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Fear of Cancer Recurrence

Conceptualization and assessment

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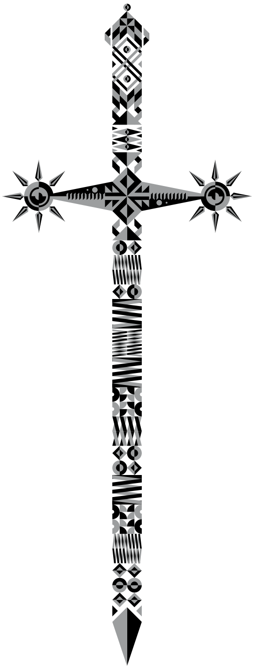

Chapter 1

General introduction

FEAR OF CANCER RECURRENCE

Cancer has a high incidence in the Netherlands with more than 100,000 new patients treated each year for various diagnoses of cancer [1]. During the last decennia survival of cancer patients has improved significantly for reasons such as population screening, secondary prevention strategies and improvements in primary and systemic treatment options. Due to this improved outcome, the prevalence of cancer patients is also increasing. As a result more patients are faced with the long-term complications of their cancer treatment, and the psychological burden of cancer treatment. One of the psychological complaints in cancer survivorship is fear of cancer recurrence. Fear of cancer recurrence (FCR) has been described as the Sword of Damocles that hangs over patients for the rest of their lives [2,3]. Although consensus on defining FCR is lacking, Vickberg's definition is often used: *"FCR can be defined as the fear that the cancer will return or progress in the same organ or in another part of the body"* [4]. Both fear of progression [5] and fear of recurrence [4] are used as terms in the scientific literature to describe fears about the spread or recurrence of cancer [6]. These descriptions are often handled as comparable on a conceptual level [7] and fit within the definition proposed by Vickberg [4], and are therefore referred to as FCR in this introduction. Research has shown that FCR is a common concern for many cancer patients who have ended their treatment and are in remission [2,8]. Furthermore, it is the most commonly identified unmet psychosocial need for help of cancer patients and survivors [9-14] and among the most important reasons for consulting a psychologist [15]. FCR is a normal, adequate response to the experience of a potentially life-threatening disease. Low to moderate levels of FCR are characterized by the ability to reassure oneself after being confronted with triggers. However, some patients experience long-lasting and severe FCR. These severe levels of FCR coincide with increased functioning impairment, psychological distress, and lower quality of life [4,7,8,16-25]. Furthermore, studies show that fearful cancer patients are significantly less likely to accept discharge from a cancer center and follow-up with a primary care provider [26], and prefer a longer (life-long) follow-up period than currently offered (5 years) [27]. FCR is also associated with greater utilization of healthcare resources, such as number of medications taken and visits to an emergency room [28], unscheduled visits to one's family physician, and use of complementary and alternative medicines [29], all suggesting that FCR is likely to increase costs to the healthcare system [28].

ASSESSMENT OF FEAR OF CANCER RECURRENCE

Recent systematic reviews [8,30] report over 30 FCR measures available to researchers and clinicians ranging from purpose-designed longer scales (> 10 items; n=4), brief FCR specific scales (2-10 items; n=17), FCR specific subscales within quality of life or psychosocial assessment instruments (n=11), or single items within longer questionnaires (n=7) [8]. However, relatively few of the available tools have data on both internal and external forms of validity, and only a few scales have comprehensive data available on their psychometric properties [30]. Only one study has attempted to establish a clinical cut-off score by using a purpose-designed face-to-face semi-structured interview of FCR as a gold-standard measure [31]. However, this diagnostic interview has not been validated. The lack of gold-standard diagnostic criteria limits comparison between studies, the capacity to adequately evaluate the criterion validity of different FCR scales, and the development of screening tools and FCR-specific interventions [30].

CLINICAL LEVELS OF FEAR OF CANCER RECURRENCE

Currently, there are no established criteria for defining clinical levels of FCR [30]. Using non-validated cut-off scores applied to self-report measures, it is estimated that across different cancer sites and assessment tools, half of cancer survivors suffer from moderate to severe levels of FCR [8]. Despite the absence of a consensus definition of clinical FCR, the literature points to some key characteristics of severe FCR including a perceived risk of recurrence that is disproportionate to actual risk, functional impairment resulting from FCR, a long duration and greater severity of the problem, and frequent self-examination and demands for medical tests for potential signs of recurrence [30]. A recent study investigated the co-morbidity pattern between FCR and anxiety disorders in patients with cancer [6]. The results showed that there is a small group of patients who suffer from clinical FCR without simultaneously suffering from an anxiety disorder, but also some patients suffer from an anxiety disorder, lacking clinical FCR. In this study, less than 10% of the cancer patients were diagnosed with comorbid FCR/anxiety disorder. Post-hoc analyses showed that the patients with high FCR were equally burdened by accompanying mental and somatic symptoms (pathological worry, general anxiety, depressive symptoms and somatic complaints) as the group of cancer patients who suffer from an anxiety disorder. In addition Simard and Savard [31] developed a semi-structured interview on FCR to document psychiatric comorbidity of patients with clinical levels of FCR. Their results revealed that cancer survivors with clinical levels of FCR had more current psychiatric disorders (60%) than cancer survivors with non-clinical levels. Anxiety disorders, especially panic disorder (20%) and generalized anxiety disorder (GAD) (16%), were the most frequent comorbid psychiatric disorders sharing characteristics with FCR such as the presence of physical symptoms triggering intrusive thoughts associated with FCR and persistent and excessive worry about health, future, or other real-life problems. Therefore, FCR seems to share several underlying mechanisms with anxiety disorders [31]. However, the majority of survivors do not appear to experience comorbid conditions suggesting that FCR can be a unique problem of cancer survivorship.

THEORETICAL MODEL OF FEAR OF CANCER RECURRENCE

As early as 1997, an initial cognitive-behavioral multidimensional formulation of FCR was proposed [32], based on Leventhal's Self-Regulation Model [33]. This self-regulation model hypothesizes that stimuli or symptoms generate a subjective representation of a somatic problem or health threat and concomitant emotions (e.g. fear/distress), leading to coping procedures and appraisals of outcomes. In accordance with this model, Lee-Jones and colleagues formulated a FCR-specific model in which the patient's emotional reaction (e.g. fear) can result from interpretations of the threat of cancer. These are triggered by the perception of internal cues (e.g. physical symptoms) and/or external cues (e.g. media about cancer). Behavioral (e.g. body checking) and physiological responses (e.g. somatic symptoms of anxiety) can be the result of and might again influence the previous processes. Although this model has had an important contribution to the field of FCR, it remains theoretical and is not evidence-based.

DETERMINANTS OF FEAR OF CANCER RECURRENCE

There is a growing body of research on predictors and correlates of FCR, as evidenced by the recent publication of three reviews of the literature on this topic [7,8,25].

Strong evidence was observed about the relationship between FCR and age indicating that younger cancer survivors reported higher FCR. With regard to physical symptoms, strong evidence emerged for global side effects, fatigue, pain and body image/appearance complaints suggesting that cancer survivors with more frequent or higher number of physical symptoms experienced greater FCR. For psychological characteristics, strong evidence emerged for positive correlations between FCR and distress, depression, anxiety and avoidance/intrusion. Negative associations were consistently found between FCR and quality of life or functional domains indicating that cancer survivors who expressed higher FCR reported lesser global quality of life or wellbeing, emotional/mental, physical, role, social and cognitive functioning.

Inconclusive evidence with regard to demographic characteristics was found for gender, education, marital status, income, employment and ethnicity. For treatment-related variables, the role of stage of disease, having had a recurrence or metastatic disease, treatment type, length of treatment, additional treatment (chemotherapy, radiotherapy), type of surgery and comorbidity remains inconclusive. In terms of psychological characteristics inconclusive evidence emerged for anxiety disorders, risk perception, social support, self-esteem, and optimism.

Relatively new mechanisms that could play a role in FCR but which are not yet extensively studied in this context are implicit processes. Research on implicit processes provides new ways to understand why people engage in dysfunctional behaviors. To date most research on implicit processes has been conducted within the context of the anxiety disorders literature. An attentional bias to threat is thought to play a maintaining role in anxiety disorders and positive findings of several innovative attention bias modification (ABM) and cognitive bias modification interventions (CBM) which aim to reduce attentional bias towards threat and consequently reduce anxiety have been published[34-36]. Only one previous study [37] has studied whether attentional bias towards threat was linked to FCR and found an attentional bias towards cancer-related stimuli, however no difference in high or low FCR.

COURSE OF FEAR OF CANCER RECURRENCE

The majority of studies conducted on FCR used cross-sectional designs in which the relationship between time since diagnosis and severity of FCR gives an indication whether FCR increases, decreases or remains stable over time. Only a few studies [5,38] found a significant relationship, concluding from these cross-sectional study designs that FCR remains stable over time. This finding was confirmed by longitudinal studies as shown by the systematic review of Simard and colleagues [8]. Multiple longitudinal studies [9,17-19,22,23,39-57] assessed the course of FCR within periods ranging from 3 months to 6 years. Most studies reported no change over time [5,24,40-51,55], some studies showed that FCR decreased after diagnosis or cancer treatment and remained stable thereafter [9,19,41,46,52-54,56,57], and only a few studies reported increased FCR over time [42,47]. Altogether research up to now suggests that FCR is stable over time.

INTERVENTIONS FOR FEAR OF CANCER RECURRENCE

To date, there are very few intervention studies that have targeted FCR as a primary or secondary outcome in disease-free survivors. One published randomized controlled trial has found evidence to support the efficacy of two short-group interventions (cognitive behavior group therapy vs. supportive-experiential group therapy) to reduce FoP [58]. Compared to the care as usual control group, FoP decreased significantly over time. Patients with metastases and recurrence of cancer gained most from the interventions. To our knowledge four separate large-scale trials of FCR-specific interventions are currently conducted in the Netherlands [59], UK [60], Canada [61] and Australia [62]. In these trials different approaches are used varying from blended therapy (cognitive behavior therapy and e-Health)[59] to individual therapy sessions including emotional expression, behavioral management, cognitive restructuring, relaxation, and caregiver incorporation [60], a cognitive-existential group intervention [61], and cognitive behavior therapy with components of meta-cognitive therapy and acceptance and commitment therapy (ACT) [62]. Furthermore, FCR is addressed as secondary outcome in several intervention studies targeting improvement of generic emotional outcomes in breast cancer survivors with Web-based self-management [63], Mindfulness-Based Stress Reduction [64,65], an uncertainty management intervention [66] a communication coaching intervention [67] and an emotion regulation intervention [68]. The above mentioned interventions cover a range of varying intervention ingredients due to the fact that little is known about moderating and mediating factors.

OUTLINE OF THE THESIS

This thesis focuses on patients with breast cancer, colorectal cancer and gastro-intestinal stromal tumors (GIST). The studies on patients with breast and colorectal cancer provide insight into a population with a high incidence in the Netherlands with more than 13,000 new patients annually for both diseases, whereas GIST are diagnosed infrequently (approximately 250-300 new patients annually). The studies on patients and survivors with colorectal cancer and GIST provide data on both men and women and therewith allow the comparison between these groups. Patients with a GIST were studied because of their unique long-lasting treatment in the metastatic phase, and uncertainty with regard to the length of remission.

Since validated measures with appropriate cut-off points were lacking, the research described in this dissertation started with the validation of the Cancer Worry Scale (CWS). The CWS was originally developed to assess concerns about developing cancer among individuals at risk for hereditary cancer. In **chapter 2** we investigated whether this questionnaire could function as reliable and valid instrument to differentiate between breast cancer survivors with high and low FCR. We hypothesized that with the cut-off point established in this study, it was possible to differentiate between high and low FCR in subsequent studies. Using the CWS we then aimed to establish the prevalence of high FCR.

In addition to the self-report assessment of FCR in **chapter 2**, it was investigated if high FCR could also be detected in an implicit way. Based on the knowledge that anxious individuals are often faster to detect and process threat-relevant stimuli and are more easily distracted from other tasks by these stimuli, an Emotional Stroop Task with different sets of stimulus words was performed in **chapter 3**. It was hypothesized that breast cancer survivors would display selective attention towards cancer-related stimuli on the Emotional Stroop Task and that women with high FCR would show significant longer reaction times than women with low FCR.

Since feelings of anxiety, stress and uncertainty often occur when cancer patients visit the hospital for medical check-ups, we investigated in **chapter 4** whether there were differences between cancer survivors who were treated with curative intent and patients on ongoing continuous treatment regimes who visit the hospital on a regular basis for medical check-ups in a sample of patients with GIST.

A more detailed description of FCR in a retrospective study of a group of colorectal cancer survivors is provided in **chapter 5** where we were interested in the content of FCR and therefore focused on specific triggers, functional impairments and coping strategies. In **chapter 6**, the theoretic model of FCR was refined and updated with recent literature findings and tested. Finally, **chapter 7** entails a general discussion of the studies presented in this dissertation and discusses implications for future research.

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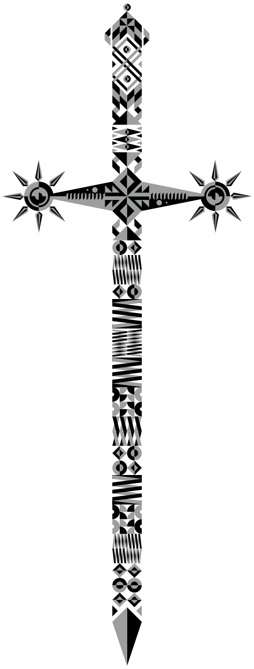

Chapter 2

The Cancer Worry Scale: detecting fear of recurrence in breast cancer survivors

Custers JAE, van den Berg SW, van Laarhoven HWM,
Bleiker EMA, Gielissen MFM, Prins JB.

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ABSTRACT

Background: In 9-34% of cancer patients, the fear of cancer recurrence becomes so overwhelming that it affects quality of life. Clinicians need a brief questionnaire with a cut-off point that is able to differentiate between high- and low-fearful survivors.

Objective: This study investigated if the Cancer Worry Scale (CWS) could serve as an instrument to detect high levels of fear of recurrence in female breast cancer survivors.

Methods: One hundred ninety-four female breast cancer patients were assessed up to 11 years after their primary treatment for cancer. The women returned the questionnaires including the 8-item CWS, 2 items of the Cancer Acceptance Scale, the Checklist Individual Strength-Fatigue subscale, and the Cancer Empowerment Questionnaire.

Results: A cut-off score of 13 versus 14 (low: ≤ 13, high: ≥ 14) on the CWS was optimal for detecting severe levels of fear of recurrence. A cut-off score of 11 versus 12 (low: ≤ 11, high: ≥ 12) was optimal for screening. The Cronbach α coefficient of the CWS was .87; evidence to support the convergent and divergent validity of the CWS was also obtained. The CWS is able to detect high levels of fear of recurrence.

Conclusion: The CWS is a reliable and valid questionnaire to assess fear of recurrence in breast cancer survivors.

Implications for Practice: With the CWS it is possible for nurses to screen breast cancer survivors for severe levels of fear of cancer recurrence. Thereby, nurses can screen and assist survivors in accessing appropriate and available support.

INTRODUCTION

In recent years, improved methods of early diagnosis and better treatments of breast cancer have led to a growing number of survivors. One of the problems cancer survivors may need to deal with is fear of cancer recurrence (FCR). Fear of cancer recurrence can be defined as the fear or worry that the disease will return or progress in the same organ or in another part of the body.[1] Even though FCR may be common, some survivors report fear that is continuously and excessively elevated and becomes so overwhelming that they have difficulties in performing their daily and social activities.[2-11] This high level of fear is characterized by a perceived risk of recurrence that is often disproportionate to the actual risk, functional impairment resulting from FCR, a long duration and greater severity of the problem and frequent self-examination and demands for medical tests for potential signs of recurrence.[12,13] The percentages of cancer survivors experiencing high levels of FCR range from 9% to 34%.[2-3,14-17] The specific nature and cognitive mechanisms of FCR are unknown. This may be at least partly explained by the complexity and the heterogeneity of the phenomenon. The model of Lee-Jones[10] hypothesizes that FCR is a multidimensional construct. The patient's emotional reaction (fear) can be the result of interpretations and cognitions of the threat of cancer released by perceived internal cues (eg, physical symptoms) and/or external cues (eg, follow-up appointments). This fear can lead to problematic behaviors, including anxious preoccupations, avoidance, and excessive checking, contributing to an increased fear response.[10,16] Timely and adequate detection of high levels of FCR will be a first step toward treatment methods for FCR in order to improve the well-being of breast cancer patients after treatment.

To identify women who have high levels of FCR, clinicians need a brief questionnaire that imposes little burden on the patient. A recent systematic review of Thewes et al[18] identified 20 relevant multi-item self-report measures to examine FCR. Relatively few brief measures were found to have comprehensive validation and reliability data available. Furthermore, empirically based cutoff scores for these instruments are lacking.

The aim of this study was to investigate whether the Cancer Worry Scale (CWS) can be used as an appropriate instrument to detect FCR in breast cancer survivors. The CWS is an 8-item scale used to measure worry about the risk of developing cancer (again) and the impact of worry on daily functioning among individuals at risk for hereditary cancer.[19-21] This scale is short, has acceptable internal consistency, and has been translated into Dutch. In this study the psychometric qualities of the CWS were estimated in a sample of breast cancer survivors by investigating if the CWS achieved a high reliability coefficient and convergent and divergent validity. Convergent validity of the CWS was estimated by using the concept of FCR and the concept of fatigue, previously found to be positively correlated with FCR in cancer patients.[22] Divergent validity of the CWS was estimated using the concept of psychological empowerment[23] that represented participants' reports of intrapersonal and interpersonal strengths. This concept was expected to correlate weakly and negatively to FCR because personal strengths and cancer worries are 2 different and opposite constructs. In addition, to determine the optimal cutoff point for the CWS as a diagnostic instrument to indicate excessive FCR, a receiver operating characteristic (ROC) analysis with 2 items of the Cancer Acceptance Scale (CAS) and the CWS was performed. Because FCR has been identified as one of the most common psychological challenges for cancer patients, a short questionnaire to identify patients who have high levels of FCR would be clinically valuable. Screening women for severe levels of FCR is a first step to gaining insight into the mechanisms involved, and it could provide nurses with guidance to provide support and assistance for these women.

METHODS

Participants

Participants were assessed 1 to 11 years after their primary treatment for breast cancer at the Department of Medical Oncology of the Radboud University Medical Centre, Nijmegen, in the Netherlands. In order to participate, patients had to be treated with curative intent, ended surgery and their primary treatment, and were disease-free. They could still be receiving hormonal therapy or trastuzumab. Finally, participants had to be able to read and write in Dutch.

Procedure

Contact information for breast cancer survivors who were eligible to participate was obtained by an oncologist (H.W.M.v.L) at the Department of Medical Oncology of the Radboud University Medical Centre, Nijmegen, in the Netherlands. An information letter about the purpose of the study was mailed to all breast cancer survivors together with a booklet including questionnaires on demographic variables and study questionnaires measuring FCR, empowerment and fatigue. The breast cancer survivors gave informed consent by returning the booklet. Participants who did not want to participate did not have to return the booklet. Reasons for not participating in the study were not collected. Medical data including cancer stage were extracted by the researcher from the medical record.

Instruments

Cancer Worry Scale (CWS)

The original, English version of the CWS consists of 6 items and has been used in research to assess concerns about developing cancer or developing cancer again and the impact of these concerns on daily functioning among individuals at risk for hereditary cancer.[24-28] Cancer worries addressed by this scale were assessed in women with abnormal mammograms without breast cancer[24], first-degree relatives of ovarian cancer patients,[25] and women with a family history of breast cancer.[26-28] Douma and colleagues[19] translated the CWS into Dutch and added 2 items to the original CWS that address worries about family members and future surgery. With this extended 8-item version, studies on cancer worry were conducted among individuals at risk for familial adenomatous polyposis,[19] Li-Fraumeni syndrome,[20] and members of a family with a history of von Hippel-Lindau disease.[21]

The 8 items of the CWS are rated on a 4-point Likert scale ranging from “never” to “almost always”. Scores range from 8 to 32. Higher scores indicate more frequent worries about cancer. Cronbach α varied from .88 to .89 in samples among individuals at risk for hereditary cancer.[19-21]

Modified version of the Cancer Acceptance Scale

The modified version of the CAS, which is derived from the original CAS (7 items; Cronbach α = .85), assesses fear of disease recurrence and consists of 2 items: “I worry about the cancer returning” and “I am anxious about my health”.

Both items are rated on a 4-point Likert scale ranging from “does not apply to me at all” to “completely applies to me.” Scores range from 2 to 8. The 2 items are commonly used both in research and in clinical practice at the Department of Medical Psychology as well as in the Expert Centre Chronic Fatigue of the Radboud University Medical Centre, Nijmegen, for patients experiencing postcancer fatigue.[22,29]

Cancer Empowerment Questionnaire

The Cancer Empowerment Questionnaire (CEQ) assesses 4 components of the concept ‘psychological empowerment’ in cancer patients: personal strength (19 items), social support (9 items), community (6 items), and health care (6 items). The 40 items are rated on a 5-point Likert scale ranging from “strongly disagree” to “strongly agree”. Total scores can range from 40 to 200. Higher scores indicate stronger feelings of empowerment. Cronbach α was .94 in a sample of breast cancer survivors.[30]

Checklist Individual Strength, Fatigue Severity Subscale

Fatigue severity has been measured by the fatigue severity subscale of the Checklist Individual Strength, Fatigue Severity Subscale (CIS-Fatigue). The CIS-Fatigue contains 8 items, and each item is scored on a 7-point Likert scale ranging from "Yes, that is true" to "No, that is not true". A score of 35 or higher on the subscale fatigue severity indicates severe feelings of fatigue. A score between 27 and 35 indicates heightened experience of fatigue. The CIS showed good reliability (Cronbach α's varying from .83 to .92) and construct validity in the work situation as well as in the clinical setting (chronic fatigue syndrome).[31-34]

Statistical Method

Prior to SPSS (version 16.0) data analysis, all relevant data were screened for normality. A principal factors method was used to fit the common factor model to the CWS.

Receiver operating characteristic analysis is a technique that evaluates a test performance by providing information relevant to the full range of scores that need to be taken into account in making a decision about a threshold for, in this study, indicating excessive fear of disease recurrence in this population. A ROC curve (graph of sensitivity against 1-specificity for CWS against 2 items of the CAS) was plotted. The accuracy properties sensitivity, specificity, and positive and negative predictive values were assessed at each cutoff point of the CWS against the 2 items of the CAS, and the area under the ROC curve and its 95% confidence interval were examined. A screening instrument should identify as many fearful survivors as possible. The proposed cutoff point should maximize the proportion of women experiencing FCR scoring positive (sensitivity) and maximize the proportion of negative test results corresponding to nonfearful women (negative predictive value). To differentiate fearful women from nonfearful women, an optimal cut-off point should have high sensitivity and specificity, which maximizes the proportion of patients whose test results are accurate.[35] The internal consistency for the CWS was calculated using Cronbach α.

Validity refers to whether an instrument actually measures what it is supposed to measure. Convergent validity involves the extent to which test scores correlate in a meaningful way with measures of concepts that are theoretically related. In this study, convergent validity of the CWS was measured by calculating Pearson correlation coefficients for the CWS with the CIS-Fatigue and the 2 items of the CAS. A moderate correlation was expected between fatigue and the CWS.[23]

Divergent validity tests whether concepts that theoretically are supposed to be unrelated are in fact unrelated. Divergent validity was measured by calculating Pearson correlation coefficients for the CWS with the CEQ; a small and negative correlation was expected.

RESULTS

Sample Characteristics

Three hundred thirteen women received an invitation to participate in the study, of whom 207 (66%) returned the questionnaires. Of these, 194 women completely filled out the CWS and the 2 items of the CAS, which was required for analyses regarding the ROC curve.

The mean age of the sample was 57.0 (SD, 10.2) years (range, 30-88 years). The mean time since surgery was 4.74 (SD 2.3) years (range, 1-11 years). Most of the women (78%) were diagnosed with early-stage breast cancer (stages I and II). In 7% of the cases, there were no data available on the breast cancer stage. About half of the women (48%) underwent surgery combined with chemotherapy and radiotherapy. After primary treatment, 68% of the women received hormonal therapy (22% actively at time of data collection) and 12% trastuzumab. Forty-three percent of the women had completed tertiary education, and about half of the women had paid work outside the home (45%).

There were no differences between the early-stage breast cancer group and the stage III breast cancer group with respect to age ($F_{1,\,178} = 2.53$, $P = .113$), time since diagnosis ($F_{1,\,168} = 0.53$, $P = .467$) and CWS scores ($F_{1,\,178} = 1.37$, $P = .244$). The stage III breast cancer group was treated more often with chemotherapy and radiotherapy compared to the early-stage breast cancer group ($\chi^2_1 = 4.76$, $P < .05$; and $\chi^2_1 = 36.21$, $P < .05$, respectively).

There were small, significant negative correlations between age and CWS scores ($r = -0.198$, $P = .006$) and time since diagnosis and CWS scores ($r = -0.213$, $P = .004$). No correlation was found between cancer stage and CWS scores ($r = 0.115$, $P = .126$) (Table 1).

Table 1. Demographic and Medical Characteristics of the Study Sample

	Breast Cancer Survivors (N=194)	
Mean age, y	57.0	SD, 10.2
Education		
Primary	10	5%
Secondary	98	51%
Tertiary	83	43%
Employment		
Paid work outside home	88	45%
Retired	42	22%
Home management	41	21%
Disablement insurance act	20	10%

Table 1. Demographic and Medical Characteristics of the Study Sample (continued)

	Breast Cancer Survivors (N=194)	
Sick leave	12	6%
Voluntary work	7	4%
Non-employed	3	2%
Study	2	1%
Years since surgery	4.74	SD, 2.3
Breast cancer stage		
Stage I	20	11%
Stage II	120	67%
Stage III	40	22%
Treatment modalities		
Surgery + chemotherapy + radiotherapy	93	48%
Surgery + chemotherapy	68	35%
Surgery + radiotherapy	16	8%
Surgery only	16	8%

Factor Analysis

The Kaiser-Meyer-Olkin analysis produced by the principal component analysis yielded an index of 0.90, and the Bartlett's test of sphericity was highly significant $\chi^2_{28} = 858$, $P < .001$, indicating that the distribution of CWS data met the psychometric criteria for exploratory factor analysis. The scree test of eigenvalues plotted against factors suggested a 1-factor solution. All items loaded at 0.40 or greater on the factor and so were retained. The factor accounted for a substantial proportion of total item variance (55.2%) (Table 2).

Table 2. Principal Component Analysis Solution for the Cancer Worry Scale (CWS): Items and Component Loadings

CWS Item	**Component Loading**
1. How often have you thought about your chances of getting cancer (again)?	0.82
2. Have these thoughts affected your mood?	0.72
3. Have these thoughts interfered with your ability to do daily activities?	0.63
4. How concerned are you about the possibility of getting cancer (again) one day?	0.87
5. How often do you worry about developing cancer (again)?	0.87
6. How much of a problem is this worry?	0.82
7. How often do you worry about the chance of family members developing cancer?	0.42
8. How concerned are you about the possibility that you will ever need surgery (again)?	0.69

Receiver Operating Characteristic Curve

The mean CWS score was 13.4 (SD, 3.9), with a range of 8 to 30. The mean of the 2 items of the CAS was 5.0 (SD, 1.4), with a range of 2 to 8. Seventy-eight survivors (40%) were diagnosed with FCR using the 2 items of the CAS (CAS > 5). The mean CWS scores were significantly higher for women who were fearful (CAS > 5; mean, 16.4) than for those women who were not fearful (CAS ≤ 5; mean, 11.4), $t_{116} = -10.08$, $P < .001$.

The area under the curve of the ROC analysis showed an 88% ($P < .001$; confidence interval, 0.83-0.93) probability that a randomly selected patient defined as a case by the 2 items of the CAS scores higher on the CWS than a randomly selected patient defined as a noncase. On the basis of the ROC curve, the cutoff score for screening was 11 versus 12 (low: ≤ 11, high: ≥ 12), with a sensitivity of 96%, a specificity of 56%, a positive predictive value of 60%, and a negative predictive value of 96%. With a cutoff point of 11 versus 12, 39% of the women were identified as being fearful for a recurrence of the disease. The optimal cutoff score for differentiating fearful from nonfearful was 13 versus 14 (low: ≤ 13, high: ≥ 14), with a sensitivity of 77% and a specificity of 81%. The positive and negative predictive values were 73% and 84%, respectively. With a cutoff point of 13 versus 14, 31% of the women were identified as being fearful for a recurrence of the cancer (Table 3, Figure).

Table 3. Accuracy Measures for Cancer Worry Scale (CWS) Scores According to 2 Items of the Cancer Acceptance Scale for 194 Women Who Survived Breast Cancer

CWS Cut-off Score	No. (%) ≥ Cut-off	Sensitivity, %	Specificity, %	PPV, %	NPV, %
8 vs 9	78 (40)	100	14	44	100
9 vs 10	77 (40)	99	28	48	97
10 vs 11	76 (39)	97	37	51	96
11 vs 12	75 (39)	96	56	60	96
12 vs 13	70 (36)	90	67	65	91
13 vs 14	60 (31)	77	81	73	84
14 vs 15	51 (26)	65	91	84	80
15 vs 16	42 (22)	54	92	82	75
16 vs 17	32 (17)	41	95	84	71
17 vs 18	25 (13)	32	99	96	68
18 vs 19	17 (9)	22	100	100	66
19 vs 20	13 (7)	17	100	100	64
20 vs 21	10 (5)	13	100	100	63
21 vs 22	6 (3)	8	100	100	62

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

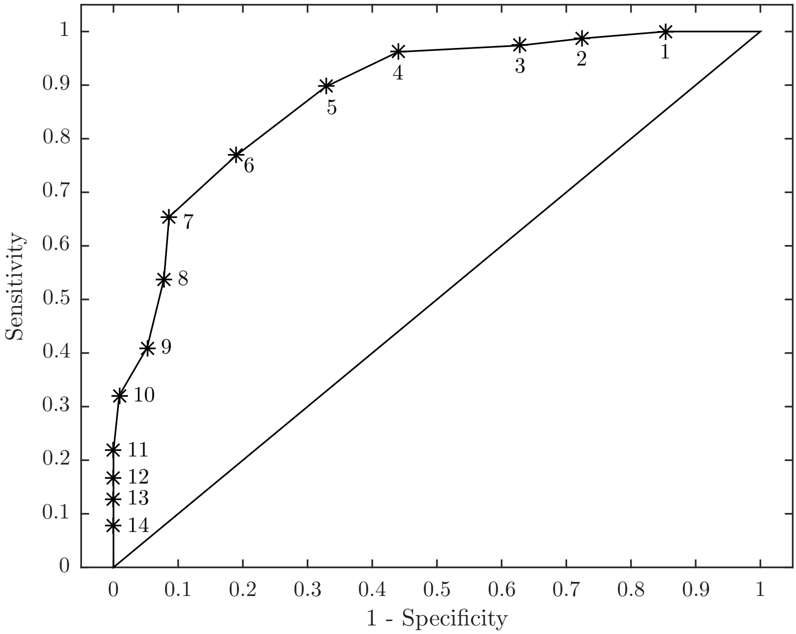

Figure 1. Receiver operating characteristic curve of Cancer Worry Scale (CWS) scores against the 2 items of the Cancer Acceptance Scale. Labeled points correspond to CWS scores as follows: 1: 8 versus 9; 2: 9 versus 10; 3: 10 versus 11; 4: 11 versus 12; 5: 12 versus 13; 6: 13 versus 14; 7: 14 versus 15; 8: 15 versus 16; 9: 16 versus 17; 10: 17 versus 18; 11: 18 versus 19; 12: 19 versus 20; 13: 20 versus 21; 14: 21 versus 22.

Measure of Agreement

In 80% of the cases, there was agreement between the 2 items of the CAS and the CWS concerning the presence or absence of a FCR diagnosis. The degree of agreement was analyzed using Cohen's kappa and was 0.58 (SE, 0.06), a correspondence that is generally regarded as satisfactory.[36,37]

Reliability

A CWS score was derived by summing the 8 items, with scores ranging from 8 to 30. The CWS yielded a high internal consistency reliability coefficient (Cronbach α = .87).

Validation Analyses

Convergent validity

Correlation analyses indicated a significant and strong association between the CWS and the 2 items of the CAS ($r = 0.75$, $P < 0.001$). There was also a significant but moderate association between the CWS and the CIS-Fatigue ($r = 0.34$, $P < 0.001$), indicating a low moderate relation[38] between feelings of fatigue and FCR.

Divergent validity

Correlation analysis indicated a weak but significant negative association between the CWS and the CEQ ($r = -0.22$, $P < 0.001$), indicating a weak relation[38] between FCR and absence of psychological empowerment.

DISCUSSION

Overall, this study supported the reliability and validity of the CWS in a sample of breast cancer survivors. Results of the factor analysis revealed that the 1-factor solution could be retained and that all 8 items contributed sufficiently to the factor. Furthermore, the CWS showed satisfactory discriminatory power relative to the 2 items of the CAS, indicating that it is an appropriate screening instrument to identify those women who experience high levels of FCR with a cutoff point of 11 versus 12 for screening and a cutoff point of 13 versus 14 for differentiating a case from a noncase.

With regard to the study sample, there was a high response rate in that 66% of the women filled in and returned the questionnaires. The mean age of the sample as well as the work situation was comparable to other studies that conducted research on the breast cancer population in the Netherlands, although the educational level was somewhat higher.[39,40]

Although this study has a number of advantages, including the high response rate, the cutoff points, and the good psychometric properties of the scale, there are some limitations. Focusing on female breast cancer survivors rather than a mixed cancer population including males prevents generalizing the results to other cancer groups and to male cancer survivors. Future research needs to measure these variables and define cutoff points of the CWS with male cancer survivors. Because of the variation in objective risk of recurrence among different cancer types, FCR is for some survivors more real and justified than for others, resulting in higher levels of fear[6]. It would be interesting to measure FCR in different cancer type populations and define cutoff points of the CWS for each type.

The findings in this study can be limited by the heterogeneity of the sample. However, with regard to the ranges of age and time since surgery, the correlation with the CWS scores was so small that it is unlikely that this would have a substantial impact on the results of the ROC analyses.

In this study the modified version of the CAS was used as standard in the ROC analyses. One could question whether this is the most appropriate measure to use knowing that psychometric properties are available for the original CAS, but not of the modified scale. However, the 2 items showed a high intercorrelation (r = 0.58) and are commonly used in clinical practice to identify high levels of FCR in cancer survivors experiencing postcancer fatigue. Moreover, it is the only available short questionnaire that is translated into Dutch and therefore the only available questionnaire to use as the standard in the ROC analysis.

The divergent and convergent validity of the CWS was good. The 2 items of the CAS were found to measure the same construct of FCR as the CWS. Furthermore, fatigue and FCR appeared to be distinct problems that partially overlap. The CEQ measured a different construct than the CWS in that there was a low relation between feelings of psychological empowerment and FCR. In the future, it would be important to assess how the CWS relates to generalized feelings of anxiety and depression.

Fear of cancer recurrence is considered a common concern during survivorship and has been linked to poorer psychological adjustment, increased emotional distress, and lower quality of life. Detection is crucial in managing FCR. This study has shown that the CWS is an adequate questionnaire to identify women with high levels of FCR and thus may have an important contribution in the care of breast cancer survivors.

IMPLICATIONS FOR PRACTICE

Even though fear of recurrence is common, some survivors report more fear than others. High levels of FCR can become a significant and chronic problem for cancer survivors. Because of the limiting consequences for quality of life, FCR needs to be acknowledged as a major topic in psychosocial oncology priority in both research and care. With the psychometrically sound CWS, it is possible for nurses to detect high levels of FCR and provide the appropriate support to these survivors (eg, psychoeducation or referral to a psychosocial expert).

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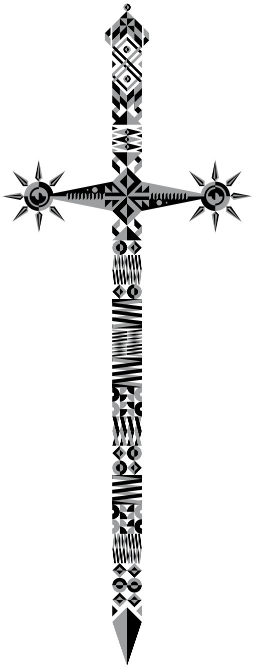

Chapter 3

Selective attention and fear of cancer recurrence in breast cancer survivors

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ABSTRACT

Background Anxious people show an attentional bias towards threatening information.
Purpose It was investigated whether an attentional bias exists for cancer-related stimuli in breast cancer survivors and if different levels of fear of cancer recurrence would lead to different patterns of selective attention.
Methods Breast cancer survivors with high (n=35) and low (n=32) fear of cancer recurrence were compared to 40 healthy female hospital employees. Specificity of attentional biases was investigated using a modified Emotional Stroop Task. Self-report measures were used to assess depression and anxiety, feelings of fatigue and experienced traumas.
Results Compared to control participants, breast cancer survivors with both high and low levels of fear of cancer recurrence showed increased interference for cancer-related words, but not for other word types.
Conclusions The findings suggest a specific attentional bias for cancer-related words in breast cancer survivors that is independent of level of fear of cancer recurrence.

INTRODUCTION

Research on implicit cognitive processes provides new ways to understand why people engage in dysfunctional behaviors. It is widely recognized that individuals vulnerable to anxiety disorders are characterized by enhanced sensitivity to aversive stimuli [1-4]. Cognitive theories have proposed that enhanced vulnerability is explained by the selective processing of threatening information [5,6]. In anxiety, selective processing is defined as an attentional bias towards threatening information. As a result, anxious people are often faster to detect and process threat-relevant stimuli and they are more easily distracted from other tasks by these stimuli [7]. Due to the attentional bias, threat-related stimuli become more salient, and as a result, the subject's estimation of danger is enhanced, leading to a subsequent rise of anxiety and emotional disturbances [8,9]. Therefore, an attentional bias to threat is thought to play an etiological and maintaining role in anxiety disorders [10]. Studies on interventions in which implicit cognitive processes related to anxiety are influenced by cognitive bias modification, reported positive findings [11-13]. Fear of cancer recurrence is a type of anxiety that has become increasingly important since better treatment options for breast cancer have led to a growing number of survivors. Fear of cancer recurrence can be defined as the fear or worry that the cancer will return or progress in the same organ or in another part of the body [14]. In some survivors, the fear of cancer recurrence is continuous and excessive and becomes so overwhelming that it leads to difficulties in daily life [15-24]. In the literature, the percentages of cancer survivors experiencing moderate to high levels of fear of cancer recurrence range from 22-87% [25]. This suggests that for a substantial number of cancer survivors, this fear becomes a significant problem.

Attentional biases in anxiety disorders have often been demonstrated with modified versions of the Emotional Stroop Task in which participants are instructed to name the colors of the ink in which valenced words are printed, while trying to ignore the meaning of the word. The words vary in their relevance to the participants (e.g., neutral, unpleasant). The rationale behind the task is that anxious participants will show delayed color-naming times for threat-related words compared to neutral words because the threat-related words are particularly distracting and interfere with the color-naming process [5].

Color-naming interference by threat-related words has frequently been shown in anxious populations. In patients with medical conditions, interference was less frequently observed. MacLeod and Hagan studied women at risk for gynecologic cancer with standardized anxiety and depression questionnaires and an Emotional Stroop Task. After several weeks, about half of the sample was found to have cervical cancer and these newly diagnosed women filled out an emotional distress questionnaire. Pre-diagnosis delayed color naming for subliminally presented words on the Emotional Stroop Task predicted post-diagnosis emotional distress [26]. In a study examining women with and without a family history of breast cancer, healthy women who identified a first-degree relative with breast cancer reported interference effects for cancer-related stimuli [27,28]. Furthermore, Taylor and colleagues investigated the role of attentional bias in the development of persistent insomnia by comparing the performance of people with cancer who developed acute versus persistent insomnia on an Emotional Stroop Task with cancer-related and sleep-related word cues. Only the persistent insomnia group demonstrated attentional bias for sleep-related words whereas both groups demonstrated attentional bias for cancer-related words [29]. The study of Carpenter and colleagues showed that women with deleterious BRCA1/2 mutations evidenced more biased cancer-related cognitive processing (more interference on the Emotional Stroop Task) than noncarriers, and women with a personal history of breast or ovarian cancer evidenced more biased cancer-related cognitive processing (longer response latencies on the Emotional Stroop Task) than women with no such history [30]. A study using a different paradigm (modified probe position task) to investigate attentional bias related to cancer found that breast cancer patients are biased in their attention to verbal stimuli specifically related to cancer and that attentional patterns in response to cancer words were different for words presented supraliminally (bias to attend to cancer words) versus words presented subliminally (oriented away from cancer words) [31]. In the studies described above, attentional bias to cancer-related stimuli was found in different samples. A relation between attentional bias and fear of cancer recurrence was never the topic of interest. Selective attention to threatening external triggers in a patients' environment (funeral, television programs about cancer) or internal bodily signs, sensations or symptoms (nodule, fever) can lead to enhanced worrying, anxious preoccupations or estimation of danger and therewith engagement in dysfunctional behaviors, avoidance, and excessive checking, again leading to an increased fear response and emotional disturbances. Measuring implicit cognitive processes in cancer survivors with fear of cancer recurrence will advance our understanding of the development and maintenance of fear of cancer recurrence and can provide new routes for interventions (e.g., Cognitive Bias Modification) to reduce this fear.

The aim of the present study was to investigate whether breast cancer patients with fear of cancer recurrence show an attentional bias towards cancer-related stimuli. Breast cancer patients experiencing high levels of fear of cancer recurrence were compared to breast cancer patients experiencing low levels of fear of cancer recurrence and to female hospital employees on an Emotional Stroop Task with cancer-related words (e.g., "chemo"). It was hypothesized that patients show most color-naming interference to threatening stimuli in their own domain of threat, meaning that they would display longer color-naming times when presented with cancer words, indicating cognitive interference when confronted with these stimuli. Furthermore, it was hypothesized that the highest interference in breast cancer survivors would occur for those with high levels of fear of cancer recurrence. In addition, feelings of anxiety and depression, levels of fatigue, and traumatic experiences were assessed in order to demonstrate the integrity of the groups.

METHODS

Participants

Three groups were included in the present study: Female breast cancer survivors with high levels of fear of cancer recurrence, female breast cancer survivors with low levels of fear of cancer recurrence, and a control group consisting of healthy female hospital employees with no history of cancer. Female hospital employees were selected because these women are expected to be as familiar with the hospital-related stimuli as the breast cancer survivors are, while they do not necessarily experience them as threatening. The breast cancer survivors were assessed 1-10 years after their primary treatment for breast cancer. To be eligible, the women had to be treated with curative intent, ended their primary treatment and were disease-free at the time of participation. Although they had finished surgery and their primary treatment, they could still receive hormonal therapy or a specific antibody (trastuzumab). In addition, all participants had to be able to read, write, and speak Dutch fluently.

Contact data of 313 breast cancer survivors were obtained by an oncologist (HvL) at the Department of Medical Oncology of the Radboud University Medical Center, Nijmegen, in the Netherlands. A questionnaire booklet including a modified version of the Cancer Acceptance Scale and the Cancer Worry Scale as measurements for fear of cancer recurrence was sent by mail. The breast cancer survivors were asked to return the questionnaire and give their approval to provide more information about this study. Two hundred and seven women (66%) returned the questionnaires. Of these, 131 women gave their approval of which 55 were highly fearful for a cancer recurrence (Cancer Acceptance Scale>5), 46 had low levels of fear of cancer recurrence (Cancer Acceptance Scale<5), and 30 women experienced moderate levels of fear of cancer recurrence (Cancer Acceptance Scale=5). Parallel to the study, the Cancer Worry Scale was validated with a diagnostic cutoff point (low ≤13; high ≥ 14) [32]. Women who scored high or low on both the Cancer Acceptance Scale and Cancer Worry Scale were included in the study.

Instruments

Stroop Task

A list of 15 cancer-related stimulus words was derived along with four additional lists of words. The latter were needed for purpose of comparison, to confirm specificity of effects. They consisted of 15 hospital-related words to assess non-cancer disease-related information processing; 15 non-disease-related negative words to assess general threat-related information processing; 15 positive words to assess processing of non-threatening, but emotionally valenced information; and 15 neutral words to assess the mental challenge of color-naming in the absence of threatening or otherwise emotionally valenced stimuli.

The positive, negative, and neutral words were generated from lists appearing in previous studies using similar Stroop tasks [27,33]. The list of hospital-related words was generated by a group of researchers in the medical field, clinical psychologists, and medical psychologists. To generate a pool of potential stimulus items for the cancer condition, this group was asked to write down all of the words they thought were related to breast cancer and cancer in general. These words were compared to the word stimuli used in the study by Erblich et al. [27] and finally 15 words were selected. All words are listed in Table 1.

All words were in Dutch and single words, and there were no significant differences in word length between the five word types. A blocked presentation mode was used

Table 1 Words (translated from Dutch) per category used in the Emotional Stroop Task

Breast cancer	Hospital	Negative	Positive	Neutral	Color
Chemo	Wheelchair	Shame	Happiness	Hammer	Red
Amputation	Stretcher	Embarrassing	Valuable	Broom	Blue
Radiation	Ambulance	Solitary	Joy	Vacuum cleaner	Green
Pain	Doctor	Uncertain	Holiday	Furniture	Yellow
Bald	Nurse	Humiliating	Kind	Magazine	
Scar	Stethoscope	Feeling of guilt	Love	Socket	
Metastases	Scan	Failure	Victory	Powder	
Sick	Pills	Shyness	Cheerful	Pencil	
Nodule	Infusion	Antisocial	Sunshine	Garment	
Mammography	Medicines	Isolation	Smile	Waste-paper basket	
Malignant	Syringe	Nervous	Glad	Fork	
Tumor	X-ray	Fail	Beach	Umbrella	
Cancer	Waiting room	Worthless	Friendship	Brush	
Exhausted	Operating room	Incompetent	Merry	Stove	
Biopsy	Thermometer	Incapable	Cosy	Keys	

and five word tables were created, corresponding to the five word categories. In each table, the 15 different words of a single category were presented twice, yielding a total of 30 words per table. These 30 words were placed into five columns, each containing six words. The words were presented in the colors green, yellow, red and blue. The distribution of print colors was the same for each table. The tables were shown on a computer screen as colored words presented against a black background with a resolution of 1,024x768 pixels.

Participants were seated in front of a computer screen and were instructed to name, as rapidly and as accurately as possible, the color of the ink in which each stimulus word was printed, while ignoring the content of the word. Presentation of each word table was started by the experimenter by means of a mouse click. The experimenter also ended each table presentation by a mouse click immediately after the last color was named. The time between the two mouse clicks was automatically recorded and stored, and later analyzed as the main dependent variable. The presentation order of the five tables was random, and a practice table including sequences of colored XXXXX strings instead of words was presented before the five experimental tables. While the five experimental tables were presented, the experimenter was blind to the task conditions on the screen and was strategically seated with her back towards the participant. After the five tables were presented, a control condition - identical to the practice table - and the incongruent color condition of the original Stroop task (e.g., the word "blue" printed in red ink) were displayed as a measure of executive functioning [34]. For each of the tables, incorrect responses were recorded as errors by the experimenter on a sheet displaying the correct order of the colors.

Questionnaires

Modified version of the Cancer Acceptance Scale

The modified version of the Cancer Acceptance Scale assesses the patient's fear of disease recurrence and consists of two items. Both items are rated on a 4-point Likert scale ranging from "Does not apply to me at all" to "completely applies to me". Scores range from 2 to 8 [35,36]. In the present sample, Cronbach's $\alpha = 0.95$.

Cancer Worry Scale

The Cancer Worry Scale consists of eight items and has been used in research to assess concerns about developing cancer or developing cancer again and the impact of these concerns on daily functioning. The eight items of the Cancer Worry Scale are rated on a 4-point Likert scale ranging from "never" to "almost always." Scores range from 8 to 32 [37]. A diagnostic cut-off score of 14 or higher (sensitivity 77%; specificity 81%) indicates severe feelings of fear of cancer recurrence [32]. In the present sample, Cronbach's α = 0.97.

Checklist Individual Strength

The Checklist Individual Strength measures four aspects of fatigue: subjective fatigue, reduced motivation, reduced activity, and reduced concentration. It consists of 20 statements in which the respondent has to indicate on a 7-point Likert scale to what extent the particular statement applies to him or her (1 = Yes, that is true; to 7 = No, that is not true). Scores range from 20 to 140. The Checklist Individual Strength has good reliability [38,39]. In the present sample, Cronbach's α = 0.93.

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale is a 14-item self-report screening scale that was originally developed to indicate the possible presence of anxiety and depressive states in the setting of a medical outpatient clinic. It contains two 7- item scales: one for anxiety and one for depression both with a score range of 0 to 21. The Hospital Anxiety and Depression Scale have good reliability and validity [40,41]. In the present sample, Cronbach's α = 0.91.

Impact of Event Scale

The Impact of Event Scale was included to assess the frequency of intrusive and avoidant phenomena after the traumatic experience of cancer. Its 15 items are divided into two dimensions: "Intrusion" (7 items) and "Avoidance" (8 items). For every statement, the respondent answers on a 4-point scale whether this was present- 0 (not at all), 1(rarely), 3(sometimes), or 5 (often)-during the past 7 days. The Impact of Event Scale has good reliability and validity [42]. In the present sample, Cronbach's α = 0.95.

Visual Analogue Scale

A Visual Analogue Scale was used to measure feelings of anxiety. Participants specified their current level of anxiety using a Visual Analogue Scale that ranged from 0 (indicating not anxious at all) to 10 (indicating very anxious).

Procedure

This study was conducted after institutional approval by the Medical Ethical Committee. Participants provided written informed consent prior to participation. The assessment was administered at the Radboud University Medical Center, Nijmegen at the Department of Medical Psychology. Participants first completed the Stroop Task, then they completed the questionnaires. At the end of the assessment, participants were debriefed and offered a small present in return for their participation.

Analyses

Repeated-measures ANOVA of the dependent variable (reaction time), with word type as within-subjects factor and group as between-subjects factor were performed to detect the critical group x word type interactions. Significant interaction effects were followed-up with repeated-measures ANOVAs for each group, with planned contrasts between the reaction times of the cancer list and the four remaining lists and the control condition.

RESULTS

Demographic and Medical Characteristics

Based on the scores of the Cancer Acceptance Scale, 46 female breast cancer survivors with high levels of fear of cancer recurrence and 37 female breast cancer survivors with low levels of fear of cancer recurrence participated in the study. Since only women who scored high or low on both the Cancer Acceptance Scale and Cancer Worry Scale were included in the analyses, data of 35 female breast cancer survivors with high levels of fear of cancer recurrence and 32 female breast cancer survivors with low levels of fear of cancer recurrence were analyzed. There were no differences between women who approved and women who did not approve to enter the study with regard to time since surgery t (194) = -1.70, $p = 0.09$, or disease stage χ^2 (2, 193) = 0.18, $p = 0.91$. However, there was a significant difference between the groups with regard to age t (205) = -3.69, $p < 0.001$ indicating that approvers (M = 55.5; SD = 9.8) were significantly younger than non-approvers (M = 60.7; SD = 10.0).

Forty female hospital employees participated in this study as a control group. The female hospital employee group was significantly younger than the two patient groups, $F(2,106) = 10.47$, $p < 0.05$, but there were no significant differences between the three groups with regard to marital status or children. With regard to the medical data for the two breast cancer survivor groups, a significant difference was found for time since surgery, indicating that survivors in the low-fearful group were significantly longer in remission than the high-fearful group, t (62) = 2.74, $p < 0.05$. There were no significant differences between the groups with regard to stage of disease, χ^2 (2, 63) = 0.39, $p = 0.48$. Demographics and medical variables are reported in Table 2.

Emotional Stroop Task- Attentional bias

Due to the significant age differences between patients and controls, age was included as a covariate in the analysis. A 3x5 repeated-measures analysis of covariance (ANCOVA) was performed with group as between-subjects factor (high-fearful, low-fearful, hospital employees) and word type as within-subjects factor (cancer, hospital, negative, positive,

Table 2 Demographic and medical characteristics

	High fear	Low fear	Hospital employees
Number (*N*)	35	32	40
Mean age (SD)	53.9 (10.1)	56.8 (8.5)	48.1 (5.7)
Personal situation			
Married/partner	30 (85.7%)	22 (68.8%)	31 (77.5%)
Divorced	0 (0%)	4 (12.5%)	5 (12.5%)
Living alone	3 (8.6%)	4 (12.5%)	4 (10.0%)
Widowed	2 (5.7%)	2 (6.3%)	0 (0%)
Children			
Yes	26 (74.3%)	25 (78.1%)	29 (72.5%)
No	9 (25.7%)	7 (21.9%)	11 (27.5%)
Mean years since surgery (SD)	4.4 (2.4)	5.9 (2.4)	
Stage of disease at diagnosis			
I	3 (8.5%)	3 (9.4%)	
II	23 (65.7%)	21 (65.6%)	
III	8 (22.9%)	5 (15.6%)	
Unknown	1 (2.9%)	3 (9.4%)	

neutral). No significant main effect of age was found, *F*(1, 103) = 1.86, $p = 0.18$, partial eta^2 = 0.02: There was no difference in color-naming times between older and younger participants. No interaction effect was found between age and word type. Furthermore, the critical word type x group interaction was statistically significant, indicating that the patterns of color-naming times differed between the three groups, *F*(7.4, 379.8) = 2.40, $p < 0.05$, partial eta^2 = 0.05. All three groups displayed longer color-naming times for cancer words than for the other words. Post-hoc tests revealed that for cancer words, the breast cancer survivor groups displayed significantly longer reaction times than the control group ($p < 0.05$). There was no difference between high- and low-fearful survivors ($p > 0.05$). Further inspection of the data showed no differences between high- and low-fearful survivors ($p > 0.05$), neither for the cancer words nor for any other word type. Reaction time data by word type and group are displayed in Table 3.

Original Color-Word Stroop Task

A 2x3 repeated-measures ANCOVA was conducted with word type (control, incongruent) as within-subjects factor, group (high-fearful, low-fearful, hospital employees) as between-subjects factor, and age as a covariate. The results revealed a significant interaction between age and word type indicating that older participants had longer reaction times on the incongruent color condition than younger participants, *F*(1,103) = 6.22, $p < 0.05$, partial eta^2 = 0.06. No significant group x word type interaction was

Table 3.
Mean reaction times (sec) and standard deviations of the Emotional Stroop Task

	High-fearful	Low-fearful	Control
Emotional Stroop Task			
Cancer list	28.6 (6.7)	28.5 (5.3)	23. 5 (4.0)
Hospital list	24.8 (5.5)	23.9 (4.8)	21.5 (3.4)
Negative list	24.5 (5.9)	24.5 (5.5)	21.7 (3.4)
Positive list	24.3 (5.1)	24.2 (4.7)	21.5 (3.4)
Neutral list	23.7 (4.9)	24.4 (4.9)	21.5 (3.4)
Original Stroop Task			
Control list	20.8 (3.8)	20.3 (3.7)	19.2 (2.4)
Incongruent color list	40.2 (9.0)	40.5 (9.4)	35.1 (8.0)

found, indicating that there was no difference between the groups in cognitive speed or flexibility, $F(2, 103) = 1.16$, $p > 0.05$.

Error Rates

With regard to the number of errors, the results did not reveal a significant group x word type interaction, $F(12, 588) = 1.52$, $p > 0.05$.

Questionnaires

Mean scores and standard deviations are displayed in Table 4. With regard to the cancer-related questionnaire, the high-fearful breast cancer survivors scored significantly higher than the breast cancer survivors with low levels of fear of cancer recurrence. Impact of Event Scale Intrusion: $F(1,65) = 58.32$, $p < 0.001$; Impact of Event Scale Avoidance: $F(1, 65) = 27.36$, $p < 0.001$.

For the Checklist Individual Strength, the Visual Analogue Scale, and the Hospital Anxiety and Depression Scale, high-fearful breast cancer survivors scored significantly higher than both low-fearful breast cancer survivors and the control group. Checklist Individual Strength Total $F(2, 104) = 17.02$, $p < 0.001$; Visual Analogue Scale $F(2, 104) = 18.02$, $p < 0.001$; Hospital Anxiety and Depression Scale Total $F(2, 104) = 36.57$, $p < 0.001$. There were no significant differences between low-fearful breast cancer survivors and the control group on these questionnaires.

DISCUSSION

To the best of our knowledge, this study is the first to focus on attentional biases in breast cancer survivors with fear of cancer recurrence. The aim of the present study was to

Table 4 Means and standard deviations per group on the questionnaires

	High-fearful	Low-fearful	Controls
Impact of event scale $_{\text{Intrusion}}$	20.4 (9.3)^{a}	5.2 (6.7)^{b}	
Impact of event scale $_{\text{Avoidance}}$	16.7 (9.1)^{a}	5.7 (8.1)^{b}	
Checklist individual strength $_{\text{Total}}$	76.2 (26.8)^{a}	54.4 (23.9)^{b}	46.0 (17.6)^{b}
Hospital anxiety and depression scale $_{\text{Total}}$	14.8 (7.8)^{a}	5.1 (4.0)^{b}	5.1 (3.9)^{b}
Visual analogue scale	3.2 (2.8)^{a}	0.8 (1.1)^{b}	0.8 (1.6)^{b}

a vs. b: $p < 0.001$.

investigate whether breast cancer survivors with high levels of fear of cancer recurrence show an attentional bias towards cancer-related words. The results revealed that both high-fearful and low-fearful breast cancer survivors showed more interference by cancer words than the healthy controls, indicating the role of personal relevance: patients show most pronounced color-naming interferences on the specific class of threatening stimuli related to their own domains of personal concern [43]. Given that the present results did not yield support for the hypothesis that the highest interference in breast cancer survivors would occur for those with high levels of fear of cancer recurrence (i.e., no difference between high- and low-fearful groups), alternative explanations were considered. From the perspective of methodological issues with respect to the content of the Emotional Stroop Task the stimulus items were related to cancer in general. To find the hypothesized difference between high- and low-fearful survivors, it could be important to tailor the stimulus words specific to the fear of cancer recurrence survivors experience. It is therefore important to gain more insight in the underlying mechanism of this fear to catch the characteristics of this phenomenon in words.

From the perspective of cognitive models, the event of being diagnosed with and treated for breast cancer could have had such an impact that cancer-related stimuli are easily activated, resulting in faster detection and processing of this material in both high- and low-fearful survivors irrespective of the level of fear of cancer recurrence [7]. Furthermore, it is noteworthy to mention that the present study was conducted in a hospital setting and it is possible that this setting activated certain fear structures because the participants associate the hospital with the negative events of the cancer diagnosis, treatment, and stressful follow-up consultations.

The personal relevance explanation is supported by the specificity of the attentional bias with regard to emotional valence and hospital-related generalization. There was no generalization of the attentional bias to hospital-related words or emotionally valenced words, neither in the highly fearful survivors nor in the other two groups. This finding points to the thematic specificity and personal relevance of the attentional bias in that it is related to the topic of cancer and not merely based on threat and negative valence.

The findings of the present study contribute to the understanding of attentional biases in breast cancer survivors. An attentional bias towards cancer-related words has been demonstrated as the color-naming times were significantly longer for these words indicating difficulties disengaging attention from them. More research is needed on the topic of fear of cancer recurrence and its connection to cognitive processes since in this study words related to cancer in general were used. It would be interesting to find out which words capture specifically the concept of fear of cancer recurrence and to replicate this study to see if it would result in differences in attentional bias between high- and low-fearful survivors. Results of the questionnaires revealed significant differences between the two survivors groups in that the breast cancer survivors with high levels of fear of cancer recurrence reported mental and physical complaints whereas the breast cancer survivors with low levels of fear of cancer recurrence did not report these problems with scores identical to the control group. These results confirm the integrity of the groups indicating that high-fearful survivors encounter more psychosocial problems than low-fearful survivors. Further, survivors in the low-fearful group were significant longer in remission than the high-fearful group. Another study also found that breast cancer survivors experienced significantly more distress in the first 2 years following surgery than in later years [44]. However, although survivors with low levels of fear of cancer recurrence report explicitly less psychosocial problems, the findings of this study show implicitly an attentional bias toward cancer-related stimuli. It is important for cancer support workers to be aware of this discrepancy because this group will not appear on a distress screening but still can have negative effects of the cognitive interference.

Methodological issues in the present study merit comment. The small sample size could have limited the detection of moderate effects or effects on the various word list groups. In addition, women who approved to receive more information about the study were significantly younger than women who did not approve. This finding might compromise the representativeness of the sample. Also, a significant difference in age between the breast cancer survivors and the control group consisting of female hospital employees was observed. Within the hospital employee group, the maximum age was 63 whereas the maximum age of the cancer survivors was 78. Considering options like an age-matching procedure would be a valuable recommendation for future research as well as the addition of an extra control group since the control group was recruited in the context of cancer research which could be related to more concerns about the disease in these women compared to women in the general population. Furthermore, it should be considered whether the assessment procedures should take place in a hospital setting or in a private setting at home. In this study, the hospital setting could have influenced the results in that it re-activated the cancer-related fear structures in patients, but not in controls.

In conclusion, this study is the first to investigate Stroop interference in breast cancer survivors with fear of cancer recurrence. The main finding of this study is a specific attentional bias towards cancer-related words, found in all survivors, irrespective of their fear of cancer recurrence. A significant difference between these two groups on the self-report measures, as well as the finding that high-fearful women show more comorbid problems, point to the necessity of further research on the topic of fear of cancer recurrence and its link to cognitive processes.

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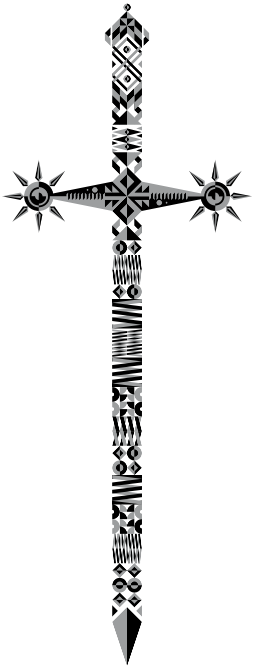

Chapter 4

Fear of Progression in patients with gastrointestinal stromal tumors (GIST). Is extended lifetime related to the Sword of Damocles?

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ABSTRACT

Background: Gastrointestinal stromal tumors (GIST) are rare and before 2000, patients had a dismal prognosis with a median survival of less than a year after tumor metastasis. However, the median overall survival has increased to more than five years following the introduction of imatinib and other tyrosine kinase inhibitors (TKI). Little is known about the psychosocial consequences of treatment of GIST, but this is important because patients now are treated and live for longer. This cross-sectional study assessed quality of life, distress, and fear of cancer recurrence or progression in patients with GIST.

Material and Methods: Eighty-six patients with localized or metastatic GIST were asked to participate. Patients completed self-report questionnaires including the EORTC-Quality of Life Questionnaire, Hospital Anxiety and Depression Scale, Impact of Event Scale, Cancer Worry Scale, and Fear of Cancer Recurrence Inventory.

Results: Fifty-four patients (median age 63.3 years) completed the questionnaires, 33 (61%) of whom were receiving TKI treatment at the time of the study. Overall, the GIST patients had a good global quality of life, but 28 patients had high levels of fear of cancer recurrence/progression. This high level of fear was not related to patient- or treatment-related variables. These patients experienced significantly higher levels of psychological distress, functional impairments, and difficulty making plans for the future than did patients with lower levels of fear.

Conclusions: More attention should be paid to specific cancer-related problems, such as fear of cancer recurrence/progression, in addition to general quality of life issues in patients with GIST.

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common sarcomas in the gastrointestinal tract, with an estimated incidence of 1–2 patients per 100 000 per year [1]. While surgical resection is the first choice of curative treatment [2], more than 40% of patients with GIST present with metastases or have GIST recurrence or metastases during follow-up [3]. GIST respond poorly to conventional cytotoxic chemotherapy and radiotherapy, with a clinical response rate of less than 5%. The insight of GIST as a mutation driven cancer has facilitated the development of targeted kinase inhibitor (TKI) therapies. Most GIST express gain-of-function mutations in the tyrosine kinase receptor KIT and/or PDGFRA genes [4], and this has revolutionized treatment options and outcomes for GIST patients [5]. Imatinib mesylate, a selective TKI, is effective in advanced disease and in the adjuvant setting [3,6,7]. Sunitinib has been approved for the second-line treatment of metastatic GIST, and more recently regorafenib has been approved for third-line treatment [8,9]. TKI treatment is chronic and orally administered. The median overall survival of patients with advanced GIST has increased from less than one year before 2001 to more than five years at the present time [10]. This longer survival makes it relevant to understand how patients deal with their disease and cope with the 'Sword of Damocles' of recurrence. In patient populations with increased survival rates, such as GIST patients, fear of cancer recurrence/progression (FCR) may be an important and realistic problem. This fear manifests itself along a continuum ranging from a normal reaction to a significantly clinical one and is reported as a frequent unmet need for supportive care [11]. FCR is not only associated with the medical situation, such as cancer itself, with recurrence or metastasis, follow-up care, or periodic examinations, but also with psychosocial concerns, such as relying on others to perform daily activities, worries about the future life, disability, or death [12]. To date, there has been little research on the psychosocial consequences of GIST, but a better knowledge of these patients' FCR would help health professionals to support these patients, especially as the availability of systemic therapy has increased the survival rate. This study investigates the quality of life and distress of patients with GIST. More specifically, it assesses the characteristics of patients who have low or high levels of FCR.

MATERIAL AND METHODS

Participants

All patients with localized or metastatic GIST included in the database of the Radboud University Medical Center, Nijmegen, the Netherlands, were reviewed for eligibility. Eighty-six eligible patients were selected who had been or were currently being treated at the center; they had undergone surgery and/or had received imatinib/sunitinib as part of their treatment. All patients were at least 18 years old and had given their written informed consent for participation. All were required to be able to read and write in Dutch.

Procedure

The study was approved by the local Medical Ethics Committee. Between June and October 2012, all eligible patients were informed about the study by one of the researchers [RT] and provided their informed consent. Thereafter, patients were asked to complete, once only, a number of questionnaires (paper or Web-based).

Assessment

Demographic / medical characteristics

Demographic data, including age, gender, marital status, partnership, children, education, and employment status, were gathered by self-report. Medical data, including disease stage at diagnosis and study participation, risk estimation, active systemic treatment at study participation, tumor location, time since initial diagnosis, primary treatment, recurrences/metastases, and disease status, were extracted from the patients' medical records by one of the researchers [RT].

Fear of cancer recurrence/progression

The Cancer Worry Scale (CWS) is used in research to assess concerns about developing cancer or developing cancer again and the impact of these concerns on daily functioning. The instructions for the CWS were adapted to make them suitable for patients who were worried about cancer recurrence or progression. The eight items of the CWS are rated on a four-point Likert scale ranging from never (1) to almost always (4). Scores range from 8 to 32 [13], with a score of 14 or higher being indicative of severe FCR (sensitivity 77%; specificity 81%). A cut-off score of 12 or higher can be used to screen for FCR [14].

Multidimensional aspects of fear of cancer recurrence/progression

The Fear of Cancer Recurrence Inventory (FCRI) was developed to assess the multidimensional aspects of FCR. The FCRI consists of seven subscales: triggers, severity, psychological distress, coping strategies, functioning impairments, insight, reassurance. The 'triggers' subscale evaluates the presence of potential stimuli activating fear. The 'severity' subscale measures the presence and severity of intrusive thoughts associated with fear. The 'psychological distress' and 'functioning impairments' subscales evaluate the potential consequences of fear. The 'insight' subscale measures the level of selfcriticism about fear intensity. The 'reassurance' and 'coping strategies' subscales measure the variety of coping strategies that can be used to cope with fear. The 42 items are rated on a five-point Likert scale ranging from 0 to 4. The FCRI is a reliable and valid self-report scale [15].

Quality of Life

The EORTC Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was developed and validated to assess the quality of life of cancer patients. It consists of 30 statements related to quality of life on five functional scales (physical, role, cognitive, emotional, social), three symptom scales (fatigue, pain, nausea/vomiting), six single symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and a global quality of life scale. Higher scores on the functional scales indicate better functioning and quality of life; higher scores on the symptom scales reflect more severe symptoms. All scores are transformed linearly and range from 0 to 100 [16]. A difference of 5–10 points was considered a small difference, 10–20 points a medium difference, and < 20 points a large difference [17].

General Distress

Psychological distress was measured with the Hospital Anxiety and Depression Scale (HADS). This questionnaire includes 14 items divided into two subscales: depression and anxiety, both seven items. Higher scores indicate more anxiety, depression, and psychological distress. The HADS does not contain any somatic items, and so there is no confounding by symptoms associated with a physical illness. A total score of 11 or higher indicates a mental disorder [18].

Cancer-specific distress

The Impact of Event Scale (IES) was included to assess the frequency of intrusive and avoidant phenomena during or after the traumatic experience of cancer. Its 15 items are divided into two dimensions: intrusion (7 items) and avoidance (8 items). A total score of 9–25 reflects moderate adaptation difficulties; a score higher than 26 indicates serious adaptation difficulties [19].

Data analyses

Prior to SPSS (version 20.0) data analysis, all relevant data were screened for normality. Means, frequencies, and descriptives were used to describe the sample. Multivariate ANOVAs were performed to assess differences between patients with high or low levels of FCR (CWS score ≥14) on several continuous variables. X^2 analyses were performed to assess differences in several categorical variables between the two groups of patients. Pearson's product moment correlations were used to assess relations between continuous variables. All tests were two-sided with a 5% probability of Type I error (alpha). Missing data only occurred in the paper questionnaires and were handled according the manual of the specific questionnaire.

RESULTS

Sample characteristics

Eighty-six eligible patients were asked to participate in the study, 55 (64%) of whom returned the questionnaires. Of these, 54 patients completed the CWS, which was required for the analyses. Reasons for non-participation were not collected. There were neither differences between responders and non-responders on demographic variables [age *t* (84) = 0.55, p = 0.58; gender X^2 (1,86) = 0.07, p = 0.79] nor on disease-related variables [time since diagnosis *t* (84) = 0.80, p = 0.43; disease phase at diagnosis X^2 (1,86) = 2.62, p = 0.11; disease phase at study participation X^2 (1,86) = 0.64, p = 0.42; primary treatment option X^2 (1,85) = 2.64, p = 0.10; risk estimation X^2 (3,86) = 4.96, p = 0.18; disease status X^2 (1,83) = 0.16, p = 0.69). Table 1 shows the patient- and treatment-related characteristics of the sample. The median age was 63 (range 21–83) years, and 29 (54%) patients were male. Forty-seven patients (87%) were married or had a partner, and 46 patients (85%) had at least one child. Thirty-two patients (59%) had completed secondary education and 23 patients (43%) were retired. The mean time from initial diagnosis to study participation was 4.8 (SD = 3.7, range 0.5–17) years. Most primary tumors were located in the stomach (n = 20), small intestine (n = 8), or rectum (n = 6). At the time of the study, 27 patients (50%) had metastatic GIST: 20 had received surgery and imatinib as treatment for metastatic GIST and seven had received imatinib alone. The remaining 27 patients (50%) were categorized as having local GIST: 24 patients had undergone surgery and seven had received imatinib postoperatively. Three patients with local GIST received imatinib in a preoperative setting. At the time of study participation, 29 (54%) patients had no evidence of disease and 25 (46%) were alive with disease.

Quality of life and distress

Table 2 shows the mean (±SD) scores for the quality of life and distress questionnaires, together with the percentage of patients who experienced high FCR, as defined with the CWS. Scores on the functional scales of the EORTC QLQ-C30 ranged from 76.9 to 84.3, indicating that the patients' quality of life was sufficient overall. Patients reported experiencing fatigue, diarrhea, and insomnia. The mean score of 15.1 on the IES indicates that the patients had moderate problems adapting to the traumatic experience of cancer. When the screening cut-off score of 12 on the CWS was used, 39 patients (72%) experienced high levels of FCR; when the diagnostic cut-off point (≥14) was used, 28

Table I. Sample characteristics (n = 54)

Age (years)	Median = 63.3; range 21-48	
Sex: male	29	54%
Marital status		
Married/partnership	47	87%
Not in partnership	7	13%
Children: yes	46	85%
Educational level		
Primary	2	4%
Secondary	32	59%
Tertiary	20	37%
Employment status		
Retired	23	43%
Employed	15	28%
Home management	9	17%
Unemployed/others	16	30%
Time since initial diagnosis (years)	Median = 3.9; range = 0.5-17	
Disease phase at diagnosis		
Local tumor	47	87%
Metastatic	7	13%
Disease phase at study participation		
Local tumor	27	50%
Surgery and/or imatinib	24	
Imatinib	3	
Metastatic	27	50%
Surgery and imatinib	20	
Imatinib	7	
Risk estimation at diagnosis		
High	32	59%
Intermediate	8	15%
Low	13	24%
Very low	1	2%
Location of tumor		
Stomach	20	37%
Small intestine	8	15%
Rectum	6	11%
Intra abdominal	4	7%
Liver	3	6%
Duodenum	3	6%
Other	10	19%
Primary treatment		
Surgery	43	80%
Imatinib	12	22%
Active TKI treatment at study participation	33	61%
Disease status		
No evidence of Disease (NED)	32	59%
Alive With Disease (AWD)	22	41%

Table 2. Baseline means and standard deviations of the EORTC-QLQ-C30, HADS, IES and % of patients experiencing high FCR (n=54)

Quality of life	Mean	(SD)
Physical functioning	84.3	(18.6)
Role functioning	76.9	(28.7)
Emotional functioning	78.4	(25.4)
Cognitive functioning	80.6	(25.6)
Social functioning	80.2	(26.5)
Global health / QoL	77.2	(19.8)
Insomnia	23.5	(30.8)
Fatigue	33.1	(27.3)
Pain	13.0	(21.9)
Dyspnea	16.7	(25.7)
Constipation	18.5	(34.7)
Appetite loss	16.7	(31.6)
Diarrhea	24.7	(29.8)
Nausea, vomiting	9.6	(15.7)
Financial difficulties	13.0	(30.7)
General distress		
HADS total	9.3	(7.8)
Cancer-specific distress		
IES total	15.1	(16.7)
Fear of Cancer Recurrence/Progression		
High FCR (CWS diagnostic cut-off point)	*n* = 28	(52%)
High FCR (CWS screening cut-off point)	*n* = 39	(72%)

CWS, Cancer Worry Scale; EORTC-QLQ-C30, quality of life module; HADS, Hospital Anxiety and Depression Scale; IES, Impact of Event Scale

(52%) patients experienced high levels of FCR. We adopted a conservative approach and defined high versus low levels of fear on the basis of a cut-off score of ≥14. Analysis of differences in quality of life and distress between the two groups revealed medium to large clinical differences on the subscales role, emotional, cognitive, and social functioning and global health/quality of life, indicating that patients who experienced high levels of fear had a worse quality of life. There were medium clinical differences on the symptom subscales insomnia, fatigue, pain, dyspnea, and financial difficulties. Patients who experienced high FCR reported significantly higher levels of general distress (50% vs. 15.4%; $p < 0.001$) and cancer-specific distress (35.7% vs. 3.8%; $p < 0.001$) than did patients who experienced low FCR (Table 3).

Table 3. Means and standard deviations of the EORTC-QLQ-C30, HADS and IES (n=54)

	Low FCR CWS < 14 *n* = 26		High FCR CWS ≥ 14 *n* = 28		
EORTC QLQ-C30	Mean	(SD)	Mean	(SD)	
Physical functioning[a]	87.9	(15.8)	80.9	(20.7)	
Role functioning[b]	86.5	(17.7)	67.9	(33.9)	
Emotional functioning[c]	93.3	(9.7)	64.6	(27.7)	
Cognitive functioning[b]	86.5	(22.6)	75.0	(27.4)	
Social functioning[b]	90.4	(15.0)	70.8	(31.3)	
Global health / QoL[b]	83.9	(17.6)	70.8	(19.8)	
Insomnia[b]	14.1	(21.4)	32.1	(35.7)	
Fatigue[b]	23.5	(23.6)	42.1	(27.8)	
Pain[b]	5.1	(14.7)	20.2	(24.9)	
Dyspnea[b]	10.3	(20.6)	22.6	(28.8)	
Constipation	17.9	(35.6)	19.0	(34.5)	
Appetite loss[a]	20.5	(36.6)	13.1	(26.2)	
Diarrhea[a]	21.8	(28.2)	27.4	(31.5)	
Nausea, vomiting	8.3	(13.5)	10.7	(17.7)	
Financial difficulties[b]	5.1	(20.4)	20.2	(36.7)	
HADS total	5.5	(4.6)	13.0	(8.7)	$p < 0.001$
IES total	6.6	(8.5)	23.1	(19.2)	$p < 0.001$
HADS total > 11	50.0%		15.4%		$p = 0.007$
IES total > 26	35.7%		3.8%		$p = 0.004$

[a] small difference 5 - 10 points; [b] medium difference 10 - 20 points; [c] large difference > 20 points. EORTC-QLQ-C30: quality of life module; HADS: Hospital Anxiety and Depression Scale; IES: Impact of Event Scale.

Characteristics of fear of cancer recurrence/progression

Demographic and medical variables

Correlation analyses revealed no association between age and FCR ($r = -0.18$, $p = 0.19$) or between time since initial diagnosis and FCR ($r = 0.12$, $p = 0.39$). χ^2 testing also did not reveal categorical medical (disease phase, risk estimation, primary treatment, disease status, active TKI treatment) or demographic (gender, partner, children) variables to be associated with FCR in either patient group.

Multidimensional aspects of fear of cancer recurrence / progression

MANOVA revealed a significant difference in the variables of the FRCI between patients who experienced high and low FCR ($F(6,47) = 9.5$, $p < 0.001$; partial eta squared = 0.55). Moreover, all dependent variables were significantly different between the two groups after Bonferroni correction (Table 4).

Table 4. Means and standard deviations FCRI

	Low FCR	High FCR		
Questionnaire	Mean (sd)	Mean (sd)	Mean difference (95% CI)	p-value
FCRI				
Severity**	13.5 (8.0)	27.7 (7.8)	-14.2 (-18.5- -9.9)	< 0.001
Psychological distress**	2.5 (2.5)	7.8 (4.2)	-5.3 (-7.2- -3.4)	< 0.001
Functioning impairments**	2.0 (3.1)	7.7 (6.5)	-5.7 (-8.5- -2.9)	< 0.001
Triggers**	8.4 (6.6)	17.6 (6.4)	-9.3 (-12.8 to -5.7)	< 0.001
Insight*	0.3 (0.7)	2.5 (3.2)	-2.3 (-3.5 - -1.0)	< 0.001
Reassurance*	0.9 (1.4)	2.6 (2.3)	-1.7 (-2.8- -0.7)	< 0.002

* $p < 0.05$; ** $p < 0.001$

DISCUSSION

This is the first exploratory study to investigate FCR and one of the very few reporting on quality of life and distress in adult patients with GIST. Only one study has focused on the general health of pediatric and adult GIST patients, reporting that individuals living with GIST experience chronic pain, post-traumatic symptoms and significant anxiety [20]. Compared with the quality of life of a reference group of cancer patients with mixed diagnoses at different disease stages, as assessed by the EORTC Quality of Life Group [21], the results of this study demonstrate that the global quality of life of adult GIST patients appears to be good, with GIST patients showing a better quality of life, physical, role, emotional, and social functioning than the reference patients, and a comparable cognitive functioning. In contrast, the GIST patients reported more problems with diarrhea than the reference patients. We found medical variables not to be associated with quality of life, and patients had low to moderate levels of distress. Interestingly, quality of life differed between patients who experienced high and low FCR, with patients with high FCR having a poorer emotional, role, cognitive, and social functioning and reporting more problems than the patients with low FCR and the reference cancer population. This shift in scores was also observed for the distress measures, indicating that patients who experienced high FCR also experienced significantly more general and cancer-specific distress than did patients who experienced less fear.

Thus while the overall quality of life seems to be better in GIST patients than in other patients with other cancers, a substantial proportion of the GIST patients (52%) reported being very fearful about cancer recurrence/progression. This is consistent with a study showing that, across different cancer sites and assessment strategies, on average 49% of cancer survivors experience moderate to severe FCR [22]. We found that the patients who experienced high FCR had more functional impairments in work, daily, and social activities, and difficulty in making plans for the future than did patients who experienced less FCR. In the systematic review of Koch and Crist [23], younger age was consistently associated with a greater FCR, whereas contradictory findings were reported for gender, educational status, marital status, and having children. We found that none of the patient characteristics were associated with FCR, and that time since diagnosis was not associated with the severity of FCR. There is mixed evidence for an association between cancer and treatment-related factors and FCR. As we found no associations between patient characteristics or cancer- and treatment-related variables, we looked for other explanations for the high proportion of fearful patients. Nowadays, GIST patients, even those with metastatic disease, can survive for a relatively long time, thanks to the availability of different treatment protocols involving TKIs. In the evaluation of this long-lasting treatment, patients are frequently evaluated with imaging modalities such as computed tomography (CT) scans. In this respect also patients who have been operated with curative intent have frequent evaluations aimed at the eventual detection of relapse of disease. Cancer patients typically feel very anxious and uncertain in the weeks before medical check-ups or consultations, worrying about their medical status and the results. Afterwards, they emotionally process the information and results given in the consultation. Thus each medical consultation is an important event accompanied by feelings of distress and uncertainty, especially if there is a high risk of cancer recurrence [24]. It is a challenge for both oncology professionals and patients to find a balance between the medical need for follow-up and the psychological issues associated with these visits. Although the administration of potentially toxic and expensive agents necessitates frequent evaluation, the frequency of follow-up visits should be established bearing in mind the psychological distress these visits cause and the risk of disease progression. It might be a case for shared decision making in which the oncology professional and the patient communicate about the medical priority of frequent follow-up investigations and the distress patients experience. Patients can even experience less distress when they are informed beforehand about expected effects of certain choices. Therewith it can prevent them from automatically attributing normal GIST-related physical symptoms or side effects (internal triggers) to progression or recurrence of the disease. With regard to external triggers, patients nowadays have access to various sources of information. Via the Internet or publications (magazines/newspapers), and with the existence of patient associations, many GIST patients have relatively easy access to websites containing disease-specific information. While this type of information may reassure patients, reducing uncertainty [24,25], it may generate anxiety because not all information that is available is relevant or applicable to the individual patient at that moment [24]. This is particularly true for GIST patients, given the diversity of medical variables (high risk vs. low risk, local tumor vs. metastasized, surgery vs. additional treatment) in the patient population. Patients would be better discussing their specific case and need for information with their oncologist because he/she can focus on the individual situation and estimate the relevance of information to the individual patient and tailor the information provided accordingly [24].

This study had a number of limitations. The patient sample was rather small (n=54), but the response rate was adequate (64%) and statistically and clinically relevant differences were found between the patients with high and low FCR. Another limitation concerns the use of the CWS to differentiate between these two groups of patients. The CWS was validated in breast cancer survivors and it may overestimate or underestimate the proportion of patients with GIST who experience FCR. However, another instrument, the FCRI, also revealed significant between-group differences on all subscales, indirectly validating the use of the CWS.

For future research it would be interesting to study the natural course of fear, taking into account the many check-up consultations that patients have to attend, and to identify predictors of high FCR. As we now have a wider knowledge of tumor-based molecular prognostic factors, it is time to focus on individual patient factors, in order to support patients living with GIST.

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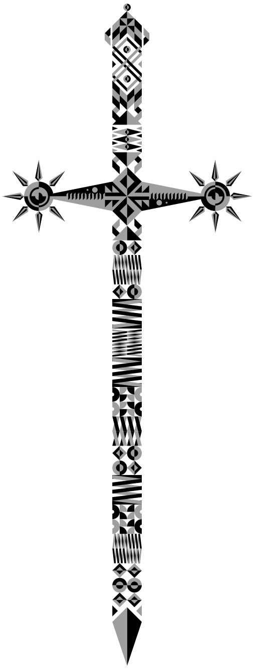

Chapter 5

Fear of cancer recurrence in colorectal cancer survivors

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ABSTRACT

Purpose Although long-term colorectal cancer (CRC) survivors generally report a good quality of life, fear of cancer recurrence (FCR) remains an important issue. This study investigated whether the Cancer Worry Scale (CWS) can detect high FCR, the prevalence, and characteristics of FCR in CRC survivors.

Methods Two hundred and eleven patients who had undergone successful CRC surgery in the period 2003 - 2010 in the Radboud University Medical Center in the Netherlands were asked to participate. All patients were sent an information letter plus questionnaires for collecting information on demographic and medical variables, FCR, distress, and quality of life.

Results Seventy-six patients (36%; median age of 67.7 years range 41-88 years) completed the questionnaires a median of 5.1 years after surgery. A cut-off score of 14 or higher on the CWS was optimal to detect high FCR. Twenty-nine patients (38%) experienced high levels of FCR, characterized by higher levels of distress, post-traumatic stress symptoms and lower quality of life. These individuals particularly reacted to disease-related triggers, felt helpless, were worried, and experienced limitations in daily functioning. High FCR was not associated with demographic or medical variables.

Conclusion Long after successful CRC surgery, FCR is a serious problem that impairs the quality of life for a substantial proportion of patients. With the CWS, it is possible to detect high FCR and thereby assist survivors in receiving appropriate care.

INTRODUCTION

Early detection and improved cancer treatment have increased the survival rate of colorectal cancer (CRC) over the past decades [1]. This has made it important to pay attention to the way survivors deal with chronic or late effects of the disease and its treatment. A number of recent studies have investigated the quality of life (QoL) of CRC survivors and have shown that while QoL is reduced after treatment completion, it gradually improves over time in the absence of disease recurrence or progression [2-5]. While a systematic review found long-term CRC survivors to have good overall QoL [6], this does not necessarily mean that these individuals do not experience problems that can influence their daily functioning. Not only can CRC survivors have specific physical complaints, such as fecal, urinary, or sexual disorders [7], but they might also have an unmet need for psychosocial help with regard to fear of cancer recurrence (FCR) [8]. FCR can be defined as the fear or worry that the disease will return or progress in the same organ or in another part of the body [9]. While a normal level of FCR can keep a person alert and aware of symptoms [10], high levels of FCR can adversely affect a person's quality of life and social activities [11-14]. Patients may focus obsessively on symptoms [10], which can restrict their ability to plan for the future and can lead to numerous unscheduled doctor appointments [15,16]. Among the few studies reporting FCR in CRC survivors the prevalence of high FCR ranges between 4% and 85% [17-22]. This wide range of percentages high FCR might be attributed to the fact that there is no consensus about what are clinically relevant levels of FCR. Furthermore, it might be attributed to the use of various instruments to measure FCR for which there are few or no psychometric data or cut-off points available [10]. In the research on FCR in CRC patients, some studies did not use a FCR specific measure [18,21], whereas others had lacking data on validity [17,19,20]. Therewith, interpretation and comparison of percentages high FCR is difficult. Recently, a semi-structured interview to identify patients with clinical levels of FCR was developed by Simard and Savard [22]. Based on this interview, cutoff scores on the severity subscale of the Fear of Cancer Recurrence Inventory (FCRI-SF) were determined. Therewith, it is possible to use this scale as gold standard measure for evaluating the criterion validity of different FCR scales. The aim of this study is to assess the capacity of the Cancer Worry Scale (CWS), validated in a sample of breast cancer survivors [23], as an instrument to detect high levels of FCR in a sample of CRC survivors. Furthermore, there has been little research on FCR in CRC survivors, its characteristics, and potential risk groups, mainly because earlier studies focused on the severity and prevalence of FCR. There is a lack of information about what specific triggers make survivors fearful, which strategies they use to cope with this fear, and the concrete consequences of FCR in daily life. This study focuses on the prevalence and characteristics of FCR in CRC survivors.

METHODS

Participants

In March 2012, participants were recruited from the Department of Surgery, Radboud University Medical Center, Nijmegen in the Netherlands. CRC survivors who had been treated with curative intent and who were disease-free (no recurrence or metastases) 1-9 years after surgery were eligible for inclusion. Participants had to be able to read and write in Dutch.

Procedure

Documented approval from the local Medical Ethics Committee was obtained prior to start of the study. Contact data of CRC survivors were obtained by a surgeon (JW), and these individuals were sent a letter describing the purpose of the study and a booklet with questionnaires on demographic variables and psychological factors. Participants gave their informed consent by returning the booklet. Clinical data were extracted from medical records by one of the researchers [SJ].

Instruments

Fear of cancer recurrence: severity

The CWS is used in research to assesses concerns about developing cancer or developing cancer again and the impact of these concerns on daily functioning. The eight items of the CWS are rated on a 4-point Likert scale ranging from “Never” to “Almost always”. Scores range from 8 to 32 [24]. A diagnostic cut-off score of 14 or higher (sensitivity 77%; specificity 81%) was validated for breast cancer survivors and indicates raised levels of FCR [23].

Fear of cancer recurrence: multidimensional aspects

The Fear of Cancer Recurrence Inventory (FCRI) was developed to assess the multidimensional aspects of FCR. The FCRI consists of seven subscales: triggers, severity, psychological distress, coping strategies, functioning impairments, insight, and reassurance. The 42 items are rated on a 5-point Likert scale ranging from 0 to 4. The FCRI is a reliable and valid self-report scale [25].

The subscale *Triggers* includes eight items, of which seven assess specific situations that make one think about the possibility of cancer recurrence; one item assesses to what degree these situations are generally avoided. The subscale *Severity* includes nine items assessing the presence, frequency, intensity and duration of thoughts associated with FCR, the perceived risk of recurrence, the legitimacy of worrying about cancer recurrence, and the presence of other unpleasant thoughts or images that come to mind in association with FCR. Recently, data were provided that this subscale may also be used as FCRI-short form to screen for clinical levels of FCR. A score of 13 or higher was optimal for screening whereas a score of 16 or higher was the optimal diagnostic cut-off [22]. The subscale *Psychological Distress* includes four items for emotions frequently triggered by thoughts about cancer recurrence. The subscale *Coping Strategies* assesses nine strategies that may be used to cope with FCR including denial, wishful thinking, or cognitive avoidance.

The subscale *Functioning Impairments* includes six items representing domains that can be disturbed by FCR. The subscale *Insight* includes three items and assesses the extent to which patients perceive their fear as excessive or unreasonable. The subscale *Reassurance* includes three items representing reassurance behaviors specific to FCR.

Distress: cancer-specific

The Impact of Event Scale (IES) was included to assess the frequency of intrusive and avoidant phenomena after or during the traumatic experience of cancer. Its 15 items (scoring 0,1,3,5) are divided into two dimensions: "Intrusion" (7 items) and "Avoidance" (8 items). A total score of 9-25 reflects moderate adaptation difficulties; a score higher than 26 indicates serious adaptation difficulties [26,27].

Distress: general

General distress was measured with the total score of the Hospital Anxiety and Depression Scale (HADS). This questionnaire includes 14 items divided into two subscales (Depression and Anxiety), each with seven items. Higher scores indicate more anxiety, depression, and psychological distress. The HADS does not contain any somatic items that could be confounded with symptoms associated with a physical illness. A total score of 11 or higher indicates high distress [28,29].

Quality of life: cancer-related

Quality of life related to CRC was measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Colorectal Cancer Module (QLQ-CR38). In this study, only scores for the functional scales and global health scale were analyzed. Higher scores on functional scales indicate better functioning and quality of life. All scores are transformed linearly and range from 0 to 100 [30,31]. A difference of 5-10 points was considered small; 10-20 points medium, and > 20 points large [32].

Data-analyses

Prior to SPSS (version 20.0) data analysis, all relevant data were screened for normality and showed normal distributions. Means and frequencies, were used to describe the sample. Only complete data for the CWS were analyzed; incomplete data were recorded as missing data and excluded from the analyses. Receiving operating characteristics (ROC) analysis was conducted to evaluate the performance of the CWS by providing information relevant to the full range of scores that need to be taken into account in making a threshold for high FCR in a population of CRC survivors. The accuracy properties sensitivity, specificity, and positive and negative predictive values were assessed at each cut-off point of the CWS against the FCRI-SF. Furthermore, the area under the ROC curve and its 95% confidence interval were examined. To differentiate high FCR from low FCR, an optimal cut-off point should have high sensitivity and specificity, which maximizes the proportion of patients whose test results are accurate [33].

Multivariate ANOVAs were performed for continuous variables, to assess differences between high and low FCR, based on the cut-off score (low: ≤13; high ≥14). Chi-square analyses were performed to assess differences between high and low FCR with regard to categorical variables. Pearson product moment correlations and independent sample *t* tests were used to assess relations between continuous variables.

For a descriptive analysis of the FCRI scores, percentages of responses to the individual questions were calculated. In order to reflect the degree of involvement with a specific item, varying from small to moderate or large, answers on the subscales Triggers, Coping and Reassurance were combined into three answer categories (1) "never/rarel", (2) "sometimes", (3) "most of the time/all the time". Answers on the subscales Severity, Psychological Distress, Functioning Impairments, and Insight were also divided into three answer categories (1) "not at all/a little", (2) "somewhat", (3) "a lot/a great deal".

RESULTS

Sample characteristics

Of 211 CRC survivors asked to participate in the study, 80 (38%) returned the questionnaires, and 76 (36%) of whom completed the CWS and were included in the analyses. There was no difference between responders and non-responders with regard to gender (X^2 (1, 211) = 0.03, $p = 0.87$), but non-responders were significantly older ($t(209) = 2.0$, $p = 0.046$). Table 1 shows the demographic and medical characteristics of the responders.

Table 1. Sample characteristics (n = 76)

Age (years)	Median 67.3; range = 41-88	
Sex: male	40	53%
Marital status		
Married/partnership	55	72%
Not in partnership	21	28%
Children: yes	64	84%
Educational level		
Primary	3	4%
Secondary	43	57%
Tertiary	25	33%
Other	5	7%
Employment status		
Retired	44	58%
Employed	20	26%
Home management	12	16%
Unemployed/others	15	20%
Time since surgery (years)	Median 5.1; range = 1.3 – 9.2	
Location of tumor		
Colon	58	76%
Rectum	18	24%
Stoma: yes	13	17%
Disease stage		
I	13	17%
II	31	41%
III	32	42%
Additional treatment		
Chemotherapy: yes	24	32%
Radiotherapy: yes	10	13%

ROC analysis

The area under the curve of the ROC analysis showed an 92% ($p<0.001$; 95%CI=0.85-0.98) probability that a randomly selected patient defined as a case by the FCRI-SF (≥16) scores higher on the CWS than a randomly selected patient defined as a non-case (Fig. 1). On the basis of the ROC curve, the optimal cut-off score to differentiate between high FCR and low FCR was 13 versus 14 (low ≤13, high ≥14), with a sensitivity of 86% and a specificity of 87%. The positive and negative predictive values were 76 and 93% respectively (Table 2).

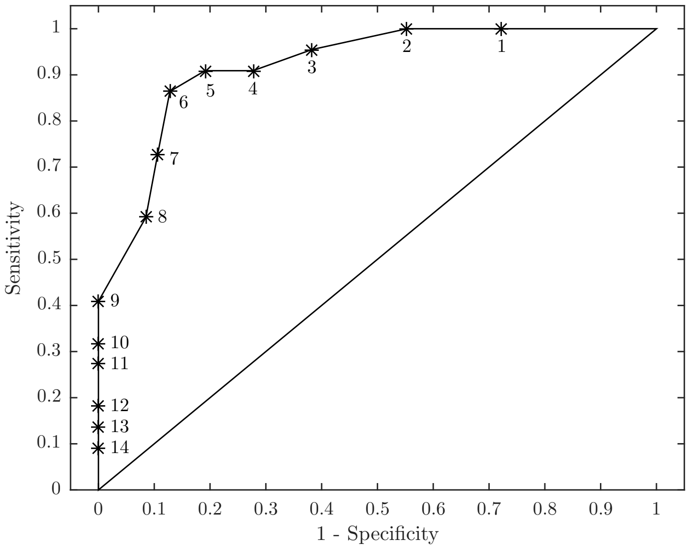

Fig. 1 Receiver operating characteristics curve of Cancer Worry Scale (CWS) scores against the FCRI-SF ≥16. Labeled points correspond to the CWS scores as follows: 1: 8 versus 9; 2: 9 versus 10; 3: 10 versus 11; 4: 11 versus 12; 5: 12 versus 13; 6: 13 versus 14; 7: 14 versus 15; 8: 15 versus 16; 9: 16 versus 17; 10: 17 versus 18; 11: 18 versus 19; 12: 20 versus 21; 13: 22 versus 23; 14: 23 versus 24.

Table 2. Accuracy measures for CWS scores according to FCRI-SF

CWS cut-off Score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
8 vs 9	100	28	39	100
9 vs 10	100	45	46	100
10 vs 11	96	61	54	97
11 vs 12	91	72	61	94
12 vs 13	91	81	69	95
13 vs 14	86	87	76	93
14 vs 15	73	89	76	88
15 vs 16	59	92	76	83
16 vs 17	41	100	100	78
17 vs 18	32	100	100	76
18 vs 19	27	100	100	75
20 vs 21	18	100	100	72
22 vs 23	14	100	100	71
23 vs 24	9	100	100	70

NPV negative predictive value, *PPV* positive predictive value

Reliability and measure of agreement

The CWS yielded a high internal consistency reliability coefficient, Cronbach α = 0.89. The correlation between the CWS and FCRI-SF was $r = 0.85$. In 87% of the cases, there was agreement between the CWS and FCRI-SF concerning the presence or absence of a FCR diagnosis reflecting a Cohen's kappa of 0.71 (SE 0.09).

Prevalence and multidimensional aspects of high FCR

According to the established cut-off point of 14 or higher on the CWS, 29 survivors (38%) had high levels of FCR. These individuals experienced significantly more psychological

Table 3. Means and standard deviations of the psychosocial variables

	Low FCR (*n*=47) **CWS < 14**		**High FCR (*n*=29)** **CWS ≥14**		
EORTC QLQ-C30	Mean	SD	Mean	SD	*p* value
Global health / QoL[c]	77.6	(19.1)	56.7	(26.7)	$p<0.001$
Physical functioning[b]	81.1	(21.9)	68.5	(30.7)	$p=0.052$
Role functioning[c]	81.7	(24.1)	59.6	(38.1)	$p=0.004$
Emotional functioning[c]	93.5	(11.3)	72.4	(23.9)	$p<0.001$
Cognitive functioning[b]	86.5	(18.9)	68.6	(25.1)	$p=0.001$
Social functioning[c]	93.7	(12.7)	62.8	(38.7)	$p<0.001$
EORTC QLQ-CR38					
Body image[c]	91.4	(15.1)	70.4	(32.8)	$p<0.001$
Sexual functioning	23.0	(22.6)	20.4	(19.8)	$p=0.623$
Future perspective[c]	88.9	(15.9)	56.8	(27.4)	$p<0.001$
General distress					
HADS total	5.5	(5.0)	13.8	(6.9)	$p<0.001$
Cancer-specific distress					
IES total	2.8	(6.3)	15.4	(14.6)	$p=0.001$
Intrusion	1.9	(3.9)	8.2	(7.9)	$p=0.001$
Avoidance	0.9	(2.5)	8.0	(7.4)	$p<0.001$
FCRI					
Triggers	6.3	(5.6)	15.5	(5.6)	$p<0.001$
Psychological distress	1.9	(2.0)	7.6	(3.5)	$p<0.001$
Functioning impairments	1.1	(2.1)	6.9	(5.3)	$p<0.001$
Insight	0.3	(0.7)	2.1	(2.2)	$p<0.001$
Reassurance	1.1	(2.0)	2.9	(3.1)	$p=0.005$

[a] small difference 5 - 10 points

[b] medium difference 10 - 20 points

[c] large difference > 20 points

distress, functional impairments, and triggers, showed more insight and sought reassurance more often than the individuals with lower levels of FCR (Table 3).

Relationship between FCR and demographic and medical variables

There were no differences in age ($t(74) = 1.58$, $p = 0.12$) or time since surgery ($t(74) = -0.31$, $p = 0.76$) between survivors with high or low levels of FCR. Chi-square tests showed categorical demographic (gender, partnership, children, educational level, employment status) and medical variables (location of tumor, stoma, disease stage, additional treatment) not to be associated with FCR.

Relationship between FCR and distress

Survivors with high levels of FCR experienced significantly more general distress ($t(73) = -5.4$, $p < 0.001$) and cancer-specific distress ($t(26.5) = -3.9$, $p = 0.001$) characterized by post-traumatic stress symptoms including significantly more intrusive ($t(31.3) = -3.8$, $p = 0.001$) and avoidant ($t(27.2) = -4.6$, $p < 0.001$) phenomena after the traumatic experience of cancer, than did survivors with low levels of FCR (Table 3).

Relationship between FCR and quality of life

Compared with low levels of FCR, high levels of FCR were associated with a poorer quality of life ($F(1,66) = 14.1$, $p <0.001$) more impaired role functioning ($F(1,66) = 8.7$, $p = 0.004$), emotional functioning, ($F(1,66) = 24.0$, $p <0.001$), cognitive functioning ($F(1,66) = 11.2$, $p = 0.001$), and social functioning ($F(1,66) = 22.9$, $p <0.001$). Moreover, there were large (>20 points) clinically relevant differences between survivors with a high or low FCR in global quality of life, role functioning, emotional functioning, and social functioning. Survivors with a high FCR had significantly more problems with body image ($F(1,70) = 13.7$, $p <0.001$) and future perspective ($F(1,70) = 39.6$, $p <0.001$) than did survivors with a low FCR (Table 3).

Descriptive analyses FCRI

Triggers Medical examinations, feeling sick or physically unwell, and an appointment with the doctor or other health professional were the most frequently reported triggers for high FCR with 48, 45 and 38% respectively reporting them “most of the time” or “all the time”.

Psychological distress When survivors with high FCR thought about the possibility of cancer recurrence, they felt helpless or resign and expressed worry, fear, or anxiety with 34 and 31% respectively reporting them “most of the time” or “all the time”.

Functioning impairments High FCR disrupted the ability to make future plans or set life goals, relationships with partner/ family, and general quality of life with 18, 17, and 17% respectively reporting them "most of the time" or "all the time".

Insight Most survivors with high FCR did not feel that they worried excessively about the possibility of cancer recurrence or that other people thought they did with 76 and 86% respectively reporting this "not at all" or "a little".

Reassurance Survivors with high FCR sought reassurance by going to the hospital or clinic for an examination or calling their doctor or another health professional with 21 and 21% respectively reporting them "most of the time" or "all the time". Few such individuals examined themselves to see if they have any physical signs of cancer with 10.7% reporting this "most of the time" or "all the time".

Coping strategies Survivors with high FCR coped with this fear by trying to convince themselves that everything would be fine or think positively, trying to find a solution, and trying to replace this thought with a more pleasant with 39, 36, and 32% respectively reporting them "most of the time" or "all the time".
These individuals did not use coping strategies such as praying, meditating or relaxation, trying to distract themselves, or trying not think about it with 75, 61 and 57% respectively reporting them "never" or "rarely".

Severity The thought that it is normal to be anxious or worried about the possibility of cancer recurrence and the experience of a lot of other unpleasant thoughts or images such as death, suffering, consequences for family when thinking about the possibility of cancer recurrence were most frequently reported with 61 and 52% respectively reporting them "most of the time" or "all the time".

DISCUSSION

This is one of the few studies to specifically focus on the prevalence and features associated with FCR in CRC survivors. FCR remains a significant problem for some CRC survivors even years after diagnosis, when routine follow-up care has normally ended. This study supported the reliability and criterion validity of the CWS in a sample of CRC survivors. Furthermore, the CWS showed good discriminatory power relative to the FCRI-SF, indicating that it is an appropriate instrument to identify those individuals who experience high FCR. Similar to the validated cut-off score in a sample of breast cancer survivors [23], a cut-off score of 14 or higher was optimal for differentiating a case from a non-case. With this cut-off point, about one third (38%) of the survivors experienced high levels of FCR a median time of 5 years after surgery. Levels of FCR were not different for men or women, age, or medical characteristics. These findings are partly in line with the recent systematic review of Simard and colleagues [11] which showed moderate evidence (4 studies evidence; 12 studies no evidence) for a relation between FCR and gender, and only weak to moderate evidence for a relation with disease and treatment characteristics. Although a relation between FCR and age is often observed in the literature, there was no significant correlation in this study. A possible explanation could be that there participated both males and females in this study. The systematic review of Simard and colleagues[11] namely revealed that in 18 studies, of which eight included samples of only males, no significant relationship with age was found. It might be the case that there is no association between age and FCR in male cancer survivors, and therewith, the relationship in this mixed sample disappeared.

In accordance with previous studies, the CRC survivors in this study reported a good global quality of life [6]. However, there were large statistically and clinically relevant differences between individuals who reported high or low levels of FCR, with high FCR being associated with a lower general quality of life, lower emotional functioning, role functioning and social functioning, and more problems with body image and future perspective. Furthermore, individuals with high FCR had higher levels of general distress and post-traumatic stress symptoms, such as avoidance and intrusions. This is consistent with the results of studies among cancer patients reporting that intrusive thoughts are more frequently related to future-oriented fears, such as FCR [34-38]. Simard and colleagues [13] revealed that the nature of these intrusive thoughts associated with FCR shares characteristics with worries, negative and uncontrollable thoughts on an issue whose outcome is uncertain but which contains the possibility a negative outcome[39]. More severe FCR tends to resemble obsession, defined as recurrent thoughts and images, experienced as intrusive and inappropriate, causing anxiety and psychological distress [40]. This was also supported by the results of this study since CRC survivors with high FCR reported unpleasant thoughts or images such as death, suffering, or consequences for family when thinking about the possibility of cancer recurrence as one of the most frequently occurring features of FCR. Furthermore, the results showed that high FCR is characterized by reactions to specific triggers, negative thoughts and feelings accompanied by reassurance behavior. Interestingly, reassurance behavior mainly consisted of contact with one's medical professional. Body checking occurred less frequently. An explanation for this finding might be that it is more difficult for CRC survivors to check their body for symptoms of recurrence than for breast cancer survivors. CRC survivors might be more focused on their defecation than on their body. Since CRC survivors with high FCR do not experience their fear as excessive or unreasonable (insight) but the focus seems meanwhile to be on dysfunctional thoughts or behaviors, CRC survivors with high FCR may benefit from cognitive behavior therapy [41-44].

The study had some limitations. The low response rate (38%) and small sample size means that results might not be representative. It is possible that survivors who have been disease-free for a number of years might not want to think about hospitals and cancer research. Alternatively, it might be the survivors with the most severe problems, with high levels of FCR, or distress who do not participate. Despite the small sample size, statistically and clinically relevant differences were found between individuals with high and low levels of FCR, and descriptive analysis was possible.

Another limitation is the difference between responders and non-responders, which could be indicative of selection bias. However, compared to the Dutch cancer population at the time of this study, age categories, and gender distribution were quite similar, indicating that is was a representative sample [45].

Although reliability and criterion validity of the CWS were established in a population of CRC survivors, not all components of validity were assessed. Future research should address multiple components of validity.

CONCLUSIONS

This study emphasizes the need to focus on specific problems rather than general QoL, but these findings should be confirmed with a larger sample using a prospective design. We are currently investigating FCR, distress, and QoL in the first year after the diagnosis of CRC. Future research should aim to develop an evidence-based intervention for CRC survivors with high FCR, and the results of the current study may provide starting points for such an intervention.

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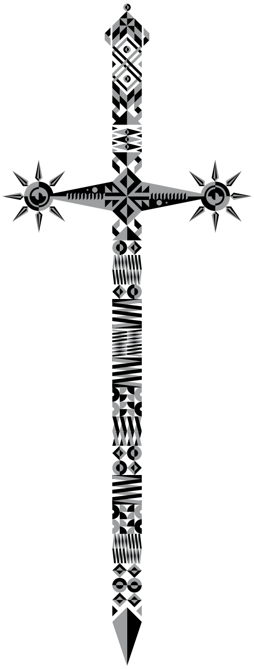

Chapter 6

Towards an evidence-based model of fear of cancer recurrence for breast cancer survivors

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In revision.

ABSTRACT

Background In understanding fear of cancer recurrence (FCR), it is important to conceptualize it as a multidimensional problem in which internal or external cues trigger interpretations and cognitions of the threat of cancer, leading to an increase of fear. This fear may result in dysfunctional behaviors, such as limited planning, body checking and seeking professional advice, again enhancing an increased fear response. This study simultaneously assessed the relations in the hypothesized model of FCR.

Methods 1205 breast cancer survivors, 0-5 years after the end of primary breast cancer treatment were invited to participate in this study. Participants received a questionnaire booklet including questionnaires on demographics and psychosocial variables including FCR. Data analysis consisted of the estimation of direct and indirect effects in simple and multiple mediator models.

Results A total of 460 women (38%) participated in the study. Median age was 55.8 years (range 32 – 87). Indirect effects via FCR were found for all mediation models with limited planning (R^2=.28) and body checking (R^2=.11-.15) as behavioral response variables, with the largest effects for limited planning. A direct relation was found between feeling sick and seeking professional advice, not mediated by FCR. Different moderators were found for each of the models tested.

Conclusions In the first tested models of FCR, all internal and external cues were associated with higher FCR. In the models with limited planning and body checking as behavioral response, an indirect effect of cues via FCR was found. An evidence-based model of FCR may facilitate the development of appropriate interventions to manage FCR in breast cancer survivors.

INTRODUCTION

With increasing breast cancer survival rates, it has become more important how survivors deal with psychosocial consequences of the disease and treatment. After curative treatment and in the absence of a physical threat, breast cancer survivors frequently have worrying thoughts about 'the possibility that the cancer may return or progress in the same organ or in a different part of the body', which is widely adopted as definition for fear of cancer recurrence (FCR) [1]. Among breast cancer survivors FCR is commonly identified as an unmet psychosocial need for which they want help [1-6]. When FCR becomes severe it coincides with psychological distress, lower quality of life and functional impairments [7-9]. Since guidelines for the treatment of FCR are lacking, health care providers often do not know how to deal with FCR. In developing adequate care, identifying potential targets for interventions is important. Furthermore, available models in which possible predictors are part of a multidimensional entity are scarce. Only three theoretical models have been presented in literature; two therapeutic models developed to guide new interventions [10,11] and the explanatory model of Lee-Jones which is most often cited by researchers [12]. All three models incorporate the cognitive and emotional reaction to cues. None of these models have been tested.

Lee-Jones and colleagues (1997) proposed a theoretical model based on Leventhal's Self Regulation Model of Illness [13]. This self-regulation model hypothesizes that external and internal stimuli generate a subjective perception of a somatic problem or health threat and concomitant emotions (eg., fear/distress), leading to coping strategies and appraisal of health outcomes. Representations, coping strategies, and appraisal are affected by self and social context.

Leventhal's theoretical framework is not specific to FCR. However, it gives insight in why patients react differently to the news that they have cancer and why some are more fearful than others for cancer recurrence. In accordance with Leventhal's model, Lee-Jones and colleagues hypothesized that a person's FCR will vary depending on their cognitive reaction to illness. The formulation of FCR proposed that cues play a role in activating cognitive responses associated with FCR. On the one hand internal (somatic) cues are interpreted as reminders of the disease or as threat that the illness may have returned. On the other hand external cues associated with the disease (eg., medical check-ups, exposure to media) will increase worrying thoughts about a possible recurrence. High FCR can result in anxious preoccupations followed by personal checking behavior, uncertainty, and consequently limited planning for the future, or misinterpretation of neutral bodily symptoms and, as a consequence, seeking professional advice.

Recently, three systematic reviews on FCR revealed a growing body of research on predictors and correlates of FCR [7-9]. Overall, the three reviews demonstrated an association between FCR and age, presence or severity of physical symptoms, psycho-

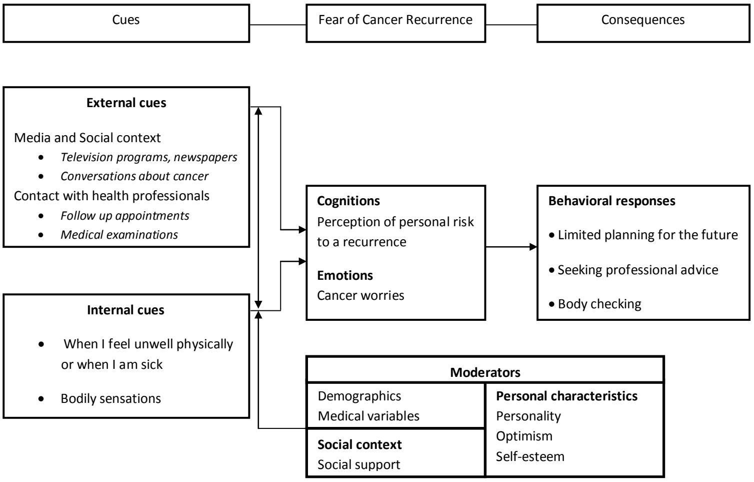

Fig. 1. Hypothesized model of FCR.

logical distress, quality of life or functioning impairments, coping responses, cues (new symptoms, pain and follow-up appointments), personality characteristics and social support. We incorporated the main findings from this literature update in the model of Lee-Jones, leading to a new model of FCR (See Fig. 1). Every women confronted with the diagnosis of breast cancer has to learn to cope with normal cues (eg., flu / television programs about cancer). It is hypothesized that women with certain characteristics that can make one vulnerable to FCR (eg., less optimism) perceive a higher personal risk of developing a recurrence which is accompanied with fear. It is also hypothesized that because of their high FCR and elevated perceived risk of recurrence, these women seek more reassurance from health professionals, frequently engage in body checking and experience limited planning for the future. The aim of the present study was to test the new hypothesized model of FCR and test the moderating and mediating relationships in the model to discover underlying mechanisms of FCR.

METHODS

Participants

1205 eligible breast cancer survivors from three hospitals in the Netherlands (Isala Klinieken Zwolle, n=461, Jeroen Bosch Hospital 's-Hertogenbosch, n=410 and Canisius Wilhelmina Hospital Nijmegen, n=334) were contacted by an information letter of their physician. It was explicitly stated in this letter that women both with and without FCR could participate. The breast cancer survivors were assessed 0–5 years after their primary treatment. To be eligible, women had to be treated with curative intent and disease-free at the time of participation. Hormonal therapy or treatment with a specific antibody (trastuzumab) were not exclusion criteria. All participants had to be able to read and write in Dutch.

Procedure

Documented approval from the local Ethics Committee was obtained prior to start of the study. By returning informed consent, the women agreed to participate. As part of an ongoing prospective study, participants received a questionnaire booklet including questionnaires on demographic, medical and psychosocial variables. Questionnaires could either be filled in online or in paper-and-pencil form.

Instruments

Cues – Internal cues

Attention to internal bodily sensations

The Body Vigilance Scale (BVS) measures the tendency to attend to internal bodily sensations (internal cues). The BVS consists of five questions. Four questions concern the degree of attentional focus, perceived sensitivity to changes in bodily sensations, the average amount of time spent attending to sensations, and the frequency of attending to bodily sensations. The fifth question concerns the severity of 13 anxiety-related bodily sensations (heart palpitations, chest pain, numbness, tingling, shortness of breath, faintness, vision changes, dizziness, hot flash, sweating/clammy hands, upset stomach, nausea, choking/throat closing). Items are rated on a 10-point VAS [16]. In this study Cronbach's α = .91.

Feeling sick

Feeling sick as internal cue was assessed with a single item of the subscale Triggers of the Fear of Cancer Recurrence Inventory (FCRI): 'When I feel unwell physically or when I am sick, I think about the possibility of cancer recurrence'. This item is rated on a 5-point Likert scale ranging from 0-4. The FCRI is a reliable and valid self-report scale [17].

Cues – External cues

External cues – contact with health professionals

External cues related to contact with health professionals were measured with two items of the subscale Triggers of the FCRI: 'An appointment with my doctor or other health professional' and 'Medical examinations make me think about the possibility of cancer recurrence'. Both items are rated on a 5-point Likert scale ranging from 0-4 [17]. In this study Cronbach's α = .84.

External cues – media and social context

External cues related to the media and social context were assessed with four items of the subscale Triggers of the FCRI: 'Television shows or newspaper articles about cancer or illness', 'Conversations about cancer or illness in general', 'Seeing or hearing about someone who is ill' and 'Going to a funeral or reading the obituary section of the paper make me think about the possibility of cancer recurrence'. Items are rated on a 5-point Likert scale ranging from 0-4 [17]. In this study Cronbach's α = .89.

Fear of cancer recurrence – Cognitions and emotions

Fear of Cancer Recurrence: severity

The Cancer Worry Scale (CWS) has been used in research to assesses concerns about developing cancer (again) and the impact of these concerns on daily functioning. The eight items of the CWS are rated on a 4-point Likert scale ranging from 'Never' to 'Almost always'. Scores range from 8 to 32 [18]. The CWS was validated for breast cancer survivors. A diagnostic cut-off score of 14 or higher (sensitivity 77%; specificity 81%) indicates severe feelings of fear of cancer recurrence [19]. In this study Cronbach's α = .88.

Consequences

Limited planning for the future

Limited planning for the future was assessed with one item of the subscale Functional Impairments of the FCRI: 'my ability to make future plans or set life goals are disrupted by my thoughts or fears about the possibility of cancer recurrence'. Items are rated on a 5-point Likert scale ranging from 0-4 [17].

Seeking professional advice

Seeking professional advice was assessed with two items of the subscale Reassurance of the FCRI. 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', 'I go to the hospital or clinic for a an examination'. The items are rated on a 5-point Likert scale ranging from 0-4 [17]. In this study Cronbach's α = .85.

Body checking

Body checking was assessed with a single item of the subscale Reassurance: 'I examine myself to see if I have any physical signs of cancer'. This item is rated on a 5-point Likert scale ranging from 0-4 [17].

Moderator – Personal characteristics

Personality

Personality factors were measured by the Big Five Inventory (BFI) including Extraversion, Neuroticism, Conscientiousness, Agreeableness, and Openness to Experience. The BFI consists of 44 items, each scored on a 5-point Likert scale [20]. In this study Cronbach's α = .63.

Optimism

The Life Orientation Test (LOT) was developed to assess individual differences in generalized optimism versus pessimism. The LOT consists of 12 items, each scored on a 5-point Likert scale [21]. In this study Cronbach's α = .54.

Self-esteem

The Rosenberg Self-Esteem scale was used to measure self-esteem with 10 items scored on a 5-point Likert scale. Higher scores indicate higher self-esteem [22]. In this study Cronbach's α = .20.

Moderator – Social context

Social Support

Social support was measured by the Social Support List subscale Discrepancies (SSL-D) [23]. The SSL-D measures the perceived discrepancy in actual support and desired support. The questionnaire assesses six types of social support: emotional interactions, problem-focused emotional support, esteem support, instrumental interactions, social companionship, and informational support. Total scores of the SSL-D range from 34-102. The SSL-D has good reliability and content validity [24] and was used in studies of patients with somatic complaints [25]. In this study Cronbach's α = .94.

Data-analyses

All analyses were performed with SPSS version 20.0. Relationships between FCR and demographic and medical variables were assessed with independent sample t-tests and one-way ANOVAs. Pearson product moment correlations between FCR severity (CWS) and other variables of *r* .20 - .80 were incorporated in the model. We estimated the model parameters with PROCESS [26]. PROCESS is a plug-in for SPSS which enables easy estimation of direct effects, indirect effects, and interactions. In addition, PROCESS estimates the significance of the indirect effect using bootstrapping which is the preferred method [27]. Direct and indirect models were analyzed separately for each exogenous variable. Therewith 12 mediation models were analyzed. We could have simplified this by performing three mediation analyses, however, we also performed moderation analyses on the same mediation models. Since PROCESS does not allow moderated mediation analyses with more than one exogenous variable, we have analyzed all exogenous variables separately in the mediation analyses as well as in the moderated mediation analyses.

RESULTS

Demographic and medical characteristics

Of the 1205 women who were eligible and asked to participate in this study, 565 (47%) were interested in receiving more information about the study. Of these, 460 women signed informed consent and returned the questionnaire booklet. Study participants were compared to 539 non-responders demonstrating that participants were significantly (*t*(993,635) = 5.77, *p* <.001) younger (M = 56.69, SD = 9.6) than non-responders (M = 60.64; SD = 11.9). Of the women who filled out the CWS, 250 (55%) had high FCR according to the cut-off point >13 on the CWS. Table 1 shows the patient- and treatment-related characteristics of the sample.

Relation FCR and demographic/medical variables

With regard to demographic variables, a significant relationship was found between FCR and education (*F*(2,441) = 5.26, *p* = .006), indicating that women who completed tertiary education (M = 13.78, SD = 3.6) experienced less FCR than women who completed primary (M = 15.44, SD = 4.9) or secondary education (M = 15.00, SD = 4.2). Furthermore, there was a significant relationship between FCR and having children (*t*(445) = -2.37, *p* = .018), indicating that women with children (M = 14.94, SD = 4.3) experienced more FCR than women without children (M = 13.66, SD = 4.0). No relationship was found between FCR and age (*r* = -.04, *p* = .415), or between FCR and partnership (*t*(438) = -.13, *p* = .899). No significant relationships were found between FCR and medical variables; time since diagnosis (*r* = -.04, *p* = .381), chemotherapy (*t*(448) = -.11, *p* = .909), radiotherapy (*t*(447) = .55, *p* = .584), or hormonal therapy (*t*(448) = -.12, *p* = .906).

Table 1. Sample characteristics (*n* = 460)

Age (years)	Mean = 56.7, SD=9.6; range 32-87	
Marital status: married/partnership	367	(80%)
Children: yes	382	(83%)
Educational level		
Primary	89	(19%)
Secondary	224	(49%)
Tertiary	139	(30%)
Unknown	8	(2%)
Employment status		
Employed	217	(47%)
Home management	145	(32%)
Retired	91	(20%)
Volunteering	66	(14%)
Sick leave	37	(8%)
Disablement insurance act	33	(7%)
Unemployed / others	90	(20%)
Time since initial diagnosis (years)	Mean = 2.8; SD = 1.3	
Surgery: yes	460	(100%)
Additional treatment		
Chemotherapy	330	(72%)
Radiotherapy	348	(76%)
Hormonal therapy	296	(64%)
Trastuzumab	61	(13%)

Relation FCR and psychosocial variables

The personality factors 'conscientiousness', 'agreeableness' and 'openness to experience' were not included in the analyses because their correlation with FCR was <.20. All other psychosocial variables displayed correlations between .20 and .70.

Mediation Analysis

Fig. 2 shows the twelve conceptual models for the associations between four types of cues (external (1 and 2), internal (3 and 4)), FCR and three separate behavioral responses (A limited planning for the future; B seeking professional advice; C body checking). Results of the mediation analyses are displayed in Table 2. In all models, there was a positive significant relation between cues and FCR (pathway *a*). The relation between FCR and behavioral responses (pathway *b*) was significant in almost all models except for the model B1 'media and social context → FCR → seeking professional advice' and the model B3 'feeling sick → FCR → seeking professional advice'. In these two models there was no direct relationship between FCR and seeking professional advice. In model

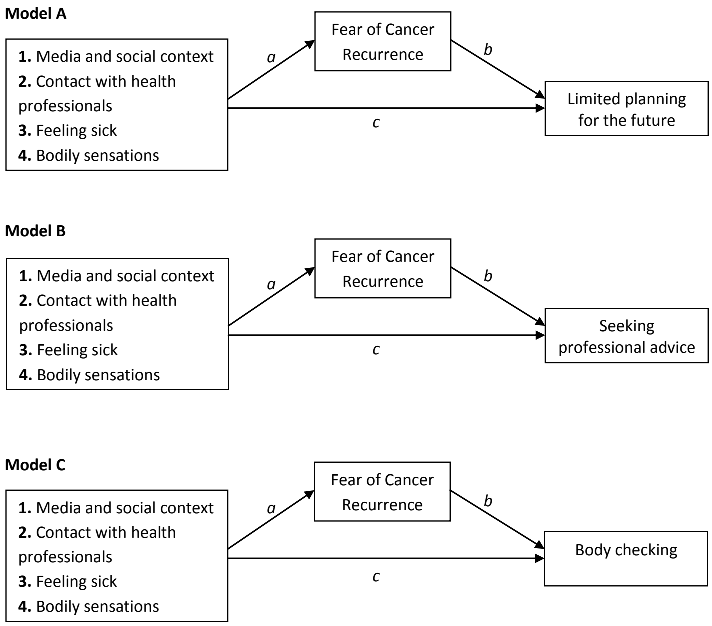

Fig. 2. Twelve models that represent the hypotheses about the triggers and consequences of FCR

Table 2. Direct and indirect effects of the individual models

Dep. Var.	Model	Trigger	R^2	*a*	*b*	*c*	Indirect effect	LLCI-ULCI[1]
Limited planning	A1	Media and social context	.278	2.64*	.128*	.000	.3397*	.2576 - .4326
	A2	Contact with health professionals	.280	1.99*	.131*	-.013	.2598*	.2009 - .3211
	A3	Feeling sick	.277	2.02*	.122*	.034	.2468*	.1784 - .3199
	A4	Bodily sensations	.282	0.19*	.132*	-.005	.0248*	.0171 - .0335
Seeking professional advice	B1	Media and social context	.026	2.64*	.021	.068	.0550	-.0262 - .1323
	B2	Contact with health professionals	.023	1.99*	.031*	-.001	.0625*	.0108 - .1207
	B3	Feeling sick	.043	2.02*	.012	.124*	.0243	-.0284 - .0938
	B4	Bodily sensations	.031	0.19*	.025*	.010	.0047*	.0006 - .0096

Table 2. Direct and indirect effects of the individual models (continued)

Dep. Var.	Model	Trigger	R^2	*a*	*b*	*c*	Indirect effect	LLCI-ULCI[1]
Body checking	C1	Media and social context	.111	2.64*	.084*	.039	.2214*	.1287 - .3096
	C2	Contact with health professionals	.117	1.99*	.076*	.099	.1522*	.0918 - .2186
	C3	Feeling sick	.124	2.02*	.073*	.118*	.1466*	.0876 - .2190
	C4	Bodily sensations	.151	0.19*	.071*	.031*	.0133*	.0071 - .0197

[1] Lower and upper limits of the bootstrap confidence interval of the indirect effect.
*p <.05

B3 however, there was a significant effect of pathway *c* indicating that feeling sick was directly associated with seeking professional advice. Furthermore, significant effects of pathway *c* were found in the models C3 and C4 with direct effects for feeling sick → body checking and bodily sensations → body checking. Indirect effects were found for all models with limited planning and body checking as behavioral response variable, with the largest effects for limited planning. For the models with 'seeking professional advice' as outcome, the indirect effect was only significant but small for the model B2 'contact with health professionals → FCR → seeking professional advice' and model B4 'bodily sensations → FCR → seeking professional advice'.

Moderated Mediation Analysis

Table 3 shows the results of the moderated mediation analysis. Social support was not found to be a significant moderator in any of the models tested. The models in which bodily sensations were defined as cues (A4, B4, C4) were not moderated by any of the moderators. Furthermore, the models that did not show an indirect effect or had really small indirect effects in the mediation analyses (B1, B3 and B4) showed no moderated mediation effect. All other models (A1, A2, A3, B2, C1, C2, C3) revealed several moderators per model. Self-esteem was the only moderator that moderated the mediation effect of all these models indicating that more self-esteem was associated with less FCR affecting the behavioral response. Neuroticism also moderated the mediation effect except for the models where 'feeling sick' was the cue (A3, C3). Optimism only moderated the mediation effect in models where the outcome variable was 'seeking professional advice' (B2) or 'body checking' (C1, C2) except for model C3 where 'feeling sick' was the cue. Last, extraversion moderated the mediation effect in model A1, C1 and C3 indicating that more extraversion was associated with less FCR affecting the behavioral response 'limited planning' and 'body checking'.

Table 3. Moderated mediation

Dep. Var.	Model	Trigger	Optimism	Self esteem	Neuroticism	Extraversion	Social Support
Limited planning	A1	Media and social context	-	-.0073*	.0699*	-.0511*	-
	A2	Contact with health professionals	-	-.0086	.0538*	-	-
	A3	Feeling sick	-	-.0056*			-
	A4	Bodily sensations	-	-	-	-	-
Seeking professional advice	B1	Media and social context	-	-	-	-	-
	B2	Contact with health professionals	-.0017*	-.0021*	.0123*	-	-
	B3	Feeling sick	-	-	-	-	-
	B4	Bodily sensations	-	-	-	-	-
Body checking	C1	Media and social context	-.0048*	-.0047*	-.0461*	-.0341*	-
	C2	Contact with health professionals	-.0041*	-.0050*	.0328*	-	-
	C3	Feeling sick	-	-.0033*	-	-.0323*	-
	C4	Bodily sensations	-	-	-	-	-

*p <.05

DISCUSSION

To the best of our knowledge this is the first study to test the hypothesized model of Lee-Jones [12]. The results showed evidence for almost all relationships in the model except for the indirect effect with seeking professional advice as behavioral response. The models with limited planning for the future as behavioral consequence showed the largest effects. In the model with seeking professional advice as behavioral response, only very small indirect effects were found for two types of cues (external triggers related to oneself; internal bodily sensations). Furthermore, there was a direct relation between feeling sick and seeking professional advice and a marginal significant direct relation between bodily sensations and seeking professional advice. These effects point in the direction that when patients experience symptoms they directly contact their health professional for advice and not as an indirect consequence of worrying thoughts or anxious feelings.

Although previous studies pointed out some moderating variables (social support [28-31]; optimism[31-35]; self-esteem[36-39]; personality factors[37]), the results of the present study showed a very inconsistent pattern. Self-esteem was the only factor that consistently moderated the indirect relationships indicating that higher self-esteem was associated with less FCR and therewith a smaller effect on the behavioral response.

However, these results should be interpreted with caution since the Cronbach's alpha of the Rosenberg Self-esteem scale was very low (α =.20) referring to a methodological problem that was not expected based on previous studies in oncology samples using this scale [39,40].

Where it was assumed that more optimistic women would experience less fear and therefore would have a more optimistic vision of the future, the results did not confirm this hypothesis. In contrast to what we expected, optimism did not moderate the mediation effect in the models with limited planning for the future as behavioral response. Again interpretation of the data is difficult since the Cronbach's alpha of the scale was suboptimal (α =.54). Neuroticism moderated the same mediation models as self-esteem except the models where 'feeling sick' was the cue. For these models no moderated mediation effect was found. This could indicate that being neurotic does not have a strengthening effect on the relationship between internal cues and higher levels of fear, as it does in the case of external cues. Extraversion was found to be an inconsistent moderator, with some models supporting it and others not. In previous systematic reviews social support was found as protector in that high levels of social support were related to lower levels of FCR [7,9]. In the present study social support was not found to be a significant moderator, which might indicate that FCR is a more intrapersonal than interpersonal phenomenon. None of the models tested which included bodily symptoms as cues were moderated. Also in the mediation models with bodily symptoms as cues, the indirect effects were small. This could probably be explained by the fact that the other types of cues and behavioral responses were derived from the FCRI which focused specifically on FCR whereas the bodily symptoms items were not filled out with respect to feelings or thoughts about FCR.

With regard to the relationship between FCR and demographic or medical variables, only lower education and having children were associated with higher FCR. Although age is commonly reported in literature reviews [7-9] to be associated with FCR, we did not find a relationship in this study. The association between FCR and age might already have been present before the start of the study since study participants were significantly younger than non-respondents. Since participants were aware of the fact that the purpose of the study was FCR, it is plausible that there was already a selection in signups for the study as confirmed by the moderate response rate of 38% and the relatively high percentage of 55% highly fearful survivors. Selection bias is an aspect that should be taken into account when designing research on FCR since a proportion of survivors recognize their FCR and express a need for help whereas other survivors cope with FCR by avoiding threat, including study questionnaires.

A limitation of this study is the cross-sectional design, which makes it difficult to draw conclusions about causality. Although the basis of this research was a strong theoretical model proposed in the literature, future research should focus on the direction of the relationships within the model to further strengthen our theoretical knowledge of FCR. The results of this study might have future implications and suggestions for different professions. For clinicians it is important to keep in mind that patients are very aware of bodily symptoms and that FCR is also triggered by information about cancer in their surroundings. Clinicians may provide tailored and correct information about one's disease status and education about symptoms that require immediate action versus symptoms that might be innocent. Once they received this information, patients might be better able to reassure themselves and adopt a wait and see approach. For psychologists the model confirms that a cognitive behavioral therapeutic approach might be a good intervention for high FCR. More specifically, the results of this study indicate that interventions targeting FCR may benefit from incorporating modules on making new plans for the future and the regulation of bodily checking behaviors. For researchers this study gives insight into how FCR model testing can be performed. Replication of this study in a longitudinal design is needed, taking into account some methodological considerations about the best questionnaires to use for risk-factors and protective factors. A greater understanding of these factors associated with FCR may assist the development of evidence-based screening programs and treatments for FCR.

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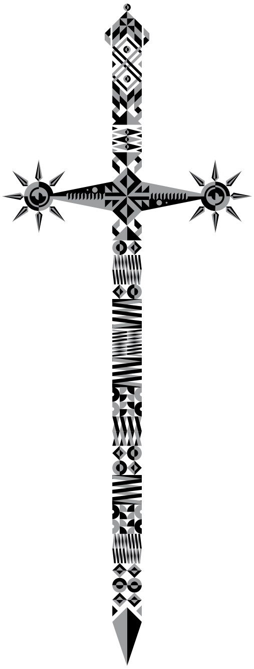

Chapter 7

General discussion

INTRODUCTION

With the rising numbers of cancer patients living with or beyond cancer for prolonged periods of time, increasing attention has been paid to the relatively new and evolving field of fear of cancer recurrence (FCR). Although in the last fifteen years many studies were conducted, approaches to conceptualize, measure and treat FCR were fragmented. Many questions still remain: eg., 'Why do some patients suffer more from FCR than others?', 'How can we detect those patients who are in need for help?' 'Is this a problem for which we need specific interventions?' In 2015 an international research consensus meeting with international experts in the field of FCR and two patients was held in Ottawa, Canada, in order to 1) reach consensus internationally about the definition of this phenomenon and 2) set a basis to start research that builds from this new definition into assessment tools, clinical definitions and interventions. The studies and results presented in this thesis were part of the discussion in this meeting. As a result of the discussion, a special interest group (SIG) *FORwardS* was formed. This SIG is hosted by the International Psycho-Oncology Society (IPOS) [1]. In this chapter the studies and results of this thesis will be evaluated on their merits and shortcomings. Furthermore, directions for future research will be formulated.

DEFINITION: FEAR OF RECURRENCE OR FEAR OF PROGRESSION?

Different definitions are used to describe fear of cancer recurrence in the literature. Already in 1981, Northouse [2] described FCR as 'the degree of concern reported by subjects about the chances of cancer returning at a future time'. In order to construct a new questionnaire, Vickberg [3] formulated FCR as 'the fear that the cancer will return or progress in the same organ or in another part of the body'. This definition has been widely adopted by researchers and clinicians and recently adapted by Simard and Savard [4] who added the concept of worry: 'the fear *or worry* that the cancer will return or progress in the same organ or in another part of the body'. Although the previous definitions were specific to cancer, a definition that can be applied to chronic diseases in general was proposed by Herschbach and colleagues [5]: 'the fear that the illness will progress with all its biopsychosocial consequences or that it will recur,' also referred to as fear of progression (FoP).

In this thesis, the studies on the Cancer Worry Scale (**chapter 2**), selective attention (**chapter 3**), the model of FCR (**chapter 6**) and FCR in colorectal cancer survivors (**chapter 5**) focused on curatively treated cancer patients. Because of the curative intent of treatment in these samples, the term *recurrence* was used in the definition of FCR. The study on GIST patients in **chapter 4** highlights the importance of incorporating the concept of *progression* in a complete definition. Since more treatment options and lines of medicine are becoming available to cancer patients with metastatic disease, an increasing number of patients are receiving ongoing treatment for long periods [6-8]. Therewith it is semantically and basically different for patients and professionals to use the term recurrence or progression. Although a higher percentage of high fearful patients was found in the GIST population (**chapter 4**) compared to the studies with breast cancer survivors and colorectal cancer survivors, there were no differences in manifestations of the fear (triggers, consequences, emotions) between patients who were alive with the disease (FoP) and those who had no evidence of disease (FCR). On the one hand this could be interpreted as evidence that the descriptions of 'fear of recurrence' and 'fear of progression' are the same on a conceptual level [9]. On the other hand it might point to the direction that more research is needed to investigate differences in manifestations of the fear between patients who are on palliative treatment trajectories and patients who show no evidence of disease. Since the focus of many studies and questionnaires is on curatively treated patients, little is known about the experiences of patients on active ongoing treatment in the palliative setting. Taking this discussion of recurrence versus progression into account, in the expert meeting consensus was reached on a new definition of FCR: *'fear, worry or concern about cancer returning or progressing'* [1]. This definition retains a cancer-specific definition because of the already established recognition of this concept worldwide, and makes only small revisions to previous proposed definitions. It seems that this definition suits both curatively treated patients and patients on palliative treatment, because it covers the uncertainty of a new manifestation of cancer or increased disease activity, and is therefore comparable on a conceptual level. Despite revisions to the definition, the literature still contains the terms 'fear of progression' and 'fear of recurrence'. A recommendation for future research and practice should be to adapt descriptions of FCR in questionnaires to the new definition and design new research on FCR in patients on palliative treatment to investigate if the description of FCR and already established cut-off scores can be retained.

ASSESSMENT: CONSCIOUS OR UNCONSCIOUS?

Gold-standard measure

In order to help cancer survivors who suffer from high FCR, the identification of these cancer survivors has become a matter of priority. Therefore, researchers and clinicians are in need of a standardized assessment instrument that adequately evaluates FCR and distinguishes between normal and high levels. The optimal strategy to determine whether a screening tool is valid to identify a specific condition is to compare its result with a 'gold standard' measure that refers to the best performing measure available

[10]. In psychology, structured clinical interviews are regularly used as gold standard measures (eg., the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID) to identify anxiety disorders [11]). For such a gold standard, consensus about the definition and what constitutes high levels is required. This might be a reason for the lack of a gold standard in the field of FCR. Until now, only one semi-structured interview on FCR (SIFCR) exists. The SIFCR has been recently developed by two psychologist experts in the field of psycho-oncology [10], based on the content and format of the SCID and literature on FCR. On the basis of this semi-structured interview cut-off scores are established for the severity subscale of the fear of cancer recurrence inventory (FCRI-SF), frequently used by researchers to define high FCR.

Cut-off scores

Besides the use of a gold-standard measure, establishing cut-offs scores also relies on the interpretation of psychometric properties (sensitivity versus specificity) of the instrument. In the context of FCR assessment, sensitivity refers to the proportion of individuals who experience high FCR having a positive test result, whereas specificity refers to the proportion of negative test results corresponding to low fearful individuals. For a scale to be useful as a screening instrument, the proposed cut-off score should maximize the sensitivity because the purpose of screening is to identify as many fearful patients as possible. To be used as a diagnostic instrument, it should maximize the specificity because a diagnostic instrument should avoid misdiagnosis of high FCR as much as possible. To be useful as an instrument to differentiate high FCR from low FCR, it should have high sensitivity and specificity, which maximizes the proportion of patients whose test results are accurate [12]. Since the studies described in this thesis were observational and not primarily focused on screening (high sensitivity) or for instance inclusion in an intervention study (high specificity), we choose for a cut-off score on the Cancer Worry Scale that maximized the proportion of patients with accurate test results (both sensitivity and specificity around .80; **chapter 2**). Based on these statistical considerations regarding sensitivity and specificity, it was difficult to compare the performance of the CWS to detect high FCR with the later published and frequently used FCRI-SF. The FCRI-SF proposed two cut-off points, one for screening and one for optimal specificity which require different considerations about the psychometric properties. Although the cut-off scores were based on different psychometric considerations, the study on colorectal cancer survivors (**chapter 5**) shows that there was agreement between the CWS and FCRI-SF concerning the presence or absence of a high FCR in 87% of the cases indicating that these two instruments performed in a comparable way. However, recently a replication of the study by Simard and Savard [10] in which the cut-off scores were defined based on the semi-structured interview as gold standard was conducted by Jones and colleagues [13], showing that a cut-off score of 22 on the FCRI-SF was associated with optimal sensitivity and specificity rates for the screening of high levels of FCR. This cut-off score is remarkably higher than the cut-off score of 13 that was previously recommended [10]. However, this higher cut-off score is in line with the observations of clinicians who see patients with high FCR or select them for an intervention study. They often report that by using higher cut-off scores those patients are selected that display fear that is dysfunctional and interfering with daily life. Obviously more research is needed to detect the optimal cut-off score but we can tentatively state that both the FCRI-SF (cut-off score 13) and CWS (cut-off score 14) are able to detect those patients with moderate to high levels of FCR, but these are probably not suitable for detecting those patients who have excessive FCR and are in need for help. This is an important fact to keep in mind when reading and interpreting the chapters in this thesis. We believe that the 'moderate to severe' FCR samples included in these studies are appropriate for the observational and descriptive aims of this thesis. However, these samples would not be well suited to include in an intervention study specifically tailored to FCR since the need for help in these patients may be less urgent. Recommendations for future research based on this thesis would be to either validate the Cancer Worry Scale based on a structured clinical interview or validate the FCRI-SF for the Dutch population and use the higher cut-off score. Meanwhile in the refinement and translation of a gold standard, a solution among researchers might be to use the 10% highest scores to make comparisons between different measurement tools possible.

Self-report versus implicit measures

Where traditionally anxiety was measured with self-report questionnaires (eg., Hospital Anxiety and Depression Scale, Visual Analogue Scale) there is an emerging field of anxiety assessment which relies on the use of implicit processes. Implicit processes refer to processes that are not readily captured by conscious introspection, are difficult to control, are efficient or effortless, can occur unintentionally or outside of conscious awareness [14], but that nevertheless influence behavior [15]. Assessment of implicit processes has already been performed with different tasks (eg., dot-probe task [16]; emotional Stroop task [17]) in different types of anxiety (eg., generalized anxiety disorder [18], social anxiety [19], spider phobia [20]). With a realistic threat such as FCR several methodological difficulties appear in both self-report and implicit assessment. First, it is important to keep in mind the timing and setting of assessment. It is known from the results of **chapter 6** of this thesis that FCR is associated with medical check-ups and doctor appointments. Patients are nervous and anxious in the week(s) before a medical examination or check-up and relieved after hearing good news about their medical condition. Furthermore, patients can become anxious following a variety of triggers (eg., hearing of someone who has received a cancer diagnosis, Pink Ribbon month October for breast cancer). For research purposes it is important, however often difficult, to take into account these 'confounding' factors. With regard to the setting, from a classical conditioning viewpoint visiting the hospital can be accompanied by memories, associations and feelings of the period of being diagnosed and treated for cancer and this might elevate levels of fear. As the latter could have been a confounding factor in the study on implicit processes (**chapter 3**), we believe that assessment of FCR should preferably not take place in a hospital setting. Second, a specific question on the need for help can be used to indicate the severity of FCR. Often self-report questionnaires do not incorporate such a question and with implicit measures it is even more difficult to map the need for help. Questions on the need for help can be helpful in defining high FCR. Patients scoring high on FCR questionnaires and also reporting a need for help might benefit from a more intensive intervention such as face-to-face contact with a psychologist. Patients showing a discrepancy between scores on a questionnaire and self-reported need for help (high FCR score on questionnaire but no need for help and low FCR score but high need for help) might benefit from other types of help/support. For patients with low scores on a FCR questionnaire but a high need for help, psycho-education or a low intensity intervention such as a self-management program might be helpful. For patients with high scores on a FCR questionnaire but no need for help, explaining options for help by health professionals in case they do need it sometime might be sufficient. For the purpose of intervention studies, an indication of need for help and openness to the intervention is very important. For research purposes it is not yet clear how to handle and interpret these discrepancies. It would be interesting for future studies to incorporate a need for help question into FCR measures to compare those patients who display a need for help and those who can cope with high FCR themselves. This might also be helpful for the development of tailored interventions for FCR.

Third, research on anxiety disorders demonstrates attentional biases towards threatening information [18-20]. However, until now only two studies on attentional bias have been conducted in the field of FCR. In the study of selective attention described in **chapter 3** and in a study of Butow et al. [21], attentional biases were found for cancer-related words. The attentional bias in both studies was not different for patients with high or low FCR as assessed by self-report, indicating that after the overwhelming experience of a cancer diagnosis and treatment, cancer patients in general seem to have a bias towards cancer-related words. Although it would be interesting to speculate about this discrepancy between self-report and implicit assessment of FCR it might be too early to draw the firm conclusion that there exists a discrepancy. The knowledge about and materials for measuring FCR in an implicit way is still very premature. There is yet no set of validated stimuli that tap into the issue of FCR specifically and there is still debate [22,23] about which implicit instrument is best to use in which setting. At this moment a prerequisite for research with implicit measures is the exploration and validation of useful stimuli. Qualitative studies with patients expressing the content of FCR depicted in words and images might be a useful method for this aim. Furthermore, the use of eye-tracking techniques will provide more insight into the direction of attention for certain stimuli. With use of eye-tracking techniques, a direct and continuous record of the allocation of attention over an extended interval of time can be provided for multiple stimuli competing for attention [24]. Using eye-tracking technology, attention towards or away from certain stimuli can be examined. Taking these considerations into account, influencing or modifying these implicit processes might add value to the development of interventions for FCR. Positive findings are published of interventions, based on cognitive bias modification (CBM), in which implicit cognitive processes related to anxiety are influenced by direct modification of attention via repeated practice on cognitive tasks [25-27].

Fourth, selection bias is an aspect that is often present in studies of anxious individuals and also affects the study of FCR. It seems that there are two groups of avoiders. Firstly there are the patients who acknowledge that they are fearful but show an avoidant reaction as measured by for instance the Impact of Event Scale (IES) [**chapter 3 and 5**]. Secondly, there is a group of patients who avoid everything related to cancer (eg., hospitals etc.). These patients may not attend follow-up consultations, and are likely not to participate in studies on anxiety. To incorporate these individuals in research on FCR other options of data collection might be considered. For instance, with the use of Internet peer support via contact with other patients in online communities has increased. This could be a platform where patients share their feelings or worries with other patients. It would be interesting to find out if users of online communities differ from those who participate in research studies and to conduct content analyses of texts investigating their topics of concern.

COURSE OF FCR

Exploring the course of FCR is necessary for several reasons. First, it gives insight into the development and stability of FCR. This is important to provide the appropriate level of support to patients. If patients experience high FCR that remains stable or even increases over time, longer and more intensive interventions might be needed [28]. Second, prospective longitudinal designs enable us to examine the role of potential determinants and consequences of FCR by investigating the direction of relationships. Several longitudinal studies were conducted over the past years [29] with varying follow-up periods (3 months [30] to 6 years [31]) and various data collection points (between two [32-38] and seven [39]). These variations limit comparison among studies and raise questions on how to assess this 'natural' course best. At what point in the cancer continuum should FCR assessment start? How often should we measure FCR and with what time interval to get a reliable assessment? How to observe and analyze individual fluctuations, and map triggers linked to these fluctuations? Is it possible that researchers induce fear by assessing FCR too frequently? Involving patients (or patient advocates) in getting answers to these questions would be very helpful.

With regard to the timing of starting FCR assessment, recruitment of patients and collection of data is often difficult in the period before start of treatment. Patients are often overwhelmed with the cancer diagnosis or have insufficient time to complete the baseline assessment prior to treatment. The few longitudinal studies measuring baseline FCR prior to treatment did find highest FCR levels at this point with a significant reduction in fear between the pre- and post-treatment assessments [38-41] The reduction can be explained by the heightened general psychological distress that occurs at the time of diagnosis, and distress is usually highly correlated with FCR [42]. Therefore, it is questionable if FCR as unique concept can be measured at diagnosis or start of treatment. Besides, since the cancer has not been treated yet at this point the concept of recurrence is not yet applicable and fear refers to the cancer, its treatment and prognosis. It seems that measuring FCR post-treatment is more reliable and easier to interpret. With regard to frequency of measuring FCR, most studies report results on FCR scores of the total sample. When using for instance two measurement points, an increase, decrease or stable level over time is visible. However this does not imply that all patients exhibit the same trajectories between the measurement points. Given the fact that FCR is linked to multiple triggers (**chapter 6**) FCR levels might fluctuate over time dependent on encounters with certain triggering situations. Dunn and colleagues [39] displayed this variability in FCR scores of seven data collection points in a spaghetti plot of individual trajectories. To more accurately identify FCR trajectories, it is recommended to include more than two measurement points in studies. Furthermore, in order to investigate predictors of these inter-individual differences in initial levels of FCR and changes over time, different statistical approaches (eg., multilevel models) should more often be adopted instead of the typically used linear or logistic regression analyses [39]. With regard to the time interval between consecutive FCR assessments, it remains unknown whether FCR can be induced by reminding patients too often of their worries, cancer diagnosis or health status. Questionnaires on FCR might then be functioning as triggers and compromise the reliability of FCR assessment. It would be interesting for future research to investigate this possible phenomenon and determine the optimal time interval between assessment points. By asking patients what possibly could have influenced their level of FCR at the time of reporting, insight can be gained about possible triggers. Overall, involvement of experienced clinicians and patients in designing novel research could be extremely helpful in solving these issues.

MODEL AND INTERVENTIONS

In **chapter 6** the hypothesized theoretical model of FCR proposed by Lee-Jones [43] was tested and largely confirmed. Although this model was tested on a cross-sectional dataset, it gives insight into the interplay of different variables associated with FCR. Replication of the model on longitudinal data is necessary to establish causal relationships. Because the hypothesized theoretical model is agreed upon by international FCR experts of the consensus meeting we believe that the confirmed model can be guiding for clinicians, psychologists and other health professionals. **Chapter 6** revealed relationships between FCR and different types of triggers such as medical check-ups, bodily sensations, or media on cancer. Clinicians could play an important role in anticipating on these triggers. By giving patients accurate information on their disease status, patients will become for instance less fearful of information about cancer (via media or social context) that is not applicable to their individual situation. In addition, patients need education and information about bodily symptoms that require serious attention versus symptoms that might be relatively innocent belonging to a viral infection for instance. If patients know that some symptoms require a wait and see approach for a couple of days, this information might be helpful to regulate fear responses. For psychologists, the model of FCR can be helpful in designing interventions to normalize FCR. The question arises whether interventions should be specifically focused on FCR as a primary outcome, or that interventions focusing on emotional adjustment with FCR as a secondary outcome would be equally effective in reducing FCR. It is difficult to draw firm conclusions on this issue since several randomized controlled trials targeting FCR are still in progress [44-47]. Little evidence from completed trials is available and insufficient evidence is currently available to recommend either specific FCR or generic interventions. Short-term effects were found for both FCR specific interventions (two short-group interventions (cognitive behavior therapy (CBT); supportive-experiential group therapy) compared to care as usual [48]) and generic interventions (6 sessions mindfulness-based stress reduction (MBSR) [49]; emotion regulation group [50]; Web-based self-management [51]) compared to care as usual, and one generic intervention without a control condition (8 sessions MBSR [52]). Of these studies showing a short-term effect, 3 out of 5 studies also investigated the long-term follow-up effect [48,50,51]. Only the specific FCR group interventions [48] showed a long-term follow-up effect of longer than 6 months. Most of the intervention studies used a group session design; however it would be interesting for future research to see if there is a difference in outcomes between group session interventions [46,48-50,52] and individual therapy [44,45,47,51].

Although more research on interventions is needed, the treatment effects of both specific and generic interventions are promising and might be a good starting point for an 'umbrella' approach encompassing multiple interventions tailored to the specific level of fear and need for help for each cancer survivor. Patient education via brochures or websites with correct and complete information on FCR might be suitable for survivors with low, normal, levels of FCR. For survivors with moderate levels of FCR a low-intensity intervention like an online self-management program including modules on FCR could be appropriate equipping them with personal skills that support them in dealing with FCR. Survivors with high FCR might benefit most from a more intensive intervention such as face-to-face CBT or MBSR interventions.

METHODOLOGICAL CONSIDERATIONS OF THE DISSERTATION AND FUTURE DIRECTIONS

Based on progressive insights gained from the studies described in this thesis, several recommendations for future directions can be formulated. As previously mentioned researchers and clinicians need a gold standard measure to detect patients with excessive FCR. The questionnaires and associated cut-offs used in our studies to assess severity of FCR (Cancer Worry Scale, **chapter 2-6**; Fear of Cancer Recurrence Inventory, **chapter 4,5**) might not be the optimal instruments to detect excessive FCR. This is due to the current lack of a gold standard clinical interview, which in turn is difficult to develop without a clear definition of what constitutes clinical levels of FCR. Consensus from psychologists, medical doctors and patients should be reached about the manifestations of excessive FCR in order to develop and validate a clinical interview. A next step would be research focusing on the validation of FCR questionnaires and establishing new cut-off scores according to the gold standard clinical interview. Although in **chapter 5** a first attempt was made to investigate content of FCR, this dissertation did not use a qualitative method. This is a limitation since this type of research might be very helpful in gaining insight into the manifestations and content of FCR. Furthermore, the evolving area of implicit processes associated with FCR is in need of more validated stimuli (pictures and words) capturing this specific type of threat (**chapter 3**). Patients' qualitative reports of their thoughts and associations when confronted with triggers might advance the development of experimental tasks in this research area. In the process of gathering further information on content and manifestations of high FCR, attention should also be paid to patient populations with a poor prognosis like pancreatic cancer. For these patients existential issues as part of FCR might be more prominent for instance. Since the studies in this thesis were focused on patient populations with a relative favorable prognosis, it is not possible to generalize findings to patients with worse prognoses. More research on differences and similarities in FCR between different stages of prognoses is important to cover both the continuum of fear and the continuum of different diagnoses. A second issue lacking in the studies described in this thesis is the assessment of comorbidity.

Recent studies show relationships between FCR and both physical [53] and psychiatric [10] (history of) comorbidity. Physical comorbid conditions can be accompanied by physiological symptoms, which might be interpreted as signs of disease recurrence [53]. For psychiatric comorbidity, patients with severe FCR had more often current psychiatric disorders than cancer survivors with non-clinical levels of FCR. A trend in the same direction for past psychiatric disorders was found [10]. Taken these findings into account, it seems important for future research to address the issue of comorbidity as it can be valuable in the prediction of which patients are more vulnerable to suffer from high levels of FCR.

In order to optimize care for patients with high FCR, systematic assessment of FCR is desirable. Accompanying discussion with this proposition is whether this systematic assessment should take place in routine follow-up care, follow-up by dedicated nurses or the general practitioner. In view of the fact that in routine follow-up little time is available for psychosocial issues and the medical examinations are associated with high FCR, it may be feasible to instruct nurse specialists in how to assess FCR and how to refer patients who are in need of help. The national and international recognized instrument to screen for a variety of psychosocial issues in clinical practice is the Distress Thermometer (DT). In the Dutch context this is most often completed by the patient together with nurse specialists. When patients indicate problems with anxiety and a need for help on the DT, dedicated nurse specialists should be encouraged to screen for FCR using an FCR specific instrument and to explore whether help with FCR is needed. This systematic assessment of psychosocial issues can also be useful in the transition from follow-up care in the hospital to general practice setting.

Most important is that assessment of FCR will be a systematic part of follow-up, independent of the discussion in which setting this follow-up should take place.

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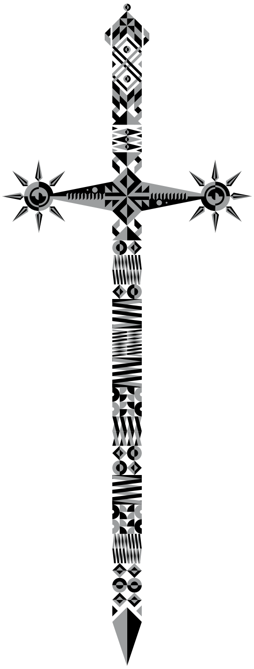


Chapter 8

Summary

Samenvatting

SUMMARY

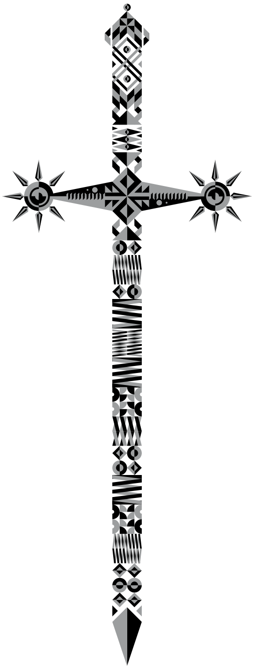
Since survival of cancer patients has improved significantly the last decennia, more attention should be paid to the psychological burden of having been treated for this life-threatening disease. This thesis focused on fear of cancer recurrence (FCR) described as the '*fear, worry or concern about cancer returning or progressing'* in three different patient populations (breast cancer survivors, colorectal cancer survivors, and patients with gastrointestinal stromal tumor (GIST)). **Chapter 1** provided background on the current state of knowledge on FCR. More specifically, different aspects of FCR including definition, prevalence, assessment, clinical levels, determinants, course, theoretical model and interventions were outlined. In order to detect those patients and survivors for whom FCR becomes so overwhelming that it affects quality of life, **Chapter 2** described the validation of the Cancer Worry Scale (CWS). This study aimed to validate an instrument which could accurately differentiate between high and low levels of FCR. Therefore, 194 female breast cancer survivors filled out questionnaires including the CWS. Results showed that a cut-off score of 13 versus 14 (low ≤13, high ≥ 14) on the CWS was optimal for differentiating between high and low levels of FCR. A cut-off score of 11 versus 12 (low ≤ 11, high ≥ 12) was optimal for the purpose of screening. Reliability and validity of the CWS were supported indicating that it is a promising instrument to detect elevated levels of FCR. Previous studies involving people with anxiety disorders demonstrate an attentional bias towards threatening information amongst anxious individuals. To find out if it was possible to assess FCR in an implicit way using methods other than self-report (CWS), an experimental study using the Emotional Stroop Task was conducted in **Chapter 3**. This study investigated whether such a bias exists for cancer-related stimuli in breast cancer survivors. Furthermore, it was hypothesized that different levels of FCR would lead to different patterns of selective attention. Breast cancer survivors with high (n=35) and low (n=32) FCR were compared to 40 healthy female hospital employees. Specificity of attentional biases was investigated using a modified Emotional Stroop Task including cancer-related words, hospital-related words, positive, negative and neutral words. Self-report measures were used to assess depression and anxiety, feelings of fatigue and traumas experienced. Results revealed that compared to control participants, breast cancer survivors with both high and low levels of FCR showed increased interference for cancer-related words, but not for other word types. These findings suggest a specific attentional bias for cancer-related words in breast cancer survivors that is independent of level of FCR. **Chapter 4** described the study on fear of progression in patients with a rare type of cancer called gastrointestinal stromal tumors (GIST). GIST's are rare and before 2000, patients had a dismal prognosis with a median survival of less than a year after tumor metastasis. However, the median overall survival has increased to more than 5 years following the introduction of imatinib and other tyrosine kinase inhibitors (TKI). Little is known about the psychosocial consequences of treatment of GIST, but becomes increasingly important due to new treatments accompanying prolonged survival. In a cross-sectional design, quality of life, distress, and fear of cancer recurrence or progression in patients with GIST was investigated. Eighty-six patients with localized or metastatic GIST were asked to participate. Patients completed self-report questionnaires including the EORTC-Quality of Life Questionnaire, Hospital Anxiety and Depression Scale, Impact of Event Scale, Cancer Worry Scale, and Fear of Cancer Recurrence Inventory. Fifty-four patients (median age 63.3 years) completed the questionnaires, 33 (61%) of whom were receiving TKI treatment at the time of the study. Overall, the GIST patients had a good global quality of life, but 28 patients had high levels of fear of cancer recurrence/progression. Interestingly, this high level of fear was not related to patient- or treatment-related variables. Patients with elevated levels of fear experienced significantly higher levels of psychological distress, functional impairments, and difficulty making plans for the future than did patients with lower levels of fear. The main conclusion from this study was that in addition to general quality of life issues in patients with GIST, it is also important to pay attention to specific cancer-related problems such as fear of cancer recurrence/progression since a substantial part of patients suffers from high levels of fear. **Chapter 5** described an exploratory study in colorectal cancer survivors. Although long-term colorectal cancer (CRC) survivors generally report a good quality of life, FCR is an important issue. This study investigated 1) whether the CWS was valid and reliable in a population of colorectal cancer survivors, 2) the prevalence of FCR, and 3) characteristics and representations of FCR in CRC survivors. Two hundred and eleven patients who had undergone successful CRC surgery in the period 2003 - 2010 in the Radboud University Medical Center in the Netherlands were asked to participate. All patients were sent an information letter plus questionnaires for collecting information on demographic and medical variables, FCR, distress, and quality of life. Seventy-six patients (36%; median age of 67.7 years; range 41-88 years) completed the questionnaires a median of 5.1 years after surgery. A cut-off score of 14 or higher on the CWS was optimal to detect high FCR. Twenty-nine patients (38%) experienced high levels of FCR, characterized by higher levels of distress, post-traumatic stress symptoms, and lower quality of life. These individuals particularly reacted to disease-related triggers, felt helpless, were worried, and experienced limitations in daily functioning. High FCR was not associated with demographic or medical variables. Taken together these findings suggest that long after successful CRC surgery, FCR is a serious problem that impairs quality of life for a substantial proportion of CRC survivors. Using the CWS it is possible to detect high FCR, and therefore attention should be paid to this assessing this specific cancer-related problem amongst CRC survivors in order to provide appropriate care.

In understanding FCR, it is important to conceptualize it as a multidimensional problem in which internal or external cues trigger interpretations and cognitions of the threat of cancer, leading to an increase of FCR. This fear may result in dysfunctional behaviors, such as limited planning, body checking and seeking professional advice, again enhancing an increased fear response. **Chapter 6** assessed these relationships in the hypothesized model of FCR. A large sample of breast cancer survivors (n=1205), who were 0-5 years after the end of primary breast cancer treatment were invited to participate in this study. Participants received a questionnaire booklet including questionnaires on demographics and psychosocial variables including FCR. Data analysis consisted of the estimation of direct and indirect effects in simple and multiple mediator models. A total of 460 women (38%) participated in the study. Median age was 55.8 years (range 32 – 87). Indirect effects via FCR were found for all mediation models with limited planning and body checking as behavioral response variables, with the largest effects for limited planning. A direct relation was found between feeling sick and seeking professional advice, not mediated by FCR. Different moderators were found for each of the models tested. We concluded that in the first tested models of FCR, all internal and external cues were associated with higher FCR. In the models with limited planning and body checking as behavioral response, an indirect effect of cues via FCR was found. An evidence-based model of FCR may facilitate the development of appropriate interventions to manage FCR in breast cancer survivors. **Chapter 7** contains the discussion of this thesis in which the results of the studies were presented into a broader perspective by evaluating their merits and shortcomings. Several recommendations for future research were made.

SAMENVATTING

De overlevingskansen van patiënten met kanker zijn sterk verbeterd in de afgelopen decennia. Daarbij is het belangrijk om meer aandacht te besteden aan de psychosociale gevolgen van het zijn behandeld voor deze levensbedreigende ziekte. Dit proefschrift richt zich op de angst dat de kanker terugkeert, in het Engels 'fear of cancer recurrence' genoemd, afgekort als FCR. Deze angst wordt omschreven als de "angst, zorgen of bezorgdheid dat de kanker terugkeert of verder uitbreidt". In drie verschillende patiëntpopulaties (borstkanker, colorectaalkanker en patiënten met gastro-intestinale stromale tumor (GIST)) werden studies naar FCR uitgevoerd. **Hoofdstuk 1** verstrekt achtergrondinformatie over de huidige stand van kennis over FCR. In dit hoofdstuk werden verschillende aspecten van FCR geschetst zoals de definitie, prevalentie, meetinstrumenten, klinische niveaus, determinanten, natuurlijk beloop, theoretisch model en interventies. Om patiënten en mensen die verder leven na de behandeling van kanker (survivors) bij wie FCR zo overweldigend is dat de kwaliteit van leven beïnvloed wordt te detecteren, werd in **hoofdstuk 2** een validatiestudie uitgevoerd om te onderzoeken of de Cancer Worry Scale (CWS) geschikt was om nauwkeurig onderscheid te maken tussen hoge en lage niveaus van FCR. Hiervoor vulden 194 vrouwelijke borstkanker survivors een aantal vragenlijsten in waaronder de CWS. De resultaten toonden aan dat een cut-off score van 13 versus 14 (laag ≤13, hoog ≥ 14) op de CWS optimaal is om het onderscheid tussen hoge en lage niveaus van FCR te maken. Een cut-off score van 11 versus 12 (laag ≤ 11, hoog ≥ 12) was optimaal voor screening. Betrouwbaarheid en validiteit van de CWS werd ondersteund wat aangeeft dat het een veelbelovend instrument is om verhoogde FCR detecteren. Om erachter te komen of het naast zelfrapportage (CWS) ook mogelijk is om FCR te meten op een onbewuste manier, werd een experimenteel onderzoek met de emotionele Stroop taak uitgevoerd in **hoofdstuk 3**. Eerdere angst studies lieten zien dat angstige mensen een aandachtsbias vertonen richting bedreigende informatie. Op basis van deze bevindingen werd onderzocht of een dergelijke aandachtsbias bestaat voor kanker-gerelateerde stimuli bij borstkanker survivors. Hierbij werd verondersteld dat verschillende niveaus van FCR zouden leiden tot verschillende patronen van selectieve aandacht. Borstkanker survivors met een hoge (n = 35) en lage (n = 32) FCR werden vergeleken met 40 gezonde vrouwelijke ziekenhuismedewerksters. Specificiteit van de aandachtsbias werd onderzocht met behulp van een gemodificeerde Emotionele Stroop Task waarbij gebruik werd gemaakt van kanker gerelateerde woorden, ziekenhuis gerelateerde woorden, positieve, negatieve en neutrale woorden. Vragenlijsten werden gebruikt om depressie en angst, gevoelens van vermoeidheid en ervaren trauma's in kaart te brengen. Uit de resultaten bleek dat in vergelijking met de gezonde ziekenhuismedewerksters, de borstkanker survivors met zowel hoge als lage niveaus van FCR meer interferentie toonden voor kanker-gerelateerde woorden, maar niet voor andere categorieën woorden. Deze bevindingen suggereren een specifieke aandachtsbias voor kanker-gerelateerde woorden bij borstkanker survivors die onafhankelijk is van het niveau van FCR. **Hoofdstuk 4** beschrijft de studie over angst voor progressie van kanker bij patiënten met een zeldzame vorm van kanker genaamd gastrointestinale stromale tumoren (GIST). GIST's zijn zeldzaam en vóór het jaar 2000 hadden patiënten een sombere prognose met een mediane overleving van minder dan een jaar na de tumor metastase. Echter, de gemiddelde algemene overleving is gestegen tot meer dan 5 jaar na de introductie van imatinib en andere tyrosine kinase inhibitoren (TKI). Er is weinig bekend over de psychosociale gevolgen van de behandeling van GIST, maar dit wordt steeds belangrijker als gevolg van nieuwe behandelingen die verlengde overleving mogelijk maken. In een cross-sectionele studie werd kwaliteit van leven, FCR, en angst voor progressie van kanker bij patiënten met GIST onderzocht. Zesentachtig patiënten met gelokaliseerde of gemetastaseerde GIST werd gevraagd om deel te nemen. Patiënten voltooide zelfrapportage vragenlijsten waaronder de EORTC Kwaliteit van Leven vragenlijst, Hospital Anxiety and Depression Scale, Impact of Event Scale, Cancer Worry Scale en Fear of Cancer Recurrence Inventory. Vierenvijftig patiënten (gemiddelde leeftijd 63,3 jaar) voltooiden de vragenlijsten. Over het geheel genomen vertoonden de GIST-patiënten een goede globale kwaliteit van leven, echter 28 patiënten ervoeren een hoge mate van angst voor terugkeer of progressie van kanker. Interessant is dat dit hoge niveau van angst niet gerelateerd was aan patiënt- of behandeling gerelateerde variabelen. Patiënten met een verhoogd niveau van angst ervoeren beduidend hogere niveaus van psychische klachten, functionele beperkingen, en hadden meer moeite met het maken van plannen voor de toekomst dan patiënten met een lager niveau van angst. De belangrijkste conclusie van deze studie was dat naast algemene kwaliteit van leven het ook belangrijk is om aandacht te besteden aan specifieke kanker-gerelateerde problemen zoals angst voor terugkeer of progressie van de ziekte aangezien een aanzienlijk deel van patiënten last hebben van hoge niveaus van angst. **Hoofdstuk 5** beschreef een observationele studie bij colorectaalkanker survivors. Hoewel colorectaalkanker survivors over het algemeen op de lange termijn een goede kwaliteit van leven rapporteren, blijft FCR een belangrijke kwestie. Deze studie onderzocht 1) of de Cancer Worry Scale (CWS) ook goede psychometrische eigenschappen had in een populatie van colorectaalkanker survivors, 2) de prevalentie van FCR, en 3) de kenmerken en representaties van FCR in colorectaalkanker survivors. Tweehonderd en elf survivors die succesvol geopereerd waren voor colorectaalkanker in de periode 2003-2010 werd gevraagd om deel te nemen aan deze studie. Alle deelnemers ontvingen vragenlijsten waarin informatie werd verzameld over de demografische en medische variabelen, FCR, en de kwaliteit van het leven. Zesenzeventig survivors (36%) voltooiden de vragenlijsten. Een cut-off score van 14 of hoger op de CWS bleek optimaal om hoge FCR detecteren. Negenentwintig survivors (38%) hadden hoge FCR, gekenmerkt door hogere niveaus van angst, posttraumatische stress-symptomen en een lagere kwaliteit van leven. Deze personen reageerden met name op ziekte-gerelateerde triggers, voelde zich hulpeloos, waren bezorgd, en ervoeren beperkingen in het dagelijks functioneren. Hoge FCR was niet geassocieerd met demografische of medische variabelen. Uit deze studie bleek dat zelfs een aantal jaren na een succesvolle operatie voor colorectaalkanker FCR een ernstig probleem is dat invloed heeft op de kwaliteit van leven in een aanzienlijk deel van de survivors. Met de CWS is het mogelijk om een hoge FCR detecteren en aandacht moet worden besteed aan dit specifieke kanker-gerelateerde probleem om de juiste zorg te bieden voor survivors.

Om FCR te begrijpen is het belangrijk om het conceptualiseren als een multidimensionaal probleem waarbij interne of externe stimuli bepaalde cognities en emoties triggeren die kunnen leiden tot een toename van angst. Deze angst kan vervolgens weer leiden tot disfunctioneel gedrag, (zoals moeite hebben met het maken van plannen voor de toekomst, het lichaam controleren op mogelijke symptomen en het consulteren van professioneel advies), hetgeen opnieuw een verhoogde angstreactie versterkt. **Hoofdstuk 6** onderzocht deze relaties in het veronderstelde theoretische model van FCR. 1205 borstkanker survivors, 0-5 jaar na het einde van de primaire behandeling van borstkanker werden uitgenodigd om deel te nemen aan deze studie. Deelnemers ontvingen een vragenlijst boekje met daarin vragenlijsten over demografische en psychosociale variabelen, zoals FCR. In totaal namen 460 vrouwen (38%) deel aan het onderzoek. De mediane leeftijd was 55,8 jaar (32-87). Indirecte effecten via FCR werden gevonden voor alle modellen waarin moeite met planning voor de toekomst en het controleren van het lichaam als gedragsmatige variabelen werden genomen. Een directe relatie werd gevonden tussen ziek zijn en het consulteren van professioneel advies. We concludeerden dat in deze studie, waarin voor het eerst de theoretische modellen van FCR uit de literatuur getest werden, dat bijna alle interne en externe triggers geassocieerd waren met een hogere FCR. In de modellen waarin moeite met het maken van plannen en het controleren van het lichaam als gedragsmatige consequenties werden genomen, werd een indirect effect van triggers via FCR gevonden. **Hoofdstuk 7** bestaat uit de discussie van dit proefschrift en plaatst de resultaten van de studies in een breder perspectief. Daarnaast werd een aantal aanbevelingen voor toekomstig onderzoek gedaan. Zo zou eerst duidelijker moeten worden wat ernstige angst voor terugkeer van kanker kenmerkt. Vandaar uit kan gewerkt worden aan het bepalen van de meest geschikte afkappunten in vragenlijsten om mensen die risico lopen op verhoogde angst te detecteren. Dit kan vervolgens gebruikt worden om als startpunt van zorg FCR systematisch in kaart te brengen in de klinische praktijk. Inmiddels is op basis van de resultaten in dit proefschrift een psychologische behandeling voor ernstige FCR ontwikkeld op de afdeling Medische Psychologie van het Radboudumc.



List of publications

PhD Portfolio

Dankwoord

Curriculum Vitae

ORIGINAL ARTICLES

Custers JAE, Gielissen MFM, Janssen SHV, De Wilt JHW, Prins JB. Fear of cancer recurrence in colorectal cancer survivors. Supportive Care in Cancer. 2016; 24(2):555-62.

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Becker ES, Ferentzi H, Ferrari G, Möbius M, Brugman S, **Custers JAE**, Geurtzen N, Wouters JM, Rinck M. Always Approach the Bright Side of Life: A General Positivity Training Reduces Stress Reactions in Vulnerable Individuals. Cognitive therapy and research. 2016; 40:57-71.

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Custers JAE, van den Berg SW, van Laarhoven HWM, Bleiker E, Gielissen MFM, Prins JB. Cancer Worry Scale: A Screening Instrument for Fear of Cancer Recurrence. Psycho-Oncology 2011; 20: S141-S142.

PHD PORTFOLIO

Name PhD student: JAE Custers
Department: Medical Psychology
Graduate School: Radboud Institute for Health Sciences

PhD period: 01-09-2011 – 01-07-2015
Promotoren: Prof. JB Prins,
Prof. JHW de Wilt,
Prof. WTA van der Graaf
Co-promotor: Dr. MFM Gielissen

	Year(s)	ECTS
TRAINING ACTIVITIES		
Courses & Workshops		
- *Workshop 'Structural Equation Modelling'*	2011	0.2
- *NCEBP (RIHS) introduction course*	2012	1.75
- *Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)*	2012	1.75
- *NCEBP (RIHS) PhD retreat*	2012	0.75
- *Workshop 'Idiographic Methods: Individual behaviour change over time*	2012	0.2
- *Course 'Small group tutoring & teaching academic thinking skills' (Docentprofessionalisering)*	2012	0.75
- *NVvO course 'Introduction Clinical and Fundamental Oncology'*	2013	1.75
- *Academic Writing*	2013	3.25
- *Start qualification educational activities*	2013	0.75
- *Masterclass 'Resilience' by Prof. Stanton*	2013	0.2
- *Onderwijsdag Medical Psychology*	2014	0.4
- *Workshop 'Getting published'*	2014	0.2
- *Radboud Da Vinci Challenge*	2014-2015	5.0
- *Masterclass 'Latent class growth analysis' Dr. Gameiro*	2015	0.2
Seminars & lectures		
- *Psychologen werkgroep IKNL (oral)*	2012	0.25
Symposia & congresses		
- *NVPO congress, Utrecht (poster)*	2012	0.5
- *ICBM congress, Budapest (oral)*	2012	1.5
- *ARPH congress, Enschede (oral)*	2013	1.0
- *IPOS congress, Rotterdam (oral + poster)*	2013	1.75
- *IPOS congress, Lisbon (oral)*	2014	1.5
- *ARPH congress, Groningen (oral)*	2014	1.0
- *NVPO congress, Utrecht (poster)*	2014	0.5
- *ICBM congress, Groningen (oral)*	2014	1.25
- *IPOS congress, Washington (oral)*	2015	1.25
- *2-day colloquium on Fear of Cancer Recurrence, Ottawa (oral)*	2015	1.0

Other

-	*Gammaraad psychosocial oncology, secretary*	2012-2015	4.0
-	*Member of the Research Consortium Oncology*	2012-2015	2.0
-	*Journal Club psychosocial oncology, secretary*	2013-2015	3.0
-	*Junior Researchers Seminar Medical Psychology, chair*	2013-2015	3.0
-	*Member of the working group 'Scientific Research' of the Dutch Society for Psychosocial Oncology (NVPO)*	2013-2015	1.5
-	*Member research board Medical Psychology*	2013-present	2.0
-	*Member of the international special interest group on Fear of Cancer Recurrence (FORWARDS)*	2015-present	0.5
-	*Journal Reviewer 'Psycho-Oncology'*	2015-present	0.1
-	*Journal Reviewer 'Quality of life Research'*	2015-present	0.1

TEACHING ACTIVITIES

Lecturing

-	*Course 'Oncology' Medical Honours students*	2011-2013	1.0
-	*Course 'Cancer Research' Tutor Biomedical Science students*	2012,2014	4.0

Supervision of internships / other

-	*Thesis supervisor Master Health Psychology, Radboud University. Thesis: Quality of life and fear of cancer recurrence in colorectal cancer survivors*	2012-2013	1.0
-	*Thesis supervisor Honours program (3 students), Radboud University. Thesis: Personally relevant words for breast cancer survivors*	2013-2014	3.0
-	*Thesis supervisor 'Science across Borders' Radboud University. Thesis: Personally relevant words for prostate cancer survivors*	2014-2015	1.0
-	*Thesis supervisor Research Master Behavioral Science, Radboud University. Thesis: Family history and breast cancer worry: the role of attentional bias*	2014-2015	2.0

TOTAL **56.85**

Radboud University Radboudumc university medical center

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Graag wil ik een aantal mensen bedanken die betrokken zijn geweest bij de totstandkoming van dit proefschrift.

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We blijven elkaar zeker zien en in navolging van Annemiek zie ik jullie sowieso @51°50′ 14.9″N 5°52′45.2″E, 22-3-2025, 6PM.
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CURRICULUM VITAE

José Custers werd op 24 oktober 1987 geboren te Weert. In 2006 behaalde zij het Gymnasium diploma aan de Philips van Horne Scholengemeenschap te Weert. Na het afronden van de bachelor pedagogische wetenschappen aan de Radboud Universiteit Nijmegen, volgde zij de tweejarige Research Master 'Behavioral Science' waarin zij onderzoek deed bij de afdeling Medische Psychologie van het Radboudumc naar onbewuste processen in relatie tot angst voor terugkeer van kanker bij vrouwen die borstkanker hebben gehad. In september 2011 kon zij het onderzoek naar deze angst voortzetten als promotieonderzoek, wat leidde tot dit proefschrift. Tijdens haar promotietraject nam José deel aan de Radboud Da Vinci Challenge, een programma voor excellente promovendi en post-docs gericht op een brede persoonlijke ontwikkeling. Momenteel werkt zij als post-doc binnen de sectie 'Kinderen en Jeugdigen' van de afdeling Medische Psychologie waarin zij onderzoek doet naar kwaliteit van leven bij kinderen met een aangeboren zeldzame ziekte. José woont samen met Wouter en hun dochter Mette in Nijmegen.

> *“In a sense, a person never really ‘gets over’ cancer:*
> *it is a* sword of Damocles *that continues to hang over the individual*
> *and his or her family for the rest of the person’s life”*

Muzzin et al., 1994

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