden na de interventie), verwachten we niet dat dit een behandelresultaat is. Concluderend hebben we geen klassen geïdentificeerd die baat hebben bij de interventie.

In **hoofdstuk 7** beschreven we de ervaringen van Nederlandse borstkankeroverlevers met de online zelfhulptraining voor FCR, aan de hand van een thematische analyse van bevorderende en belemmerende factoren. Uit de thematische analyse bleek dat deelnemers de inhoud en de voordelen van de online zelfhulptraining waardeerden, ondanks enkele technische problemen en onduidelijkheden. Voor sommige deelnemers zou ondersteuning online interventies kunnen verbeteren, terwijl professionele of lotgenotenondersteuning voor anderen juist een uitdaging vormt. Daarom bevelen we aan om op maat gemaakte interventies te ontwikkelen. Hoewel we geen significante vermindering van FCR vonden bij onze online zelfhulp, wordt deze wel gewaardeerd door deelnemers en kan het kankeroverlevers helpen om met milde FCR om te gaan, zonder dat de FCR daadwerkelijk afneemt. Bovendien kan de interventie dienen als eerste stap voor patiënten die interventies met ondersteuning te belastend vinden.

In de algemene discussie in **hoofdstuk 8** plaatsten we onze bevindingen in een breder perspectief en bespraken we relevante thema's. Met betrekking tot de FCRI-NL bespraken we dat, hoewel FCR steeds vaker wordt erkend als een multidimensionaal construct, onderzoek toch vaak nog gebruik maakt van een totaalscore. Dit roept de vraag op of een totaalscore van de FCRI dit construct wel accuraat weergeeft. Wanneer we de subschaalscores van de FCRI optellen om tot een totaalscore te komen, kan dit de interpretatie van de vragenlijst bemoeilijken, omdat een totaalscore het niveau van angst combineert met de oorzaken en gevolgen ervan. Een totaalscore vertegenwoordigt dus een niet-interpretabele combinatie van concepten. Bovendien kunnen veel verschillende combinaties van subschaalscores leiden tot dezelfde totaalscore, waardoor belangrijke klinische informatie verloren gaat. Daarom raden we het sterk af om de totaalscore van de FCRI te gebruiken, omdat onduidelijk is wat deze precies representeert. Het gebruik van een multidimensionale vragenlijst om FCR te meten blijft echter waardevol, omdat de subschalen en individuele items nuttig zijn in de klinische praktijk en bij het afstemmen van interventies op de behoeften van patiënten. Daarnaast stelden we ons de vraag of FCR wel het beste construct is om de effectiviteit van FCR-interventies te meten. Zoals eerder genoemd, varieert FCR van

'normaal' tot 'klinisch', en een zekere mate van FCR kan zelfs helpend zijn, bijvoorbeeld door therapietrouw te bevorderen of een gezonde leefstijl te stimuleren. Het doel van een interventie zou daarom niet moeten zijn om FCR volledig te elimineren. In plaats daarvan zouden we ons kunnen richten op het ondersteunen van kankeroverlevers bij het omgaan met FCR. Maar hoe meten we dan de effectiviteit van een FCR-interventie? Recent is gesuggereerd dat het meten van de impact van FCR op het dagelijks leven mogelijk een bruikbare benadering is. De FCRI subschaal die beperkingen in het functioneren meet (Functioning Impairments subscale; afgekort FCRI-FI) zou hiervoor geschikt kunnen zijn. Samenvattend denken we dat kankeroverlevers hulp nodig hebben wanneer FCR hun dagelijks functioneren belemmert. Hiervoor kunnen we kijken naar hoeveel last iemand ervaart van FCR, maar ook naar de impact ervan op het dagelijks leven.

Er kan worden geconcludeerd dat aangezien bijna de helft van alle borstkankeroverlevers enige mate van FCR ervaart, het belangrijk is om meetinstrumenten en interventies te ontwikkelen waarmee zij leren omgaan met FCR. Dit proefschrift heeft bijgedragen aan de kennis over het meten en behandelen van FCR in Nederland. We hebben de eerste uitgebreide multidimensionale vragenlijst voor het meten van FCR in het Nederlands (de FCRI-NL) beschikbaar gemaakt, deze presteert vergelijkbaar met andere vertalingen van de FCRI. We concludeerden dat de "Ernst"-subschaal van de FCRI het meest geschikt is voor het meten van FCR, terwijl de andere subschalen waardevol zijn in de klinische praktijk en bij het afstemmen van interventies op individuele behoeften. Online zelfhulp heeft potentie om FCR op een kosteneffectieve manier te verminderen. De CAREST trial toonde echter geen bewijs voor een effect van onze online zelfhulptraining "Minder angst na kanker", hoewel deelnemers de inhoud en de algemene voordelen van online zelfhulp waardeerden. Aangezien er nog nauwelijks onderzoek is gedaan naar online zelfhulp bij FCR, bevelen we verder onderzoek aan naar online interventies, zoals gepersonaliseerde interventies of interventies voor zowel kankeroverlevers als hun naasten. Daarnaast, omdat er bewijs is voor effectieve interventies met ondersteuning van een therapeut, raden we aan om verder onderzoek te doen naar online interventies die beschikbaar zijn met én zonder therapeutische ondersteuning. Gezien het groeiende aantal kankeroverlevers blijft het ontwikkelen van kosteneffectieve FCR-interventies die passen binnen een stepped-care benadering een belangrijk aandachtspunt.

Appendices

Supplementary materials
Acknowledgements (Dankwoord)
List of publications
About the author (Over de auteur)

Supplementary materials

Supplementary materials 2A. Skewness and kurtosis values, z-scores, and floor and ceiling scores of all FCRI-NL items.

FCRI-NL			Normality test			Floor score	Ceiling score
Items	Subscale		Time-1	SE	z-score	Time-1 (%)	Time-1 (%)
1	Triggers	*Skewness*	-.026	.153	-.170	5.9	10.2
		Kurtosis	-.227	.304	-.747		
2		*Skewness*	-.252	.153	-1.647	5.5	14.1
		Kurtosis	-.419	.304	-1.378		
3		*Skewness*	-.542	.153	-3.542	3.1	26.7
		Kurtosis	-.324	.304	-1.066		
4		*Skewness*	.000	.153	.000	6.3	9.0
		Kurtosis	-.308	.304	-1.013		
5		*Skewness*	-.003	.153	-.020	4.7	15.7
		Kurtosis	-.702	.304	-2.309		
6		*Skewness*	-.075	.153	-.490	8.6	12.2
		Kurtosis	-.482	.304	-1.586		
7		*Skewness*	-.195	.153	-1.275	4.3	12.5
		Kurtosis	-.265	.304	-.872		
8		*Skewness*	.536	.153	3.503	32.9	3.1
		Kurtosis	-.641	.304	-2.109		
9	Severity	*Skewness*	.165	.153	1.078	3.5	9.0
		Kurtosis	-.688	.304	-2.263		
10		*Skewness*	.155	.153	1.013	4.3	11.0
		Kurtosis	-.862	.304	-2.836		
11		*Skewness*	-.362	.153	-2.366	1.2	14.9
		Kurtosis	-.199	.304	-.655		
12		*Skewness*	-.538	.153	-3.516	4.7	20.4
		Kurtosis	-.285	.304	-.938		
13		*Skewness*	-.231	.153	-1.510	6.3	16.9
		Kurtosis	-.790	.304	-2.599		
14		*Skewness*	.245	.153	1.601	1.6	8.6
		Kurtosis	-.390	.304	-1.283		
15		*Skewness*	.606	.153	3.961	7.1	5.5
		Kurtosis	.043	.304	.141		
16		*Skewness*	.143	.153	.935	16.5	1.2
		Kurtosis	-.129	.304	-.424		

Supplementary materials 2A. Skewness and kurtosis values, z-scores, and floor and ceiling scores of all FCRI-NL items. (continued)

FCRI-NL			Normality test			Floor score	Ceiling score
Items	Subscale		Time-1	SE	z-score	Time-1 (%)	Time-1 (%)
17		*Skewness*	-.616	.153	-4.026	11.8	34.1
		Kurtosis	-.643	.304	-2.115		
18	Psychological	*Skewness*	.090	.153	.588	2.0	13.3
	Distress	*Kurtosis*	-.924	.304	-3.039		
19		*Skewness*	.080	.153	.523	12.9	12.2
		Kurtosis	-1.062	.304	-3.493		
20		*Skewness*	.396	.153	2.588	27.1	5.1
		Kurtosis	-.798	.304	-2.625		
21		*Skewness*	.345	.153	2.255	22.7	4.7
		Kurtosis	-.784	.304	-2.579		
22	Functioning	*Skewness*	1.399	.153	9.144	58.0	2.0
	Impairments	*Kurtosis*	1.269	.304	4.174		
23		*Skewness*	1.178	.153	7.699	51.4	2.4
		Kurtosis	.498	.304	1.638		
24		*Skewness*	1.073	.153	7.013	48.6	2.0
		Kurtosis	.417	.304	1.372		
25		*Skewness*	.604	.153	3.948	32.9	5.1
		Kurtosis	-.707	.304	-2.326		
26		*Skewness*	.623	.153	4.072	21.6	2.7
		Kurtosis	-.060	.304	-.197		
27		*Skewness*	.675	.153	4.412	31.8	2.0
		Kurtosis	-.275	.304	-.905		
28	Insight	*Skewness*	1.198	.153	7.830	54.9	1.6
		Kurtosis	.560	.304	1.842		
29		*Skewness*	1.920	.153	12.549	69.8	1.6
		Kurtosis	3.054	.304	1.046		
30		*Skewness*	1.757	.153	11.484	68.2	.8
		Kurtosis	2.429	.304	7.990		
31	Reassurance	*Skewness*	1.509	.153	9.863	64.7	1.6
		Kurtosis	1.242	.304	4.086		
32		*Skewness*	1.300	.153	8.497	60.4	1.2
		Kurtosis	.799	.304	2.628		
33		*Skewness*	.383	.153	2.503	25.9	2.7

Supplementary materials 2A. Skewness and kurtosis values, z-scores, and floor and ceiling scores of all FCRI-NL items. (continued)

FCRI-NL			Normality test			Floor score	Ceiling score
Items	Subscale		Time-1	SE	z-score	Time-1 (%)	Time-1 (%)
		Kurtosis	-.831	.304	-2.734		
34	Coping	*Skewness*	-.309	.153	-2.020	14.1	6.7
	Strategies	*Kurtosis*	-.880	.304	-2.895		
35		*Skewness*	-.031	.153	-.203	16.9	6.3
		Kurtosis	-.917	.304	-3.016		
36		*Skewness*	.708	.153	4.627	43.5	2.4
		Kurtosis	-.639	.304	-2.102		
37		*Skewness*	-.495	.153	-3.235	7.5	12.9
		Kurtosis	-.404	.304	-1.329		
38		*Skewness*	.100	.153	.654	21.2	1.2
		Kurtosis	-.915	.304	-3.010		
39		*Skewness*	-.191	.153	-1.248	4.3	11.4
		Kurtosis	-.138	.304	-.454		
40		*Skewness*	-.274	.153	-1.791	17.6	4.7
		Kurtosis	-.878	.304	-2.888		
41		*Skewness*	-.423	.153	-2.765	6.7	7.5
		Kurtosis	-.230	.304	-.757		
42		*Skewness*	-.162	.153	-1.059	17.6	9.8
		Kurtosis	-1.020	.304	-3.355		

Supplementary materials 2B. FCRI-NL subscales correlation matrix.[a, b]

	Triggers	Severity (FCRI-SF-NL)	Psychological Distress	Functioning Impairments	Insight	Reassurance	Coping Strategies
FCRI-NL	.81**	.85**	.81**	.78**	.70**	.37**	.35**
Triggers		.73**	.61**	.54**	.50**	.15*	.12
Severity (FCRI-SF-NL)			.68**	.58**	.62**	.23**	.09
Psychological Distress				.62**	.57**	.26**	.17**
Functioning Impairments					.65**	.24**	.11
Insight						.16**	.03
Reassurance							.24**

[a] Spearman's correlations; [b] $n = 255$
* $p < .05$; ** $p < .001$

Supplementary materials 2C. Reliability and test-retest reliability for the original French, the English, and the Dutch version of the FCRI.

	Reliability [a]			Test retest reliability [a]		
	French	English	Dutch	French	English	Dutch
	Cronbach's alpha	Cronbach's alpha	Cronbach's alpha	Pearson's correlation (1 month)	Pearson's correlation (1 month)	ICC (14 days)
	$n = 600$	$n = 350$	$n = 255$	$n = 287$	$n = 135$	$n = 95$
Triggers	.90	.93	.88	.83	.78	.81
Severity / FCRI-SF-NL	.89	.88	.85	.80	.87	.87
Psychological Distress	.86	.88	.84	.76	.79	.74
Functioning Impairments	.91	.94	.92	.70	.71	.78
Insight	.80	.85	.84	.58	.85	.74
Reassurance	.75	.71	.76	.73	.56	.56
Coping Strategies	.89	.91	.75	.75	.75	.59
FCRI-NL	.95	.96	.93	.89	.88	.84

[a] High correlation coëfficients of ($r \geq .70$) were considered sufficient

Supplementary materials 3A. Vragenlijst Angst voor terugkeer van kanker.

De meeste mensen bij wie kanker gediagnosticeerd is, zijn in meer of mindere mate bezorgd dat de kanker terug zou kunnen keren. **Met terugkeren bedoelen we de mogelijkheid dat de kanker terugkomt of zich verder ontwikkelt op dezelfde plaats of in een ander deel van het lichaam.** Deze vragenlijst is bedoeld om de bezorgdheid over terugkeer van kanker beter te begrijpen. Lees alstublieft iedere stelling en geef aan in welke mate deze **GEDURENDE DE AFGELOPEN MAAND** op u van toepassing was door het juiste nummer te omcirkelen.

	0 Nooit	1 Zelden	2 Soms	3 Meestal	4 Altijd
De volgende situaties zetten me aan het denken over de mogelijke terugkeer van kanker:					
1.	Televisieprogramma's of krantenartikelen over kanker of ziekte				0 1 2 3 4
2.	Een afspraak met mijn arts of andere gezondheidsdeskundige				0 1 2 3 4
3.	Medische onderzoeken (bv. jaarlijkse controles, bloedonderzoek, röntgenfoto's)				0 1 2 3 4
4.	Gesprekken over kanker of over ziekte in het algemeen				0 1 2 3 4
5.	Het zien van of horen over iemand die ziek is				0 1 2 3 4
6.	Naar een begrafenis gaan of de overlijdensberichten in de krant lezen				0 1 2 3 4
7.	Als ik me lichamelijk niet goed voel of als ik ziek ben				0 1 2 3 4
8.	In het algemeen vermijd ik situaties of dingen die me doen denken aan de mogelijke terugkeer van kanker				0 1 2 3 4

	0 Helemaal niet	1 Een beetje	2 Enigszins	3 Erg	4 Heel erg
9.	Ik ben bezorgd of angstig voor de mogelijke terugkeer van kanker				0 1 2 3 4
10.	Ik ben bang voor de terugkeer van kanker				0 1 2 3 4
11.	Ik geloof dat het normaal is om bezorgd of angstig te zijn over de mogelijke terugkeer van kanker				0 1 2 3 4
12.	Wanneer ik denk aan de mogelijke terugkeer van kanker, roept dit andere onplezierige gedachten of beelden op (bv. zoals de dood, lijden, de gevolgen voor mijn familie)				0 1 2 3 4
13.	Ik geloof dat ik genezen ben en dat de kanker niet zal terugkeren				0 1 2 3 4
14.	Denkt u dat u risico loopt op terugkeer van kanker?	0 Helemaal geen risico	1 Een beetje risico	2 Enigszins risico	3 Veel risico	4 Heel veel risico
15.	Hoe vaak denkt u aan de mogelijke terugkeer van kanker?	0 Nooit per maand	1 Een paar keer per week	2 Een paar keer per dag	3 Een paar keer per dag	4 Meerdere keren
16.	Hoeveel tijd per dag besteedt u aan het denken over de mogelijke terugkeer van kanker?	0 Ik denk er niet over na	1 Een paar seconden	2 Enkele minuten	3 Een paar uur	4 Meerdere uren
17.	Hoe lang denkt u al na over de mogelijke terugkeer van kanker?	0 Ik denk er niet over na	1 Een paar weken	2 Enkele maanden	3 Een paar jaar	4 Meerdere jaren

	0 Helemaal niet	1 Een beetje	2 Enigszins	3 Erg	4 Heel erg
Wanneer ik denk aan de mogelijke terugkeer van kanker, voel ik:					
18.	Bezorgdheid, vrees of angst				0 1 2 3 4
19.	Bedroefdheid, ontmoediging of teleurstelling				0 1 2 3 4
20.	Frustratie, boosheid of woede				0 1 2 3 4
21.	Hulpeloosheid of gelatenheid				0 1 2 3 4
Mijn gedachten of angsten over de mogelijke terugkeer van kanker verstoren:					
22.	Mijn sociale of vrijetijdsactiviteiten (bv. uitjes, sporten, reizen)				0 1 2 3 4
23.	Mijn werk of dagelijkse activiteiten				0 1 2 3 4
24.	Mijn relaties met mijn partner, mijn familie of naasten				0 1 2 3 4
25.	Mijn mogelijkheid om toekomstplannen te maken of levensdoelen te stellen				0 1 2 3 4
26.	Mijn gemoedstoestand of stemming				0 1 2 3 4
27.	Mijn kwaliteit van leven in het algemeen				0 1 2 3 4

	0 Helemaal niet	1 Een beetje	2 Enigszins	3 Erg	4 Heel erg
28.	Ik heb het gevoel dat ik mij buitensporig veel zorgen maak over de mogelijke terugkeer van kanker				0 1 2 3 4
29.	Andere mensen vinden dat ik mij buitensporig veel zorgen maak over de mogelijke terugkeer van kanker				0 1 2 3 4
30.	Ik denk dat ik mij meer zorgen maak over de mogelijke terugkeer van kanker dan andere mensen bij wie de diagnose kanker is gesteld				0 1 2 3 4

	0 Nooit	1 Zelden	2 Soms	3 Meestal	4 Altijd
Wanneer ik denk aan de mogelijke terugkeer van kanker, gebruik ik de volgende strategieën om mezelf gerust te stellen:					
31.	Ik bel mijn arts of andere gezondheidsdeskundige				0 1 2 3 4
32.	Ik ga naar het ziekenhuis of de kliniek voor een onderzoek				0 1 2 3 4
33.	Ik onderzoek mezelf om te kijken of ik lichamelijke tekenen van kanker heb				0 1 2 3 4
34.	Ik probeer mezelf af te leiden (bv. door verschillende activiteiten te ondernemen, televisiekijken, lezen, werken)				0 1 2 3 4
35.	Ik probeer er niet aan te denken, om het idee uit mijn hoofd te krijgen				0 1 2 3 4
36.	Ik bid, mediteer of doe ontspanningsoefeningen				0 1 2 3 4
37.	Ik probeer mezelf ervan te overtuigen dat alles goed zal komen of ik denk positief				0 1 2 3 4
38.	Ik praat er met iemand over				0 1 2 3 4
39.	Ik probeer te begrijpen wat er gebeurt en ga ermee om				0 1 2 3 4
40.	Ik probeer een oplossing te vinden				0 1 2 3 4
41.	Ik probeer deze gedachte te vervangen door een meer plezierige				0 1 2 3 4
42.	Ik zeg tegen mezelf "stop ermee"				0 1 2 3 4
	Voelt u zich gerustgesteld wanneer u deze strategieën gebruikt?				0 1 2 3 4

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Supplementary materials 3B. Assessing the suitability of the data for exploratory factor analysis.

Statistical analysis

We assessed the suitability of the data for exploratory factor analysis (EFA) by evaluating:

a) the sample size;
b) the sample to variable ratio;
c) the factorability of the correlation matrix ($r < 0.30$ indicates a lack of patterned relationships, $r > 0.90$ indicate multicollinearity);
d) the Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy (values between 0.8 and 1 indicate the sampling is adequate);
e) Bartlett's Test of Sphericity (should be significant);
f) the diagonal element of the Anti-Correlation matrix that has the 'a' superscript (should be > 0.50).[1, 2]

Results

First, we assessed the suitability of the data for EFA. The sample size of 255 and the sample to variable ratio of 255:43 / 6:1 were sufficient. The factorability of the correlation matrix showed that 39% of correlations were >.30, which is sufficient, and no correlations of >.90 were found, indicating no multicollinearity. The KMO measure of sampling adequacy value of .91 supported the factorability of the matrix and Bartlett's Test of Sphericity was highly significant (χ^2 (861) = 6491.253, $p < .001$). Evaluation of the diagonal element of the Anti-Correlation matrix that has the 'a' superscript showed that all 42 values were >.50, which means the data is suitable for analyses. Thus, all tests confirm that the data is suitable for EFA.

References

1. Williams B, Brown T, Onsman A: Exploratory factor analysis : A five-step guide for novices. Australasian Journal of Paramedicine 8:1–13, 2012
2. Yong AG, Pearce S: A Beginner's Guide to Factor Analysis: Focusing on Exploratory Factor Analysis. Tutor Quant Methods Psychol 9:79–94, 2013

Supplementary materials 3C. Score distribution.

The skewness and kurtosis values, z-scores, and floor and ceiling effects of the items of all samples are presented in the table below. The assumption for normality was violated for 34 (81%) items in *sample 1*, 40 (95%) items in *sample 2*, and 32 (76%) items in *sample 3*. Floor scores were found in 21 (50%) items in *sample 1*, 33 (79%) items in *sample 2*, and 18 (43%) items in *sample 3*. Ceiling scores were found in 5 (12%) items in *sample 1*, 2 (0,05%) items in *sample 2*, and 13 (31%) items in *sample 3*.

Skewness and kurtosis values, z-scores, and floor and ceiling scores of all FCRI-NL items of three Dutch samples.

		Sample 1						Sample 2: CAREST						Sample 3: BeMind					
FCRI-NL		Normality test				Floor score‡	Ceiling score‡	Normality test				Floor score‡	Ceiling score‡	Normality test				Floor score‡	Ceiling score‡
Item	Subscale		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)
1	Triggers	*S*	-0.026	0.153	-0.170	5.9	10.2	*S*	0.174	0.115	1.513	11.2	9.0	*S*	-0.273	0.17	-1.606	2.4	19.5
		K	-0.227	0.304	-0.747			*K*	-0.365	0.229	-1.594			*K*	-0.167	0.338	-0.494		
2		*S*	-0.252	0.153	-1.647	5.5	14.1	*S*	0.008	0.115	0.070	11.7	11.0	*S*	-0.41	0.170	-2.412	1.0	28.8
		K	-0.419	0.304	-1.378			*K*	-0.666	0.229	-2.908			*K*	-0.473	0.338	-1.399		
3		*S*	-0.542	0.153	-3.542	3.1	26.7	*S*	-0.401	0.115	-3.487	4.4	27.8	*S*	-0.797	0.170	-4.688	1.0	38.0
		K	-0.324	0.304	-1.066			*K*	-0.672	0.229	-2.934			*K*	0.531	0.338	1.571		
4		*S*	0.000	0.153	0.000	6.3	9.0	*S*	0.315	0.115	2.739	15.0	6.2	*S*	-0.258	0.170	-1.518	3.4	16.6
		K	-0.308	0.304	-1.013			*K*	-0.376	0.229	-1.642			*K*	0.127	0.338	0.376		
5		*S*	-0.003	0.153	-0.020	4.7	15.7	*S*	0.157	0.115	1.365	17.2	7.9	*S*	-0.385	0.170	-2.265	3.9	17.6
		K	-0.702	0.304	-2.309			*K*	-0.71	0.229	-3.100			*K*	-0.275	0.338	-0.814		
6		*S*	-0.075	0.153	-0.490	8.6	12.2	*S*	0.546	0.115	4.748	22.7	7.0	*S*	-0.187	0.170	-1.100	5.4	16.6
		K	-0.482	0.304	-1.586			*K*	-0.558	0.229	-2.437			*K*	-0.795	0.338	-2.352		

Skewness and kurtosis values, z-scores, and floor and ceiling scores of all FCRI-NL items of three Dutch samples. (continued)

		Sample 1						Sample 2: CAREST						Sample 3: BeMind					
FCRI-NL		Normality test				Floor score‡	Ceiling score‡	Normality test				Floor score‡	Ceiling score‡	Normality test				Floor score‡	Ceiling score‡
Item	Subscale		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)
7		*S*	-0.195	0.153	-1.275	4.3	12.5	*S*	0.138	0.115	1.200	11.0	8.8	*S*	-0.427	0.170	-2.512	2.0	26.3
		K	-0.265	0.304	-0.872			*K*	-0.559	0.229	-2.441			*K*	-0.283	0.338	-0.837		
8		*S*	0.536	0.153	3.503	32.9	3.1	*S*	0.785	0.115	6.826	40.5	3.1	*S*	0.469	0.170	2.759	21.0	4.9
		K	-0.641	0.304	-2.109			*K*	-0.402	0.229	-1.755			*K*	-0.388	0.338	-1.148		
9	Severity	*S*	0.165	0.153	1.078	3.5	9.0	*S*	0.502	0.115	4.365	20.5	3.7	*S*	-0.142	0.170	-0.835	4.9	21.0
		K	-0.688	0.304	-2.263			*K*	-0.23	0.229	-1.004			*K*	-0.891	0.338	-2.636		
10		*S*	0.155	0.153	1.013	4.3	11.0	*S*	0.612	0.115	5.322	20.5	5.1	*S*	-0.155	0.170	-0.912	6.8	22.0
		K	-0.862	0.304	-2.836			*K*	-0.138	0.229	-0.603			*K*	-1	0.338	-2.959		
11		*S*	-0.362	0.153	-2.366	1.2	14.9	*S*	-0.207	0.115	-1.800	5.7	8.6	*S*	-0.288	0.170	-1.694	0.5	22.4
		K	-0.199	0.304	-0.655			*K*	-0.245	0.229	-1.070			*K*	-0.428	0.338	-1.266		
12		*S*	-0.538	0.153	-3.516	4.7	20.4	*S*	0.157	0.115	1.365	17.0	10.8	*S*	-0.514	0.170	-3.024	2.4	28.8
		K	-0.285	0.304	-0.938			*K*	-0.981	0.229	-4.284			*K*	-0.477	0.338	-1.411		
13		*S*	-0.231	0.153	-1.510	6.3	16.9	*S*	0.022	0.115	0.191	10.4	9.3	*S*	0.298	0.170	1.753	22.4	2.0
		K	-0.790	0.304	-2.599			*K*	-0.652	0.229	-2.847			*K*	-0.786	0.338	-2.325		
14		*S*	0.245	0.153	1.601	1.6	8.6	*S*	0.291	0.115	2.530	7.7	1.5	*S*	0.248	0.170	1.459	0.5	6.8
		K	-0.390	0.304	-1.283			*K*	0.246	0.229	1.074			*K*	-0.661	0.338	-1.956		
15		*S*	0.606	0.153	3.961	7.1	5.5	*S*	0.885	0.115	7.696	21.8	1.1	*S*	0.428	0.170	2.518	3.9	8.8
		K	0.043	0.304	0.141			*K*	1.92	0.229	8.384			*K*	-0.406	0.338	-1.201		

Skewness and kurtosis values, z-scores, and floor and ceiling scores of all FCRI-NL items of three Dutch samples. (continued)

		Sample 1						Sample 2: CAREST						Sample 3: BeMind					
FCRI-NL		Normality test				Floor score‡	Ceiling score‡	Normality test				Floor score‡	Ceiling score‡	Normality test				Floor score‡	Ceiling score‡
Item	Subscale		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)
16		*S*	0.143	0.153	0.935	16.5	1.2	*S*	0.59	0.115	5.130	40.7	0.4	*S*	-0.073	0.170	-0.429	12.2	2.4
		K	-0.129	0.304	-.424			*K*	-0.344	0.229	-1.502			*K*	0.305	0.338	0.902		
17		*S*	-0.616	0.153	-4.026	11.8	34.1	*S*	0.23	0.115	2.000	40.5	13.7	*S*	-0.165	0.170	-0.971	10.2	16.1
		K	-0.643	0.304	-2.115			*K*	-1.484	0.229	-6.480			*K*	-0.459	0.338	-1.358		
18	Psychological	*S*	0.090	0.153	0.588	2.0	13.3	*S*	0.433	0.115	3.765	16.1	6.6	*S*	-0.411	0.170	-2.418	2.4	16.1
	Distress	*K*	-0.924	0.304	-3.039			*K*	-0.59	0.229	-2.576			*K*	-0.579	0.338	-1.713		
19		*S*	0.080	0.153	0.523	12.9	12.2	*S*	0.585	0.115	5.087	30.4	4.0	*S*	-0.247	0.170	-1.453	5.9	13.7
		K	-1.062	0.304	-3.493			*K*	-0.467	0.229	-2.039			*K*	-0.756	0.338	-2.237		
20		*S*	0.396	0.153	2.588	27.1	5.1	*S*	1.398	0.115	12.157	60.6	4.2	*S*	0.348	0.170	2.047	26.3	6.3
		K	-0.798	0.304	-2.625			*K*	0.861	0.229	3.760			*K*	-0.889	0.338	-2.630		
21		*S*	0.345	0.153	2.255	22.7	4.7	*S*	0.866	0.115	7.530	43.0	3.1	*S*	0.124	0.170	0.729	13.2	9.8
		K	-0.784	0.304	-2.579			*K*	-0.21	0.229	-0.917			*K*	-0.903	0.338	-2.672		
22	Functioning	*S*	1.399	0.153	9.144	58.0	2.0	*S*	3.054	0.115	26.557	82.4	1.1	*S*	0.684	0.170	4.024	42.0	0.5
	Impairments	*K*	1.269	0.304	4.174			*K*	10.083	0.229	44.031			*K*	-0.694	0.338	-2.053		
23		*S*	1.178	0.153	7.699	51.4	2.4	*S*	2.577	0.115	22.409	80.8	0.2	*S*	0.588	0.170	3.459	34.1	1.5
		K	0.498	0.304	1.638			*K*	6.261	0.229	27.341			*K*	-0.496	0.338	-1.467		
24		*S*	1.073	0.153	7.013	48.6	2.0	*S*	2.209	0.115	19.209	74.2	0.9	*S*	0.624	0.170	3.671	30.2	2.4
		K	0.417	0.304	1.372			*K*	4.633	0.229	20.231			*K*	-0.2	0.338	-0.592		

Skewness and kurtosis values, z-scores, and floor and ceiling scores of all FCRI-NL items of three Dutch samples. (continued)

		Sample 1						Sample 2: CAREST						Sample 3: BeMind					
FCRI-NL		Normality test				Floor score‡	Ceiling score‡	Normality test				Floor score‡	Ceiling score‡	Normality test				Floor score‡	Ceiling score‡
Item	Subscale		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)
25		*S*	0.604	0.153	3.948	32.9	5.1	*S*	1.962	0.115	17.061	66.7	1.8	*S*	0.436	0.170	-0.259	24.4	8.8
		K	-0.707	0.304	-2.326			*K*	3.646	0.229	15.921			*K*	-0.724	0.338	-2.142		
26		*S*	0.623	0.153	4.072	21.6	2.7	*S*	1.189	0.115	10.339	46.3	2.2	*S*	-0.044	0.170	-0.259	12.2	4.4
		K	-0.060	0.304	-0.197			*K*	0.943	0.229	4.118			*K*	-0.592	0.338	-1.751		
27		*S*	0.675	0.153	4.412	31.8	2.0	*S*	1.66	0.115	14.435	58.4	2.0	*S*	0.131	0.170	0.771	14.1	2.9
		K	-0.275	0.304	-0.905			*K*	2.707	0.229	11.821			*K*	-0.672	0.338	-1.988		
28	Insight	*S*	1.198	0.153	7.830	54.9	1.6	*S*	2.186	0.115	19.009	72.7	1.1	*S*	0.793	0.170	4.665	45.4	2.9
		K	0.560	0.304	1.842			*K*	4.526	0.229	19.764			*K*	-0.501	0.338	-1.482		
29		*S*	1.920	0.153	12.549	69.8	1.6	*S*	3.302	0.115	28.713	85.7	0.7	*S*	1.639	0.170	9.641	64.4	2.9
		K	3.054	0.304	1.046			*K*	11.195	0.229	48.886			*K*	1.947	0.338	5.760		
30		*S*	1.757	0.153	11.484	68.2	.8	*S*	2.73	0.115	23.739	82.4	0.9	*S*	1.734	0.170	10.200	68.8	3.4
		K	2.429	0.304	7.990			*K*	7.329	0.229	32.004			*K*	2.077	0.338	6.145		
31	Reassurance	*S*	1.509	0.153	9.863	64.7	1.6	*S*	1.633	0.115	14.200	67.8	2.4	*S*	1.169	0.170	6.876	58.8	1.0
		K	1.242	0.304	4.086			*K*	1.674	0.229	7.310			*K*	0.145	0.338	0.429		
32		*S*	1.300	0.153	8.497	60.4	1.2	*S*	1.75	0.115	15.217	67.4	2.2	*S*	1.289	0.170	7.582	59.5	1.5
		K	0.799	0.304	2.628			*K*	2.259	0.229	9.865			*K*	0.566	0.338	1.675		
33		*S*	0.383	0.153	2.503	25.9	2.7	*S*	0.503	0.115	4.374	29.1	2.6	*S*	0.32	0.170	1.882	25.4	3.9
		K	-0.831	0.304	-2.734			*K*	-0.545	0.229	-2.380			*K*	-0.713	0.338	-2.109		

Skewness and kurtosis values, z-scores, and floor and ceiling scores of all FCRI-NL items of three Dutch samples. (continued)

		Sample 1						Sample 2: CAREST						Sample 3: BeMind					
FCRI-NL		Normality test				Floor score‡	Ceiling score‡	Normality test				Floor score‡	Ceiling score‡	Normality test				Floor score‡	Ceiling score‡
Item	Subscale		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)		Time-1	SE	z-score†	Time-1 (%)	Time-1 (%)
34	Coping	*S*	-0.309	0.153	-2.020	14.1	6.7	*S*	0.097	0.115	0.843	34.1	6.4	*S*	-0.525	0.170	-3.088	14.1	4.9
	Strategies	*K*	-0.880	0.304	-2.895			*K*	-1.401	0.229	-6.118			*K*	-0.687	0.338	-2.033		
35		*S*	-0.031	0.153	-0.203	16.9	6.3	*S*	0.241	0.115	2.096	33.7	6.6	*S*	-0.212	0.170	-1.247	16.1	5.9
		K	-0.917	0.304	-3.016			*K*	-1.245	0.229	-5.437			*K*	-0.914	0.338	-2.704		
36		*S*	0.708	0.153	4.627	43.5	2.4	*S*	1.096	0.115	9.530	58.8	4.0	*S*	0.759	0.170	4.465	42.0	2.0
		K	-0.639	0.304	-2.102			*K*	-0.16	0.229	-0.699			*K*	-0.233	0.338	-0.689		
37		*S*	-0.495	0.153	-3.235	7.5	12.9	*S*	-0.461	0.115	-4.009	14.1	19.8	*S*	-0.156	0.170	-0.918	7.3	8.8
		K	-0.404	0.304	-1.329			*K*	-0.913	0.229	-3.987			*K*	-0.723	0.338	-2.139		
38		*S*	0.100	0.153	0.654	21.2	1.2	*S*	0.395	0.115	3.435	26.4	4.6	*S*	-0.056	0.170	-0.329	16.1	3.4
		K	-0.915	0.304	-3.010			*K*	-0.745	0.229	-3.253			*K*	-0.908	0.338	-2.686		
39		*S*	-0.191	0.153	-1.248	4.3	11.4	*S*	-0.173	0.115	-1.504	17.2	10.1	*S*	-0.021	0.170	-0.124	5.4	4.4
		K	-0.138	0.304	-0.454			*K*	-1.018	0.229	-4.445			*K*	-0.394	0.338	-1.166		
40		*S*	-0.274	0.153	-1.791	17.6	4.7	*S*	0.037	0.115	0.322	26.7	6.8	*S*	-0.008	0.170	-0.047	18.5	7.3
		K	-0.878	0.304	-2.888			*K*	-1.259	0.229	-5.498			*K*	-0.838	0.338	-2.479		
41		*S*	-0.423	0.153	-2.765	6.7	7.5	*S*	-0.129	0.115	-1.122	22.5	12.6	*S*	-0.15	0.170	-0.882	8.3	2.4
		K	-0.230	0.304	-0.757			*K*	-1.232	0.229	-5.380			*K*	-0.498	0.338	-1.473		
42		*S*	-0.162	0.153	-1.059	17.6	9.8	*S*	0.106	0.115	0.922	28.6	13.9	*S*	-0.06	0.170	-0.353	20.5	4.9
		K	-1.020	0.304	-3.355			*K*	-1.323	0.229	-5.777			*K*	-1.014	0.338	-3.000		

S: Skewness; K: Kurtosis

†Z-scores larger than 2 or smaller than -2 were considered a violation of normality; ‡Floor and ceiling effects: when >15% of the participants achieved the lowest or highest possible score.

Supplementary materials 3D. Internal consistency of the original 7-factor FCRI-NL estimated with Cronbach's alpha in three Dutch samples.

	Sample 1		Sample 2: CAREST		Sample 3: BeMind	
	Estimated Cronbach's alpha †	95% CI	Estimated Cronbach's alpha †	95% CI	Estimated Cronbach's alpha †	95% CI
	n = 255		*n* = 454		*n* = 205	
Triggers	.88	.86 - .90	.91	.89 - .92	.88	.86 - .91
Severity	.85	.82 - .88	.88	.87 - .90	.86	.83 - .89
Psychological distress	.84	.80 - .87	.88	.86 - .89	.81	.77 - .85
Functioning impairments	.92	.90 - .94	.92	.91 - .93	.92	.90 - .93
Insight	.84	.80 - .87	.87	.85 - .89	.90	.87 - .92
Reassurance	.76	.70 - .80	.77	.73 - .80	.78	.72 - .83
Coping strategies	.75	.71 - .80	.86	.84 - .88	.76	.71 - .81
FCRI-NL total scale	.93	.92 - .94	.95	.94 - .95	.92	.91 - .94

† High correlation coefficients of $r \geq .70$ were considered sufficient

Supplementary materials 5A. Hypotheses concerning the predictors.

We examined if there were factors that could predict which women benefitted from the online self-help training.[1,2] The following predictors were investigated: socio-demographic variables (i.e. age, children, living alone, education), medical variables (i.e. chemotherapy, rehabilitation, psychological care), self-efficacy for online self-help (i.e. general internet use, health-related behavior, expectations of online self-help), coping strategies, functioning impairments, psychological distress, and psychosocial problems and risk factors (i.e. physical problems, trait anxiety, depressive symptoms, social support). Careful readers will notice that we did not use the exact hypotheses and predictors mentioned in the study protocol.[1] The hypotheses concerning the predictors were adjusted to fit a LGCM context (see also the Methods section). Changes were pre-registered on Open Science Framework (OSF).[2]

The following hypotheses with regard to prediction of treatment effect were explored:

a. Age: It is expected that being younger is related to higher self-efficacy for online self-help. Therefore, the effect of the online-self-help training on FCR is expected to be lower when participants are older.
b. Children: It is expected that when there are younger (<12 years old) children living at home, level of FCR is higher, which could influence the effect of the online self-help training on FCR negatively.
c. Living alone: It is expected that participants living alone experience less social support, which could influence the effect of the online self-help training on FCR negatively.
d. Education: It is expected that participants with higher education have better computer and internet skills, and also better self-management skills than participants with lower education, which could lead to a higher effect of the online-self-help training on FCR.
e. Chemotherapy: It is expected that having undergone chemotherapy influences the cognitive abilities of patients, which in turn could influence the effect of the online self-help training on FCR negatively.
f. Rehabilitation: It is expected that having undergone rehabilitation has a positive effect on the outcome of the online self-help training.
g. Psychological care: It is expected that having received psychological help will have a positive effect on the outcome of the online self-help training.
h. General internet use: It is expected that a high score for general internet use will influence the effect of the online self-help training on FCR positively.
i. Health-related behavior: It is expected that a high score for health-related behavior will influence the effect of the online self-help training on FCR positively.
j. Expectations of online self-help: It is expected that a high score for expectations of online self-help will influence the effect of the online self-help training on FCR positively.

k. Coping strategies: Concerning coping strategies, we intended to explore the relation between coping and the effect of the online self-help training on FCR.
l. Functioning impairments: It is expected that higher impairment of functioning will influence the effect of the online self-help training on FCR negatively.
m. Psychological distress: It is expected that more psychological distress will be related to higher FCR and will influence the effect of the online self-help training on FCR negatively.
n. Physical symptoms: It is expected that more physical symptoms will influence the effect of the online self-help training on FCR negatively.
o. Trait anxiety: It is expected that a high score on trait anxiety will influence the effect of the online self-help training on FCR negatively.
p. Depressive symptoms: It is expected that a high score on depression will influence the effect of the online self-help training on FCR negatively.
q. Social support: It is expected that a high score on social support will influence the effect of the online self-help training on FCR positively.

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Supplementary materials 5B. More details of the intervention.

As described in the study protocol[1]:
"After conducting a survey on patients from the Dutch association of cancer patients' organizations, the online self-help training "Less fear after cancer" was developed by the Helen Dowling Institute (HDI), an institute for psycho-oncology in Bilthoven, the Netherlands. "Less fear after cancer" is a tailored online self-help training based on cognitive behavioral therapy. Participants start the training by filling out the FCRI[2], after which they get (automated) feedback about their scores and a suggestion about which modules to follow. The FCRI and all modules are visible on the worksheet of the intervention (Figure 1). First, participants follow two basic modules: 1) Psycho-education about FCR, its symptoms and learning to recognize symptoms of fear; and 2) The basic principles of cognitive behavioral therapy (this module is divided in two parts). After these basic modules women can choose modules that are relevant to their situation: 1) How to stop rumination, behavioral techniques to stop ruminating; 2) Action, making an action plan about what one can do when fear of recurrence pops up; 3) Relax, audio files with relaxation practices; and 4) Reassurance, how and when to seek reassurance. Each module consists of an informative part (Figure 2) and a practical part in which participants are motivated to do exercises or assignments in daily life (Figure 3). Participants are advised to take a week for each module they choose, so most participants will need four to six weeks depending on how many modules they do. It is explained that the more time they invest, the more effect they can expect from the training, but participants eventually choose themselves how much time is actually spent on the training. For every patient, the intervention will be available for three months. The most important functionality of the online self-help training "Less fear after cancer" is the worksheet, because it gives an overview of the modules and access to the intervention. By clicking on a module, participants can access the information (texts, videos, audio files) and exercises of the self-help training. Other functionalities include a library with the information and forms in pdf format, videos, audio files, and a mailbox for technical assistance. "Less fear after cancer" is fully automated and primarily non-guided and is delivered without professional support from a therapist. In this study, personal online support by an e-mail coach (the researcher) is available for the women that indicate a need for this. The e-mail coach can give technical assistance and eventually refer participants to their general practitioner or medical specialist when they indicate a need for professional help."

Figure 1. Screenshot of the "Less fear after cancer" online self-help training: worksheet.

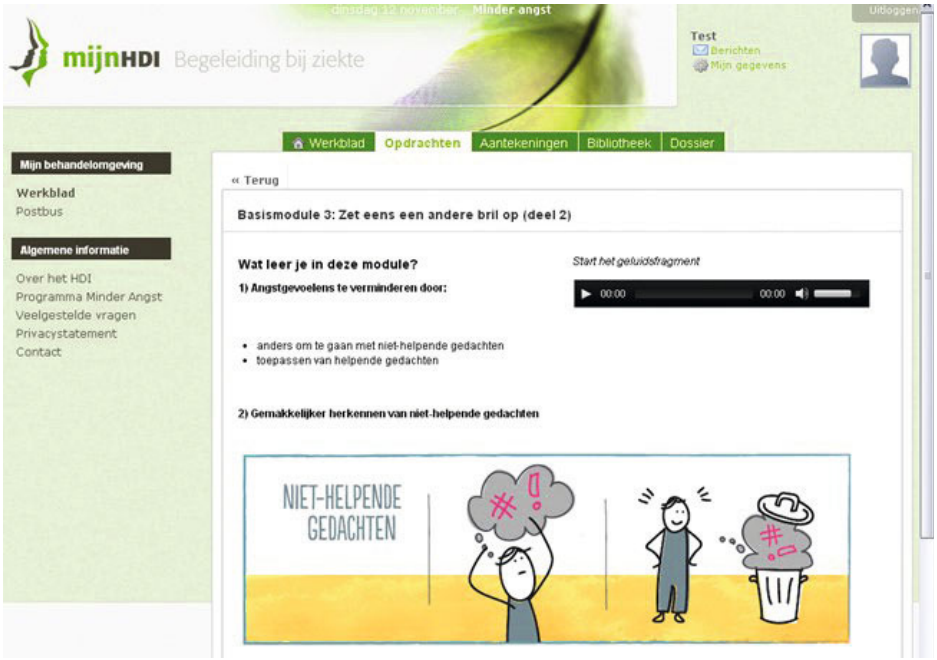

Figure 2. Screenshot of the "Less fear after cancer" online self-help training: information.

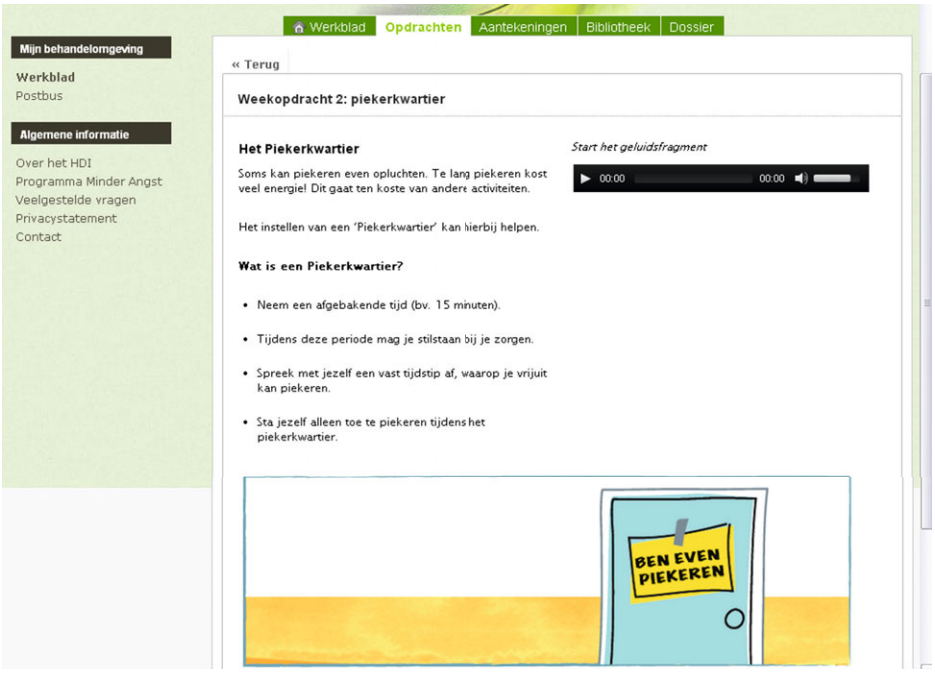

Figure 3. Screenshot of the "Less fear after cancer" online self-help training: exercise.

References

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Supplementary materials 5C. Multivariate normality statistics for total group and within groups.

	Intervention		Control		Total	
Test name	*Test statistic*	*p*	*Test statistic*	*p*	*Test statistic*	*p*
Shapiro test	W = 0.98	0.38	W = 0.97	0.006	W = 0.98	0.018
Mardia	Skewness: χ^2 = 8.94 Kurtosis: z = -0.58	0.54 0.56	Skewness: χ^2 = 5.90 Kurtosis: z = 1.27	0.82 0.20	Skewness: χ^2 = 8.33 Kurtosis: z = 0.50	0.60 0.62
Henze-Zirkler	HZ = 1.15	0.01	HZ = 0.85	0.19	HZ = 1.11	0.02
Royston's MVN	H = 12.00	0.00	H = 3.84	0.21	H = 11.27	0.01

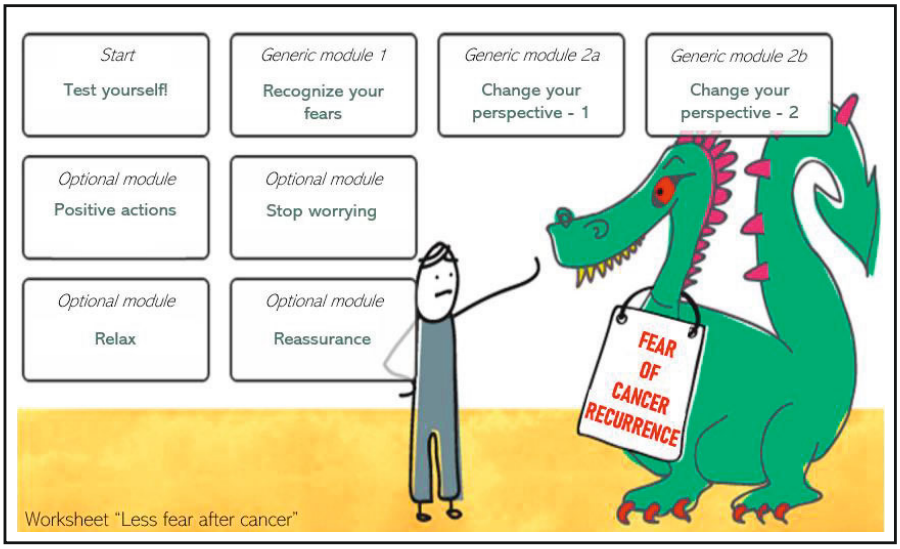
$p < 0.05$ indicates violation of the multivariate normality assumption.

Supplementary materials 6A. More information about the online self-help training "Less fear after cancer".

"Less fear after cancer" is a CBT-based online self-help training to reduce fear of cancer recurrence (FCR), which includes two generic modules about FCR and the basic principles of CBT, and four optional modules. The training is tailored, which means that participants start the training by filling out the Fear of Cancer Recurrence Inventory (FCRI-NL), after which they get (automated) feedback about their scores and a suggestion about which optional modules to follow after the general modules.

The first generic module contains psycho-education about FCR, its symptoms and learning to recognize symptoms of fear, and in the second generic module participants learn about the basic principles of cognitive behavioral therapy (this module is divided in two parts). The four optional modules contain information about making an action plan, behavioral techniques to stop worrying, relaxation practices (with audio files), and information about how and when to seek reassurance.

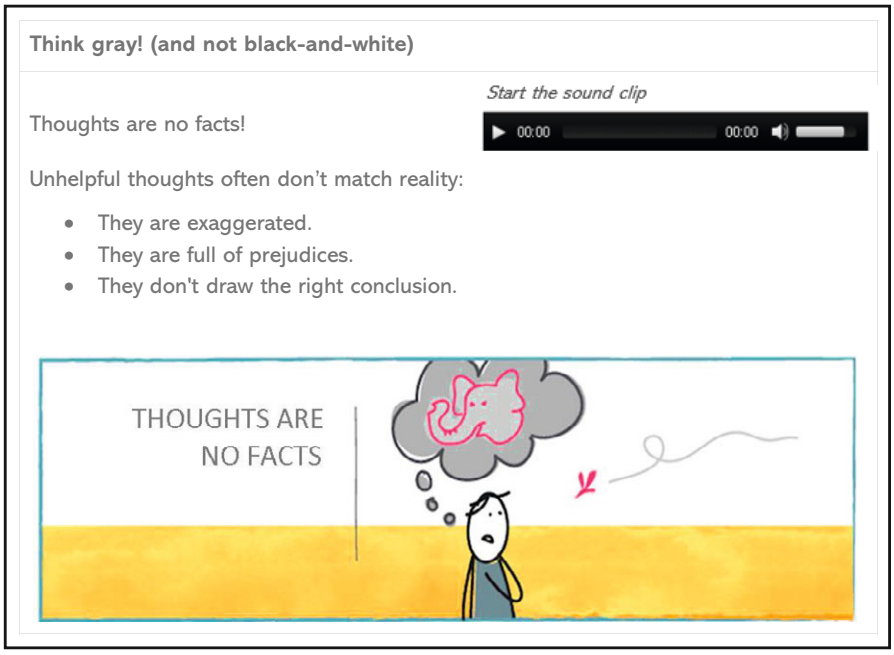
The most important functionality of the training is the worksheet, because it gives an overview of the modules and access to the intervention (translated in English):



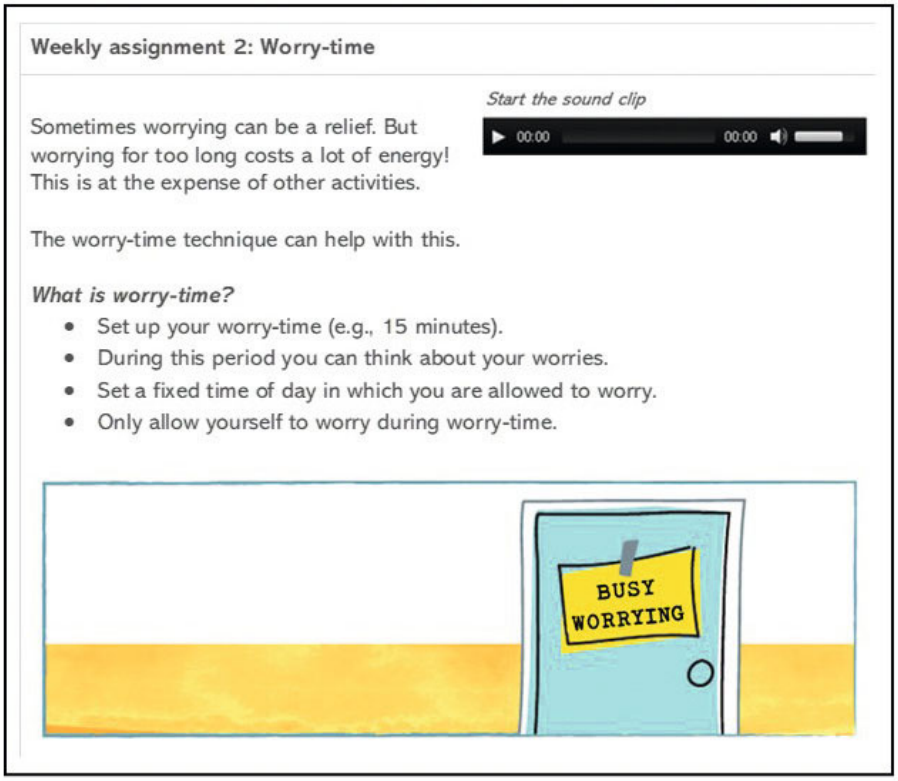
Each module consists of an informative part and a practical part:

- The informative part contains more information about the topic, which is presented in both written text and sound clips (participants can choose what they prefer). Also, there are illustrations and videos in which patients talk about their experiences with FCR and the exercises.
- In the practical part, participants are motivated to do exercises or assignments in daily life. By clicking on a module, participants can access all information (texts, videos, audio files) and exercises of that module.

Example of an informative page from generic module 2 (translated in English):



Example of an assignment from the optional module “Stop Worrying” (translated in English):



We advise participants to spend a week on each module they follow. Also, we explain that the more time they invest, the more effect they can expect from the training. Eventually, participants choose themselves which additional modules they follow and how much time they spend on the training. Most participants will need four to six weeks to complete the training, depending on how many modules they follow. All participants have access to the training for three months.

Other functionalities of the intervention include a library with the information and forms in pdf format, videos, audio files, and a mailbox for technical assistance.

Supplementary materials 6B. Statistical analyses - Extended and more detailed version.

Prior to data analysis, we checked the normality assumptions by conducting multivariate normality tests (Shapiro, Mardia, Henze-Zirkler and Royston tests in R) and univariate normality tests (ShapiroWilk test in R, in combination with q-q plots and histograms).[1] When the assumption of multivariate normality was not met, we executed transformations of the dependent variable. When transformation did not lead to multivariate normality, we used robust maximum likelihood estimation (MLR) to fit the model. P-values smaller than 0.05 were considered statistically significant. Data were analyzed according to the intention-to-treat (ITT) principle, as mentioned in the study protocol.[2] Missing data were analysed for random occurrence with Little's MCAR test for missing data.[3] Multiple imputation was used for all variables to handle the missing data on item level when data was missing completely at random.[4, 5] We handled missing data due to attrition using the full information maximum likelihood procedures incorporated in the growth model function of the Lavaan R package. Differences in number of dropouts between both groups were compared with a cross table and chi-square test.

RQ1: Long-term effectiveness of online self-help training in reducing FCR and PD

To answer the first research question (i.e., do the intervention and CAU group differ in the change in FCR/PD over time), a multigroup second order latent growth model was estimated. A second-order growth model estimates individual growth curves for each participant based on the individual FCR or PD item scores. A multigroup extension allows testing differences between interventions in the growth model parameters. We estimated the model separately for FCR and PD, because the multivariate model for both FCR and PD did not converge (most likely, the model was too large for the data). Also, since R package lavaan gave a warning for all models using robust maximum likelihood estimation (MLR) (i.e., "The variance-covariance matrix of the estimated parameters (vcov) does not appear to be positive definite! The smallest eigenvalue (= -7.784349e-16) is smaller than zero. This may be a symptom that the model is not identified"), we used maximum likelihood estimation (ML) to fit the model. Growth model analyses were performed with R statistical software (version 3.5.3), with software packages lavaan (R package for Structural Equation Modeling, version 0.6-9) and BaylorEdPsych (R-package used for checking missing data for random occurrences, version 0.5).[3, 6–8] The code used for the analyses in this study has been made openly available in the Open Science Framework (OSF) repository (https://osf.io/2sg6m/). Each of the FCR/PD models was built in five steps: Model 0 was the baseline model with five correlated longitudinal latent factors (one at each time-point), fitted separately for each treatment group. All correlations between the same item at different time points were freely estimated. Growth models assume longitudinal measurement invariance, implying that the measurement model of each

outcome (FCR/PD) is invariant across time. To test this assumption, the loadings of the five longitudinal factors were constrained to be equal across time in Model 1, and the intercepts of individual items were constrained to be equal across time in Model 2. In Model 3, we added the latent growth factors (intercept and slope) to explain individual change in the outcome over time for each treatment group separately. Lastly, in Model 4 we tested the first research question by constraining the latent slopes of the intervention and CAU group to be equal.

Goodness-of-fit of the latent growth models was assessed with the maximum-likelihood chi-square statistic (χ^2), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), the root mean squared error of approximation (RMSEA), the comparative fit index (CFI), and the Tucker-Lewis index (TLI).[9–11] The goodness of fit criteria for the fit indices are: CFI and TLI ≥ .95 and RMSEA ≤ .06.[10, 11] We used the χ^2, AIC and BIC criteria to compare models, with higher χ^2, and lower values of AIC and BIC, indicating a better model.[10, 11] Moreover, we compared each set of nested models using chi-square difference test. When models with one or more parameter constraints did not show significantly worse fit in terms of chi-square, longitudinal measurement invariance can be concluded with respect to the constrained parameter type.

RQ2: Relation between FCR and PD over time

Answering the second research question (i.e., does the association between FCR and PD decrease over time), we used a multivariate multigroup growth model including both FCR and PD scores over time. However, as this multivariate second order growth model did not converge, we used a first order growth model that models the growth parameters based on FCR and PD factor scores at each time point instead of on the questionnaire item scores. We first estimated the factor scores of the FCR and PD measurement models at each of the five time points, and subsequently used these factor scores in a multivariate multigroup first order growth model (Model 5) to investigate how change in FCR scores over time was related to change in PD scores over time and how these relations differed between the CAU and intervention group. To test whether the correlations between FCR and PD were equal over time, we added restrictions in Models 6 and 7 respectively to the intervention and CAU group. We assessed and interpreted the goodness-of-fit of the latent growth models as described above.

RQ3: Change trajectories in FCR over time and their predictors

For the last research question (i.e., what are the characteristics of patients for whom the intervention worked), we modeled a repeated measures latent class analysis (RMLCA) within the intervention group. RMLCA analyses were performed with Latent Gold (version 5.0.0).[12] The first step of this analysis was to identify the optimal number of latent classes where each class represents a different pattern of change in FCR over time. We used the Bayesian Information Criterion (BIC; tends to underestimate with

low separation and in small sample sizes), Akaike Information Criterion (AIC; tends to overestimate with higher separation and in large sample sizes), and AIC3 (offers a good compromise between BIC and AIC) to determine the number of latent classes that best fitted the data.[13, 14] Lower values of BIC, AIC and AIC3 indicate a better fit of a model relative to models with higher values.[10, 11] When not all indices indicated the same number of latent classes, the model supported by most indices was chosen. The second step of the RMCLA was to investigate which predictor variables (as mentioned in the introduction) predict class membership, using Latent Gold's omnibus Wald test of differences between the latent classes on the predictor variables. Since we assessed multiple predictors, we adjusted the significance level using the Bonferroni-Holm correction.[15] For significant predictors, we used Z values >2 or <-2 to determine which class(es) significantly contributed to the predictor effects. Positive/negative values show that participants in that class show higher/lower than average scores on that predictor.

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List of publications

van Helmondt, S.J., Lodder, P., van Woezik, R., de Vries, J., & van der Lee, M.L. (2023). CBT-based online self-help training to reduce fear and distress after cancer (CAREST randomized trial): 24 months follow-up using latent growth models and latent class analysis. Annals of Behavioral Medicine 2023, 57(9), 787–799.

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About the author (Over de auteur)

Sanne van Helmondt werd op 11 februari 1985 geboren in Bergen op Zoom. In 2003 behaalde zij haar VWO diploma aan het Mollerlyceum in Bergen op Zoom, waarna zij startte aan het Conservatorium, met als hoofdvak klarinet. Nadat zij geblesseerd raakte en noodgedwongen moest stoppen met deze opleiding, werd haar interesse in de psychologie gewekt. Haar doel werd om mensen te helpen om te leren leven met lichamelijke beperkingen of ziekten. Zij startte een opleiding Psychologie aan de Universiteit van Tilburg. Daar behaalde zij in 2010 de bacheloropleiding Psychologie & Gezondheid en in 2012 de tweejarige masteropleiding Medische Psychologie.

Na haar afstuderen startte Sanne begin 2013 aan haar promotieonderzoek bij het Helen Dowling Instituut, in samenwerking met de Universiteit van Tilburg. Tijdens deze aanstelling werkte zij ook enige tijd als basispsycholoog op werkervaringsplekken bij De Vruchtenburg en het Helen Dowling Instituut. Gedurende haar promotietraject kreeg Sanne vermoeidheidsklachten en werd uiteindelijk de zeldzame aandoening sarcoïdose (een aandoening van het afweersysteem) geconstateerd, waardoor ze haar promotieonderzoek niet binnen vier jaar kon afronden. Na haar aanstelling als promovendus werkte ze als onderzoeker bij het ILD Expertisecentrum van het St. Antonius Ziekenhuis in Nieuwegein, waar zij onderzoek deed naar vermoeidheid bij sarcoïdose en psychosociale zorg bij interstitiële longaandoeningen (waar sarcoïdose ook onder valt). In 2023 kreeg zij hiervoor de Bouwhuisprijs van Sarcoidose.nl, een prijs die jaarlijks wordt toegekend aan een onderzoeker die een meer dan normale inzet toont voor sarcoïdoseonderzoek. Daarnaast heeft zij gewerkt als praktijkondersteuner GGZ in een huisartsenpraktijk. Naast haar werk heeft Sanne haar promotieonderzoek in eigen tijd afgemaakt, wat uiteindelijk heeft geresulteerd in dit proefschrift.