MASTER THESIS

The Course and Predictors of Fear of Recurrence among Breast Cancer Survivors During the First and Second Year After Surgery

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Abstract

Background

The number of breast cancer survivors (BCS) is increasing due to early detection and improved treatment. Fear of recurrence (FoR) is a major concern among BCS which can have individual and societal consequences. Insights into the course and predictors of FoR could help to prevent (consequences of) high levels of FoR. This study aimed to get insight into the course and predictors of FoR among BCS during the first and second year after surgery.

Method

For this study, a subset of data of a larger study was used (SHOUT-BC study, Netherlands Trial Registry nr. NL8374). Participants were female BCS curatively-treated for invasive breast cancer. A total of 174 patients completed three questionnaires, respectively 1 year (t1), 1.5 years (t2) and 2 years after surgery (t3). FoR was assessed using the six-item Cancer Worry Scale. Participants were classified into stable low, stable high and fluctuating FoR-profiles. Linear mixed models were used to estimate the relationship between FoR-score at t1, t2 and t3. Predictors of FoR were analysed using linear regression models (continuous FoR-score at three timepoints) and multinomial logistic regression models (for the compiled FoR-profiles). Possible predictors were demographic, tumour and treatment characteristics, health literacy, risk perceptions, illness perceptions, quality of life, knowledge about breast cancer surveillance, patient-reported shared decision making and patient-reported received information.

Results

FoR did not change significantly over time. In total, 58% of the patients reported consistently high FoR-scores, 29.3% reported fluctuated FoR-scores and 12.6% reported consistently low FoR-scores. Age, health literacy, cure beliefs and mental health status were significantly associated with continuous FoR at least at one of the three timepoints. The total amount of explained variance was around 40% for all three final models (Nagelkerke $R2_{t1}$=0.373, $R2_{t2}$=0.378, $R2_{t3}$=0.417). Patients with lower cure beliefs (stable high OR=0.654; fluctuating OR=0.778) and patients with lower mental health scores (stable high OR=0.844) were more likely to belong to the stable high or fluctuating profile compared to the stable low profile. However, the relationship between predictors and the compiled FoR-profiles was low (Nagelkerke R2=0.300), indicating that FoR-profiles were difficult to predict with the variables available in this study.

Conclusions

The majority of BCS reported high levels of FoR at all three timepoints, indicating that FoR remained high during the first and second year after surgery. Future research should focus on the development and implementation of interventions to reduce elevated levels of FoR taking into account personal approaches, such as age, cure beliefs and mental health status. Predicting FoR was difficult with the demographic, tumour and treatment characteristics available in this study. Future research is necessary to identify at-risk groups who have a greater risk of experiencing elevated levels of FoR.

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Introduction

In recent years, the incidence of invasive breast cancer has risen and almost doubled in the Netherlands since 1989 (1, 2). Yearly, about 15.000 women are diagnosed with invasive breast cancer in the Netherlands (1, 2). Survival rates have also increased in recent years, due to improved treatment strategies and increased early detection of breast cancer (1-4). The increased incidence and survival rates led to an increase in the number of breast cancer survivors receiving follow-up care (4-8).

Follow-up care can be divided in two parts: (post-treatment) surveillance and aftercare (9). Surveillance includes physical examinations and diagnostic imaging techniques with as main aim the early detection of local regional recurrences (LRR) and second primary breast cancer (SPBC) (9-11). The Dutch guideline for breast cancer states that the surveillance of curatively cured breast cancer patients consists of an annual mammogram for at least five years (12). The term 'aftercare' is defined as "limiting the burden of disease, rehabilitation and signalling, guiding and treating (late) consequences of (the treatment of) cancer" (9, 10).

Breast cancer survivorship is often associated with psychosocial consequences (13). One of these consequences is fear of cancer recurrence (FoR) which is defined as "the fear or worry that cancer will return, progress or metastasize" and is a major concern among breast cancer survivors (14-18). Moderate FoR levels among cancer patients are expected to occur, since it is a normal and rational response to a life-threatening disease like cancer (17-19). However, most (long-term) breast cancer survivors, even the ones with a good prognosis, experience moderate FoR (14, 16-20). Possible consequences of high levels of FoR are functional impairment, anxiety disorders, post-traumatic stress symptoms, depression and increased healthcare use and costs (18, 21, 22). In addition, high FoR levels could cause an overestimation of the recurrence risk, which is negatively associated with more frequent worry, psychological distress and lower quality of life (QoL) (14, 17, 23). To prevent (severe) consequences of high levels of FoR better guidance is needed.

An important step in developing appropriate guidance is understanding the factors that are associated with (high levels of) FoR. Younger age was significantly associated with greater FoR among breast cancer survivors in several studies (16-18, 24). Simard et al. (16) investigated the possible predictors of FoR in a review and found strong evidence[1] for the following predictors: presence or severity of physical problems, distress, depression, anxiety, avoidance and lower QoL were all negatively associated with FoR. Koch et al. (17) added the following statistically significant predictors: lower educational level, undergoing breast-conservating therapy, having cancer-related consultations with a physician during the past year and considering themselves as a tumour patients. However, both studies acknowledged that the overall pattern of studies investigating predictors of FoR was heterogeneous, with other studies reporting non-significant or even contradictory findings (16, 17, 20). In addition, the studies that were included in the review used a variety of measures to assess FoR which made comparisons difficult (20).

Research on the course of FoR over time has also been performed. FoR can fluctuate during the years after treatment. It can be increased by: a cancer diagnosis from a relative, media attention, regular check-ups and/or disruption of periodic follow-up appointments (e.g. the COVID-19 pandemic) (18, 19). Simard et al. (16) reported in a review that several studies have examined the course of FoR in cancer survivors over time, but that there is little consensus between these studies and only a few studies were focused on breast cancer survivorship. A recent study by Custers et al. (25) describes that the course of FoR among breast cancer survivors has received little attention in literature and studies have varying findings (25). In about half of the studies FoR decreased over time (26-32). Other studies reported a stabilization or fluctuation of FoR over time (16, 24, 25, 33-38). However, comparing studies on the course of FoR over time is complicated, because different instruments are used to assess FoR and the timing in the clinical pathway and number of data collection points differ (25). Most studies focused on timepoints around time of diagnosis, time of surgery or time of treatment. In this way, only conclusions could be made about FoR prior- and post-diagnosis, operative period or treatment and not during the years after treatment.

It is important that breast cancer survivors get the support they need during the follow-up phase of their illness to address elevated levels of FoR and prevent high levels of FoR and its' consequences

[1] With a significant consistent finding in more than five studies.

(29). However, there is a gap between research and practice and current aftercare does not meet the needs from cancer survivors to address elevated levels of FoR (22, 35, 39). In addition, there is a growing demand for personalised follow-up care (40). In which personalised surveillance should be focused on the patients' personal risk on recurrences, which can be calculated with the INFLUENCE-nomogram (41), and personalised aftercare should be focused on the patients' needs (40). Insights into the course of FoR and possible associated factors could eventually support the adjustment of follow-up care to the patients' needs including the patients' potential risk of experiencing high levels of FoR.

This study investigates the course of FoR among breast cancer survivors during the first and second year after surgery to identify the proportion of participants with stable low, stable high and fluctuating levels of FoR using a descriptive approach. In addition, this study aims to identify possible predictors of FoR, which can help to identify breast cancer survivors who are more vulnerable to experience high levels of FoR.

Methods

Design

For this study, a subset of the data of the pre-introduction phase of the 'SHared decision-making supported by OUTcome information regarding Breast Cancer follow-up' (SHOUT-BC) study was used. This study is initiated by Santeon[2] and started in November 2019. The SHOUT-BC study investigates "the implementation and effectiveness of shared decision-making (SDM) supported by outcome information in patients and healthcare professionals who have to make a choice regarding the organisation of breast cancer surveillance" (42). The SHOUT-BC study uses a Multiple Interrupted Time Series (miTS) including seven clusters (43). Through continuous sequence of observations, taken repeatedly at equal time intervals, underlying trends can be established on outcomes of interest, which are 'interrupted' by the introduction of SDM supported by outcome data at known timepoints. The SHOUT-BC study consists of three phases: pre-introduction phase, transitionary phase and post-introduction phase. In the pre-introduction phase, the 'old situation' (the current follow-up care[3]) is observed. The transitionary phase consists of the implementation of SDM supported by outcome information with the use of a Patient Decision Aid (PtDA). At last, in the post-introduction phase, the 'new situation' (the use of SDM supported by outcome information) will be observed.

Patients and Procedures

The study population consisted of female patients, 18 years or older, facing the decision for the organisation of surveillance after receiving curative treatment for invasive breast cancer. Patients from eight regional Dutch hospitals were included. To participate in the study, patients were asked to sign informed consent. Furthermore, access to and experience with using computer devices (with internet connection) and ability to speak and write in Dutch language was required. If necessary, patients were assisted by their caregiver. Patients were excluded from the study if they were diagnosed with non-invasive breast cancer, had predisposing genetic mutations related to breast cancer, were diagnosed with recurrences or second primary tumours, received palliative treatment, received neoadjuvant systemic therapy or had dementia.

Potential participants were informed by their healthcare professional (HCP) during their first surveillance consultation, which takes place about one year after surgery. Interested potential participants received information about the study during the consultation by receiving the patient information form (PIF) and informed consent. Informed consent was signed by the potential participants who agreed to participate. The informed consent included information about the fact that participation was voluntary, and that the participant could withdraw at any moment without giving any reason. Eligible participants received three online questionnaires, the first one was sent directly after the first surveillance consultation, respectively 1 year after surgery. The two following questionnaires were sent six and twelve months after the first questionnaire, respectively 1.5 and 2 years after surgery.

In this study, data of participants who received and completed three questionnaires between November 2019 and December 2021 were analysed. Patients who did not yet receive the third questionnaire, due to time of inclusion and receipt of the first questionnaire, were excluded from the data analysis. Next, patients who failed to complete the Cancer Worry Scale (CWS) on any of the three timepoints or who did not start the questionnaire were excluded from the data analysis. Data from the post-introduction phase of the SHOUT-BC study was deleted from the dataset. Overall, 174 of 294 participants (59.2%) received and completed three SHOUT-BC questionnaires. Figure 1 shows the flowchart from eligible participants to the sample size of this study.

[2] Santeon is a cooperative organisation of seven Dutch hospitals that collaborate based on the principles of value-based healthcare to continuously improve care.

[3] Research shows that SDM is not often practiced in the current follow-up care.

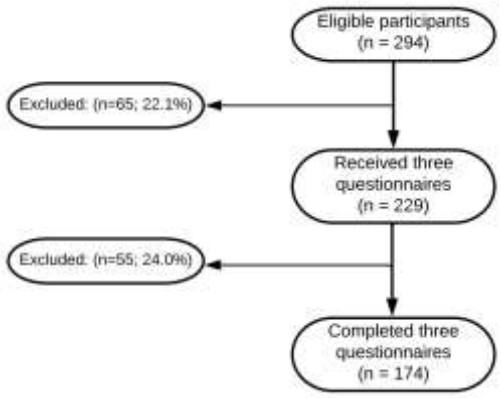

***Figure 1**: Flowchart from eligible participants to sample size of the study*

Measures

The participants received three online questionnaires. The questionnaires consisted of different components. The general questions, decision-making, thoughts about your illness, concerns about your illness, risk perception, outcome information, well-being and knowledge questions were used in this study. The exact wording of the questions and answering options can be found in Appendix A.

Fear of Recurrence

FoR was assessed using a six-item version of the Cancer Worry Scale (CWS) (44). The CWS "assesses concerns of cancer recurrence and the impact of these concerns on daily functioning" and is a valid and reliable measure for FoR in cancer patients (44).The CWS was rated on a four-point Likert scale, ranging from 'never' to 'almost always'. Total scores were calculated by summation of the six items and ranged from 6 to 24. A high score indicated high level of worry (i.e. FoR) (44). In this study, a cut-off value of 12 was used, which indicated that a score of 12 or higher meant that the patient was experiencing high levels of FoR (44).

Participants were divided into three profiles according to the course of their CWS-score over the three timepoints including a profile with stable low levels of FoR, a profile with stable high levels of FoR and a profile with fluctuating levels of FoR, this indicated the following:

- Stable low levels of FoR: Total CWS score of 11 or lower on each questionnaire
- Stable high levels of FoR: Total CWS score of 12 or higher on each questionnaire
- Fluctuating levels of FoR: Total CWS scores both above and below the cut-off value of 12 on the questionnaires.

Possible predictors of FoR

The possible predictors were: demographic, tumour and treatment characteristics, health literacy, risk perceptions, illness perceptions, QoL, knowledge about breast cancer surveillance, patient-reported SDM and patient-reported received information.

The *demographic characteristics* included **age, marital status, daily activities** and **education**. Information was derived from the general questions of the first questionnaire. The *tumour characteristics* that were examined as potential predictors were: **tumour size**, **nodal involvement**, **differentiation**, **ER-status**, **PR-status**, **HER-status** and **multi focality**. Receiving **radiation therapy, adjuvant chemotherapy** or **hormone therapy** and **type of operation** were *treatment characteristics* that were investigated as possible predictors in this study. Information about tumour and treatment characteristics were obtained from the patients' electronic health record.

Health literacy was assessed using the Set of Brief Screening Questions (SBSQ) (45). The SBSQ consisted of three questions on a five-point Likert scale. The first and third question of the SBSQ had a scale ranging from 'never' to 'always'. The second question of the SBSQ was scaled from 'not sure at all' to 'very sure'. Every question was scored from 1 till 5, any answer that was three or higher on any question of the 3-item SBSQ indicated inadequate health literacy (45).

Risk perceptions were assessed using a self-administered three-item questionnaire. The first question assessed the **recurrence risk estimation** by asking the participant about the risk of breast cancer

recurrence in the same or other breast. Answering options were: 1 in 1000, 1 in 100, 1 in 50, 1 in 25, 1 in 10 and 1 in 5. The second question assessed the **recurrence risk appraisal** by asking the participant to rate their risk of breast cancer recurrence in the same or other breast on a five-point Likert scale, ranging from 'very low' to 'very high'. The third question assessed the **comparative recurrence risk** by asking the participant to compare their own risk on breast cancer recurrence in the same or other breast to the average risk of women who have had breast cancer. The comparative recurrence risk was rated on a five-point Likert scale, ranging from 'much lower' to 'much higher'.

Illness perceptions were assessed using two domains of the Illness Perceptions Questionnaire for Breast Cancer Survivors (IPQ-BCS) (46). The two domains were: **cure beliefs** and **personal control over recurrence**. Both domains included four questions and were scored on a five-point Likert scale, ranging from 'strongly agree' to 'strongly disagree' (46). Total scores were calculated per subscale by adding up the answers. Prior to this, three items were re-coded by reversing the scores. Total scores for both subscales ranged from 4-20. Higher scores in the cure and personal control domains indicated that women had strong beliefs that their breast cancer was cured and that women thought their actions influenced the recurrence of breast cancer.

Quality of life (QoL) was assessed using the Short-Form Health Index (SF-12), which is a validated tool to assess general QoL (47). The SF-12 consisted of 12 questions with 8 scales and two summary measures: Physical Health Status (PCS) and Mental Health Status (MCS) (47, 48). Scales were scored according to the standard scoring method, which included the recoding of four items. Thereafter indicator variables were created, weighting and aggregation of indicator variables was performed and the scale scores were norm-based standardized (48). Eventually, two component scores were calculated: PCS as MCS, where higher scores indicated better physical and mental well-being (47, 49, 50).

The **patients' knowledge** about breast cancer surveillance was assessed using a self-administered ten-item questionnaire. Participants were shown ten statements about surveillance after breast cancer and were asked to choose one of the following options: 'correct', 'incorrect' or 'I do not know'. Scores ranged from 1-10. One point was awarded for each right answered question. If the participant had answered the question with 'I do not know', the question was automatically assessed as wrong.

The extent of **patient-reported SDM** was assessed using the 9-item Shared Decision-Making Questionnaire (SDM-Q-9) (51). The SDM-Q-9 is validated for use among various types of cancer survivors (52). The SDM-Q-9 assessed the patients' perceived level of involvement in the decision-making process and was rated on a six-point Likert scale, ranging from 'totally disagree' to 'totally agree'. A total score was calculated by summing up the score of the nine items, then multiplying it by 20 and dividing it by 9. In this way, the total scores were rescaled to a 0-100 range, where 0 indicated the lowest possible level of SDM and 100 indicated the highest possible level of SDM (53).

The amount of **patient-reported received information** was assessed using one item of a self-administered four-item questionnaire. In this study, only the first main question with the sub questions about emotional and mood problems, stress prior to periodic controls, risk on recurrence of breast cancer and risk of death were used. The first main question included whether the exchange of information about these topics took place. The participant was asked to answer this question using the following answer options: 'yes', 'no', 'I do not know'. If the participant had answered the question with 'I do not know', the answer was transformed into 'no'. Total scores ranged from 0-4.

Data Analysis

All statistical analyses were performed using RStudio (version: 1.3.1073).

Descriptive statistics were used to describe the participants according demographic, tumour and treatment characteristics. To obtain insight in the individual recurrence risk of the participants, the overall five-year locoregional recurrence risk was calculated using the INFLUENCE 2.0-nomogram (*available at: www.evidencio.com/models/show/2238/nl*) (54). The five-year locoregional recurrence risk could not be calculated for three participants due to missing values of one or more demographic, tumour or treatment characteristic(s).

Linear Mixed Model Fits were used with Restricted Maximum Likelihood (REML) to estimate the relationship between FoR-score and Time (i.d. the course of FoR using the three timepoints). Pairwise

comparisons were performed using t-tests with the Bonferroni Method. Preliminary analyses were conducted to ensure no violation of the assumptions. The ANOVA outcome and pairwise comparisons were reported, with p values ≤ 0.05 considered statistically significant.

We explored possible predictors of the continuous FoR-score at three timepoints using linear regression modelling. A total of 26 predictor variables (numerical and categorical) were entered in the linear regression model, including demographic, tumour and treatment characteristics, health literacy, risk perceptions, illness perceptions, QoL, patients' knowledge, patient-reported SDM and patient-reported received information. Participants with missing values were excluded from the linear regression models. Univariate and multivariate analyses were performed to ascertain associations between the continuous FoR-score at the three timepoints and the possible predictors. Preliminary analyses were conducted to ensure no violation of the assumptions. Coefficients and p values were reported, with p values ≤ 0.05 considered statistically significant. Nagelkerke's R-squared (R^2) was calculated to determine the proportion of variance explained by the final multivariate regression model.

In addition, we explored possible predictors of different FoR-profiles using multinomial logistic regression modelling. The possible predictors included demographic, tumour and treatment characteristics, health literacy, patients' knowledge, patient-reported SDM and patient-reported received information. In addition, risk perceptions, illness perceptions, and QoL were included as possible predictors and were retrieved from the first questionnaire (t1). Stable low levels of FoR was set as reference category. Participants with missing values were excluded from the multinomial regression model. Univariate and multivariate analyses were performed to ascertain associations between the compiled FoR-profiles and the possible predictors. Conditions of the final multivariate model included that there should be at least five participants in the subgroups of the categorical variables per profile for accurate predictions. Preliminary analyses were conducted to ensure no violation of the assumptions. Odds Ratios (ORs) with 95% confidence intervals (CI), Nagelkerke's R^2 and p values were reported. P values were calculated using Wald tests, with p values ≤ 0.05 considered statistically significant.

Results

Sample Descriptives

The mean age of the participants was 59.9 (SD = 9.75). Most reported being married or having a partner (76%), having no or an unpaid job (57%) and moderate levels of education (48%). The majority of the respondents (87%) had adequate health literacy. Most participants had a tumour smaller than 2 centimetres (68%), no nodal involvement (73%), differentiation grade two (48%), positive ER (90%) and PR status (80%), negative HER-status (93%) and no multi focality (89%). Treatment characteristics were represented with the majority of participants having undergone a lumpectomy (81%), radiotherapy (79%), hormone therapy (57%), and no adjuvant chemotherapy (82%). The mean five-year locoregional recurrence risk was estimated on 3.3% (SD = 2.25). Table 1 shows the demographic, tumour and treatment characteristics of the study cohort.

Table 1: *Demographic, tumour and treatment characteristics of the study cohort (N = 174).*

Characteristics	N	%	Mean (SD)	Min-max		N	%
Demographic characteristics					**Treatment characteristics**		
Age			59.9 (9.75)	29-80			
Marital status					Radiotherapy		
Single	41	23.6			No	36	20.7
Married/Partnered	133	76.4			Yes	138	79.3
Occupation					Adjuvant chemotherapy		
No or unpaid job	99	56.9			No	142	81.6
Paid job	75	43.1			Yes	32	18.4
Education level					Hormone therapy		
Low	26	14.9			No	75	43.1
Moderate	84	48.3			Yes	99	56.9
High	64	36.8					
Health literacy					Type of operation		
Inadequate	22	12.6			Lumpectomy	140	80.5
Adequate	152	87.4			Mastectomy	34	19.5
Tumour characteristics							
Tumour size	119	68.4					
< 2 centimetres	51	29.3					
2-5 centimetres	4	2.3					
> 5 centimetres							
Nodal involvement							
0	127	73.0					
1-3	43	24.7					
> 3	3	1.7					
NA	1	0.6					
Differentiation							
Grade 1	56	32.2					
Grade 2	83	47.7					
Grade 3	35	20.1					
ER-status							
Negative	16	9.2					
Positive	157	90.2					
NA	1	0.6					
PR-status							
Negative	34	19.5					
Positive	139	79.9					
NA	1	0.6					
HER-status							
Negative	161	92.5					
Positive	11	6.3					
NA	2	1.1					
Multi focality							
No	154	88.5					
Yes	20	11.5					
Five-year locoregional recurrence risk percentage			3.31(2.25)	1.3-20.4			

Abbreviations: SD, Standard Deviation; ER, estrogen receptor; PR, progesterone receptor; HER, human epidermal growth receptor

Course of Fear of Recurrence

The mean FoR-score for the 174 participants was 14.0 (SD = 3.40) at t1, 13.9 (SD = 3.52) at t2 and 13.6 (SD = 3.66) at t3. However, FoR did not change significantly over time ($F(2,346) = 2.17$, $p=0.1155$, $\eta p2 = 0.01$). At all three timepoints the mean FoR-score exceeded the cut-off value of 12, which indicated high levels of FoR. The greatest decline between consecutive timepoints was found between t2 and t3, where the mean FoR-score declined with 0.3. However, Bonferroni corrected post hoc comparisons revealed that these differences were not significant. Table 2 shows the means, SDs and ranges of the FoR-score at the three different timepoints and table 3 shows the pairwise comparisons.

Table 2: *Means, standard deviations (SDs) and ranges of the Cancer Worry Scale (six-item) to assess Fear of Recurrence at the three different timepoints.*

Timepoint	N	Mean	SD	Min-max
1 year after surgery (t1)	174	14.0	3.40	6-24
1.5 years after surgery (t2)	174	13.9	3.52	6-24
2 years after surgery (t3)	174	13.6	3.66	6-24

Table 3: *Pairwise comparisons between the three different timepoints with estimates, standard deviations (SDs) and p values.*

Comparison	Estimate	SD	p
1 year after surgery vs. 1.5 years after surgery (t1 – t2)	-0.0632	0.198	1.0000
1 year after surgery vs. 2 years after surgery (t1 – t3)	-0.3851	0.198	0.1584
1.5 years after surgery vs. 2 years after surgery (t2 – t3)	-0.3218	0.198	0.3157

Classification of participants into stable low, stable high and fluctuating levels of FoR

The 174 participants were classified into the three compiled FoR-profiles, which resulted in 22 participants (12.6%) reporting low levels of FoR at all three timepoints, indicating stable low levels of FoR. 51 participants (29.3%) reported scores which fluctuated above and below the cut-off value over the three timepoints, and the majority (n = 101, 58.0%) reported scores consistently above the cut-off value, which indicated stable high levels of FoR. Table 4 provides an overview of the three profiles. There were no significant differences comparing the demographic, tumour and treatment characteristics between the three profiles. The demographic, tumour and treatment characteristics of the participants in the three different profiles can be found in appendix B.

Table 4: *Division of participants into stable low, stable high and fluctuating levels of FoR.*

Profiles	N	% of all participants
Stable low	22	12.6
Stable high	101	58.0
Fluctuating	51	29.3

Specification of the fluctuating profile

The fluctuating profile was further divided into different levels looking at the three timepoints, this distribution is shown in table 5. Almost half of the participants of the fluctuating profile (47.1%) started with high levels of FoR at t1 and ended with low levels of FoR at t3. This included more than a quarter of the participants (27.5%) who started with high levels of FoR at t1 and t2 and then decreased into low levels of FoR at t3. Almost 30% of the participants (29.4%) with fluctuating levels of FoR started with low levels of FoR and ended with high levels of FoR. At last, almost a quarter of the participants (23.6%) were fluctuating from t1 to t2 and t2 to t3, which indicated that they started and ended with the same levels of FoR.

Table 5: *Specification of the fluctuating profile into high-high-low, high-low-high, high-low-low, low-high-low, low-low-high and low-high-high profiles based on CWS-score at the three timepoints (n=51).*

	N	%
High-High-Low	14	27.5
High-Low-High	6	11.8
High-Low-Low	10	19.6
Low-High-Low	6	11.8
Low-Low-High	3	5.9
Low-High-High	12	23.5

Predictors of FoR

Both regression models were performed with a sample size of 171, due to missing values on one or more variables of three participants.

Predictors of continuous FoR-score at the three timepoints

The results of the univariate linear regression analyses comparing demographic, tumour and treatment characteristics, health literacy, illness perceptions, QoL, knowledge about breast cancer surveillance, patient-reported SDM and patient-reported received information of participants between the continuous FoR-score at the three different timepoints can be found in appendix C. Risk perceptions were left out of these analyses, since it violated the multi-collinearity assumption. Significant variables of each univariate analysis per timepoint were taken into account in the multivariate analysis per timepoint. Nine variables (age, health literacy, nodal involvement, adjuvant chemotherapy, type of operation, cure beliefs, mental health status, physical health status and patient-reported SDM) of the 26 possible predictors were significant associated with the continuous FoR-score at least at one of the three timepoints.

The results of the multivariate linear regression analyses are shown in table 6. The total amount of explained variance was around 40% for all three final models, ranging from 37.3% till 41.7%. Age, cure beliefs and mental health status were important predictors at all timepoints. Health literacy was significant associated with FoR-score at t1. As the health literacy score increased with one unit, indicating lower health literacy, the FoR significantly increased with 0.450. Age, cure beliefs and mental health status were significant negatively associated with FoR-score at all three timepoints, indicating that younger women, lower cure beliefs and lower mental health status led to higher levels of FoR.

Table 6: *Multivariate linear regression analysis of the effect of significant predictors from the univariate analysis on continuous FoR-score at three different timepoints*

	1 year after surgery (t1)		**1.5 years after surgery (t2)**		**2 years after surgery (t3)**	
	ß	**p**	**ß**	**p**	**ß**	**p**
Age	-0.214	**0.001**	-0.167	**0.011**	-0.169	**0.007**
Health literacy	0.147	**0.026**	^	^	0.096	0.119
Nodal Involvement [1-3]	0.029	0.657	-0.059	0.383	^	^
Nodal Involvement [>3]	0.036	0.595	0.076	0.271	^	^
Adjuvant chemotherapy	^	^	-0.005	0.945	^	^
Type of operation [mastectomy]	0.013	0.844	0.121	0.074	0.112	0.071
Cure Beliefs	-0.281	**0.000**	-0.265	**0.000**	-0.357	**0.000**
Mental Health Status	-0.319	**0.000**	-0.380	**0.000**	-0.301	**0.000**
Physical Health Status	-0.018	0.788	-0.108	0.097	-0.122	0.051
Patient-reported SDM	-0.074	0.259	-0.039	0.548	-0.014	0.824
R2	***0.373***		***0.378***		***0.417***	
Regression equation (F-statistic)	***F(9,161)=10.635, p < 0.000***		***F(9,161)=10.871, p < 0.000***		***F(7,163)=16.657, p < 0.000***	

^ *This variable was not significant in the univariate analysis and is therefore not included in the multivariate analysis.*

Predictors for the FoR-profiles

The three participants with missing values were classified in the stable high (2x) and fluctuating profile. The multinomial logistic regression model is therefore performed with 22 participants with stable low levels of FoR, 99 participants with stable high levels of FoR and 50 participants with fluctuating levels of FoR. The results of the univariate multinomial logistic regression analyses comparing demographic, tumour and treatment characteristics, health literacy, risk perceptions, illness perceptions, QoL, knowledge about breast cancer surveillance, patient-reported SDM and patient-reported received information of participants between the three FoR-profiles can be found in appendix D. Nine variables (tumour size, nodal involvement, ER-status, hormone therapy, cure beliefs, mental health status, absolute risk perception, recurrence risk appraisal and comparative recurrence risk) of the 26 possible predictors were significantly different between the profiles in the univariate multinomial logistic regression analysis (table 7). These variables were therefore selected to be included in the final model. However, nodal involvement, ER-status, absolute risk perception, recurrence risk appraisal and comparative recurrence risk were left out of the final model since it did not fulfil the predefined condition (≥5 participants in the subgroup of the categorical variables in each profile).

Table 7: *Univariate multinomial logistic regression analysis of the effect of significant possible predictors on the three different FoR-profiles.*

	Stable High (n=99) vs. Stable Low (n=22)				Fluctuating (n=50) vs. Stable Low (n=22)			
	B	**OR**[1]	**95% CI**[2]	**p**	**B**	**OR**[1]	**95% CI**[2]	**p**
Tumour Size	0.637	1.890	1.011-3.532	**0.046**	0.259	1.295	0.665-2.522	0.447
Nodal Involvement	2.276	9.736	1.277-74.232	**0.028**	1.896	6.662	0.833-53.300	0.074
ER-status	0.575	1.778	0.508-6.215	0.368	2.388	10.889	1.140-104.027	**0.038**
Hormone Therapy	1.119	3.062	1.172-8.001	**0.022**	0.720	2.054	0.732-5.673	0.171
Cure Beliefs	-0.417	0.659	0.538-0.808	**0.000**	-0.221	0.801	0.652-0.985	**0.036**
Mental Health Status	-0.165	0.848	0.767-0.937	**0.001**	-0.096	0.908	0.820-1.006	0.066
Absolute Risk Perception	1.117	3.056	1.586-5.887	**0.001**	0.825	2.281	1.168-4.456	**0.016**
Recurrence Risk Appraisal	1.946	6.998	3.305-14.818	**0.000**	0.941	2.562	1.254-5.235	**0.010**
Comparative Recurrence Risk	1.096	2.993	1.632-5.486	**0.000**	0.606	1.834	0.991-3.393	0.053

[1] *OR = Odds Ratio*
[2] *CI = Confidence Interval*

The results of the final multivariate multinomial logistic regression model comparing the significant variables of the univariate analysis between the three FoR-profiles is shown in table 8. The relationship between predictors and the FoR-profiles, with cure beliefs and mental health status as important factors, was 30% (Nagelkerke R2 = 0.300) in the final model. Cure beliefs and mental health status remained significant predictors for at least one profile. The model revealed that patients with lower cure beliefs (stable high OR = 0.654; fluctuating OR = 0.778) were more likely to belong to the stable high or fluctuating profile than to the stable low profile. In addition, patients with lower mental health scores (OR = 0.844) were more likely to belong to the stable high profile compared to the stable low profile. Figure 2 presents the ORs and their respective 95% confidence intervals of the final model.

Table 8: *Multivariate multinomial logistic regression analysis of the effect of significant possible predictors from the univariate analysis on the three different FoR-profiles.*

	Stable High vs. Stable Low				Fluctuating vs. Stable Low			
	B	**OR**[1]	**95% CI**[2]	**p**	**B**	**OR**[1]	**95% CI**[2]	**p**
Cure Beliefs	-0.424	0.654	0.522-0.820	**0.000**	-0.251	0.778	0.623-0.972	**0.027**
Mental Health Status	-0.169	0.844	0.752-0.948	**0.004**	-0.108	0.898	0.799-1.008	0.069
Tumour Size	0.650	1.916	0.845-4.346	0.120	0.263	1.301	0.565-2.998	0.536
Hormone Therapy	0.831	2.297	0.677-7.790	0.182	0.689	1.992	0.583-6.809	0.272
Pseudo R2	***0.300***							

[1] *OR = Odds Ratio*
[2] *CI = Confidence Interval*

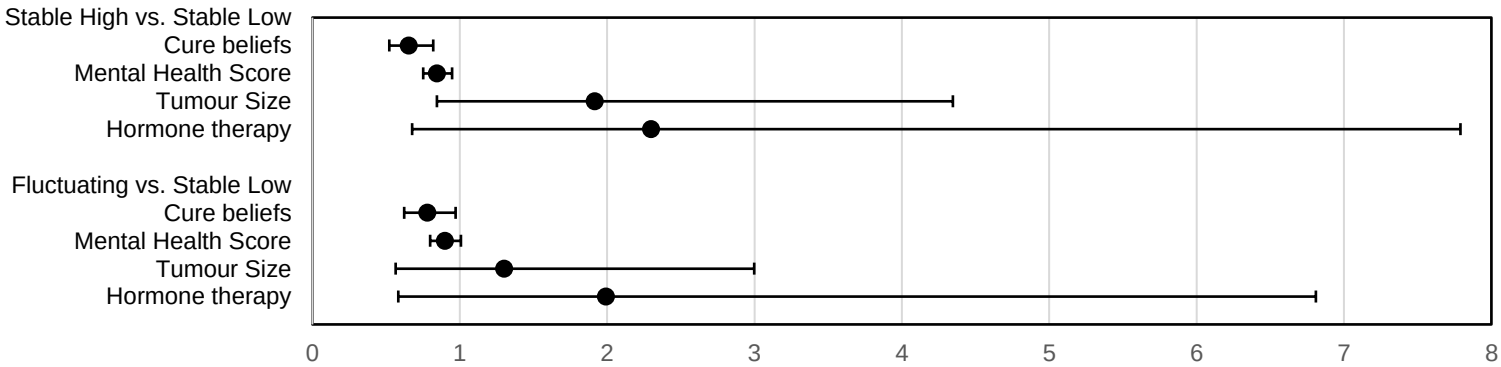

Figure 2*: Forest plot showing Odds Ratios (ORs) and their respective 95% confidence intervals of cure beliefs, mental health score, tumour size and hormone therapy predicting membership of the three FoR-profiles.*

Discussion

In this study the course of FoR among breast cancer survivors during the first and second year after surgery was investigated and predictors associated with FoR on different timepoints and for different FoR-profiles (stable low, fluctuating, and stable high) were identified.
This study found that FoR did not change significantly over time. More than half of the participants (58%) reported high levels of FoR (above the cut-off value of 12) at each timepoint, while approximately 30% reported fluctuating FoR-scores and 12% reported low levels of FoR at each timepoint. Almost 50% of the participants within the fluctuating profile started with high levels of FoR at t1 and ended with low levels of FoR at t3.
Age, cure beliefs and mental health status were found to have a significant association with higher continuous FoR-score at all three timepoints. Health literacy was significant associated with continuous FoR-score at t1. In addition, patients with lower cure beliefs and patients with lower mental health scores were more likely to belong to the stable high or fluctuating profile compared to the stable low profile.

Course of FoR

In our knowledge, this is one of the first studies that focused on the course of FoR in breast cancer patients during the first and second year after surgery. Thus far studies that investigated the course of FoR within breast cancer patients mainly focused on timepoints around time of diagnosis or surgery and compared FoR pre- and post-diagnosis or pre- and post-surgery until one year after surgery. Therefore, findings about the course of FoR remain inconclusive and it is difficult to compare findings due to different timing points and tools to assess FoR.

This study found a concerning high number of breast cancer survivors (58%) reporting stable high levels of FoR during the first and second year after surgery, indicating that FoR was high at all three timepoints. The study by Custers et al. (25) is one of the few studies that also classified their sample in participants with stable low, stable high and fluctuating levels of FoR and found that 21.6% of their participants reported high FoR-scores at each timepoint. Comparing these results with the current study shows that the amount of breast cancer survivors with stable high levels of FoR in the current study is almost three times as high as found in the study by Custers et al. (25). The study by Custers et al. (25) used a comparable sample looking at similar demographic, tumour and treatment characteristics. However, the study by Custers et al. (25) included participants 0-5 years after breast cancer surgery, with an average of 2.8 years after surgery, from one academic and two regional hospitals and assessed FoR with the complete CWS (8-item) monthly during 12 months. The current study included participants one year after surgery, from eight regional hospitals and assessed FoR with the six-item CWS three times within 12 months.

The current study specificized the fluctuating profile by looking at the FoR-levels per timepoint. Prior studies that investigated the course of FoR only looked at the amount of participants with fluctuating levels of FoR (25, 55). The current study found that almost 30% of the participants reported fluctuating levels of FoR. This is not in line with research by Custers et al. (25) who found that the majority (57.8%) of breast cancer survivors 0-5 years after surgery reported fluctuating FoR-scores and research by Savard & Ivers (55) who found that 55.4% of the breast cancer participants in their study changed at least one time from non-clinical to clinical levels of FoR in the 18 months after surgery.

Predictors of FoR

In our knowledge, this is one of the first studies that analysed predictors of FoR using three different timepoints and focused on possible predictors of different FoR-profiles. Thus far studies that investigated predictors of FoR have focused on one single timepoint, which was often early in the care process, and did not focus on FoR-profiles. The significant associations that were found between the compiled FoR-profiles and significant predictors (cure beliefs and mental health status) can therefore not be compared with other studies. However, the current study found that predicting FoR-profiles remained difficult with all predictors available in this study (Nagelkerke R2 = 0.300).

In the current study, health literacy was identified as predictor of continuous FoR-score at one year after surgery (t1). To date, little research has been conducted about the association of FoR and health literacy. A systematic review by Holden et al. (56) about the role of health literacy in cancer care showed that lower health literacy was associated with increased fear of progression within older breast cancer patients and with higher FoR in patients with head and neck cancers. HCPs could help patients with low health literacy by giving more information, time and attention and by encouraging patients to

ask questions, where it might be helpful to ask patients to repeat the received information in their own words (57).

Age, cure beliefs and mental health status were significant associated with a decrease of the continuous FoR-score at one year after surgery (t1), 1.5 years after surgery (t2) and two years after surgery (t3). This is in line with the review by Simard et al. (16), where age and QoL, both physical as mental, were identified as significant predictors of FoR in multiple studies. The significant association between FoR and cure beliefs is also found in the study by Lee et al. (58) who showed that high illness perceptions, including low cure beliefs, significantly contribute to FoR and research by Koch et al. (17) who stated that patients who consider themselves as cancer patients are significantly associated with higher levels of FoR. Follow-up care could be adjusted taken into account personal approaches by focusing on younger patients and measuring cure beliefs and mental health status.

Cure beliefs and mental health status were both significantly associated with continuous FoR at all three timepoints and the compiled FoR-profiles. HCPs could have an important role in improving cure beliefs and mental health status and possibly reducing FoR. Cure beliefs could be improved by preventing misperceptions of the recurrence risk and improving patient-provider communication. Several studies reported that patients often misunderstand their locoregional recurrence risk and anxiety is associated with these misperceptions of risk (57-59). Research by Janz et al. (57) reported that effective doctor-patient communication is critical for the patient to understand their risk of recurrence. The use of a prediction model, such as the INFLUENCE nomogram, could help by communicating and discussing the recurrence risk and making decisions about follow-up care. The INFLUENCE nomogram estimates the individual overall five-year locoregional recurrence risk, and the separate annual risks, in breast cancer patients using patient, disease and treatment characteristics (7, 11, 41). The research by Ankersmid et al. (60) showed that patients are open to the use of personalised risk assessment for recurrences in decision-making about surveillance with the condition that risk information is accessible, understandable and personal considerations are addressed. This can be achieved using a PtDA, which ensures that the patient is informed in a good and clear way in order to make a decision about their health trajectory (61, 62).
HCPs could improve mental health status by better monitoring, guiding and referring patients with poor mental health status. The HCPs could for example refer breast cancer survivors with psychosocial problems to social workers or medical psychologists within the hospital (9). This is especially important since cancer patients are reluctant in discussing mental health problems and asking for help (14). In addition, good communication between these healthcare providers is important, since discordant expectations and assumptions about who is responsible for psychosocial problems sometimes occur (14). However, the direction of the relationship between mental health status and FoR is unknown in the current study. The question is whether lower mental health status led to higher levels of FoR or that higher levels of FoR led to lower mental health status. It is therefore uncertain whether improving mental health status will reduce FoR.

Age was the only demographic characteristic (out of 4) that was significantly associated with FoR in the current study. None of the seven tumour or four treatment characteristics were significantly associated with FoR at any timepoint or within the FoR-profiles. This is interesting since the INFLUENCE-nomogram estimates the individual overall five-year locoregional recurrence risk in breast cancer patients using the same tumour and treatment characteristics available in this study (7, 11, 41). One might expect that the same tumour and treatment characteristics, that are used to calculate the five-years locoregional recurrence risk, will also be associated with the experienced FoR of the patient. For example, a patient with a high locoregional recurrence risk will also report high levels of FoR. The current study does not amplify these expectations. However, it is important to know that the participants in this study did not receive their five-years locoregional recurrence risk and are possibly not aware of the fact that their demographic, tumour and treatment characteristics affect their five-years locoregional recurrence risk. Currently the relationship between knowing the locoregional recurrence risk as a patient and experienced FoR is unknown. The review by Ahmed et al. (63) reported that the incorporation of the personalised risk estimates may increases knowledge and accuracy of risk and may enhance informed choices, but may not significantly affect the patients' anxiety. Future research should investigate whether knowing the personal locoregional recurrence risk (with the corresponding explanation of the characteristics) as a patient will influence the patients' FoR.

There was no significant association found between FoR, at any timepoint or within the FoR-profiles, and knowledge about breast cancer surveillance, patient-reported SDM and patient-reported received

information in the current study. One might expect that the amount of knowledge, perceived SDM and/or received information will influence FoR. Only few studies included patient-reported evaluation of care as possible predictor of FoR, which makes comparisons difficult (35). Research by Janz et al. (64) found a significant negative association between healthcare satisfaction, which included satisfaction with received information, symptom management and care coordination, and FoR. Other studies did not find any significant associations (35).

Strengths and limitations

This study is one of the first studies that investigated both the continuous scores at specific timepoints as the association between possible predictors and FoR-profiles during the first and second year after surgery. In this way, membership of the stable low, stable high or fluctuating profile could be predicted which eventually could be used for screening for psychosocial support to reduce elevated levels of FoR.
The main aim of the questionnaires was not to collect information about FoR. This prevented that only participants with elevated levels of FoR signed up to participate in this study (as a need for help) and in this way reduced selection bias. However, it is important to realize that there are still breast cancer survivors that cope with FoR by avoiding threat, which also includes no participation in research projects and/or fill in questionnaires. In addition, this research used data from eight hospitals spread across the Netherlands with dedicated breast cancer accounting for about 11% of Dutch breast cancer care, which indicated a representative sample. The mean age of the sample was almost 60 years one year after surgery, indicating that the sample was younger than the average breast cancer population with an age of 61 at time of diagnosis (65). The tumour and treatment characteristics of the study cohort led to an average five-years locoregional recurrence risk of 3.3% for the total study cohort. This is in line with the research by Witteveen et al. (8) who found an average five-years locoregional recurrence risk of about 3% in their study cohort for all ages.

This study used a sample size of 174 breast cancer survivors, which is a comparable sample size looking at other studies investigating the course and predictors of FoR. However, the participants were divided into three profiles with respectively 22, 51 and 101 participants per profile. In addition, the data included categorical variables with two or more levels, which leaded to subgroups with a low number (≤5) of participants. For example, there was only one participant with a negative ER-status within the fluctuating profile. Performing logistic regression models on such low numbers is difficult and predictions by the models were not always accurate, which explains the high 95% intervals in the univariate and multivariate multinomial logistic regression models. The fluctuating profile was a heterogeneous group with participants whose FoR-score increased and participants whose FoR-score decreased. Performing logistic regression models on such heterogeneous group is difficult and predictions of the models may not always be accurate. Therefore, this study specified the fluctuating profile by looking at the different levels per timepoint. However, the fluctuating profile consisted of 51 participants and dividing these participants into six different groups (table 5) automatically led to a low number of participants per group. Performing logistic regression models on such low number of participants per profile was not possible. For more accurate predictions it is recommended to extend the final multivariate multinomial logistic regression model with more participants, timepoints and/or variables (e.g. co-morbidity, depression). At last, it is important to note that the assumptions belonging to the linear regression model and multinomial logistic regression model were sometimes violated in this study.

The start of the SHOUT-BC study was in November 2019, which is before the start of the still ongoing COVID-19 pandemic. However, data collection continued during the COVID-19 pandemic. It is therefore important to note that the COVID-19 pandemic could influence the results of this study. Research by Koral & Cirak revealed that breast cancer survivors reported higher FoR during the COVID-19 pandemic compared to previous findings (19). In addition, research by Kim & Kim reported twice as much participants with clinical levels of FoR during the COVID-19 pandemic (66). Furthermore, the participants of the current study indicated that aftercare was hampered by the pandemic, especially in the first wave (end February 2020 till June 2020) due to changes in follow-up appointments, such as video appointments. The results of this study were not adjusted for the COVID-19 pandemic. It is therefore important to realize that the COVID-19 pandemic may have impacted the number of participants with stable high and fluctuating levels of FoR in this study. However, the COVID-19 pandemic had no influence on the design of the study, since the three questionnaires were consistently sent and filled in digitally within a timeframe of approximately six months between the questionnaires. Future research should address the effect of the COVID-19 pandemic on FoR in

(breast) cancer patients. The current study could include cancellation of follow-up appointments due to COVID-19 as possible predictor.
To identify low and high levels of FoR, this research used the literature based six-item CWS cut-off value of 12 (44). However, literature about the cut-off value concluded that there was a need for consensus on a definition for clinical FoR and cut-off values. We are aware of the fact that the cut-off value is not the golden standard and has not been validated for identifying clinical levels of FoR.

Further research – SHOUT-BC study

The SHOUT-BC study includes the development and implementation of a PtDA to support shared decision-making about surveillance after breast cancer (67-69). This PtDA is implemented during the transitory phase of the SHOUT-BC study and the implementation and its effectiveness is evaluated in the post-introduction phase of the SHOUT-BC study. The PtDA includes the six-item CWS to discuss FoR during the surveillance meetings and if necessary, appropriate guidance can be offered to the patient (67, 69). The expectation is that this will eventually lead to less breast cancer survivors with high levels of FoR in the post-introduction phase of the study. Once data collection of the post-introduction phase is finished, it is recommended to repeat the analyses performed in the current study using post-introduction phase data. By comparing the findings of the post-introduction phase with the findings of this study (pre-introduction phase), the effects of the PtDA on FoR could be investigated.

In addition, it might be meaningful to extent the current follow-up period of the SHOUT-BC study. For example by yearly questioning the six-item CWS till five years after surgery, which is the end of follow-up care according to the current guideline (12). It would be concerning if the amount of breast cancer survivors with stable high levels of FoR is still considerably high during the fifth year after surgery. Furthermore, it might be interesting to investigate the course of FoR until the fifth year after surgery in combination with the number of participants who are diagnosed with LRR. In this way, results could include information about the amount of diagnosed LRR within participants with stable high levels of FoR and conclusions could be made if the FoR was reasonable and realistic.

Implications for practice

The results of this study provide researchers and clinicians with a concerning high number of breast cancer survivors with stable high levels of FoR during the first and second year after surgery. This amplifies the concern that FoR is a major concern among breast cancer survivors even years after diagnosis. Adjustment of follow-up care and the development of interventions to reduce elevated levels of FoR should take into account personal approaches such as age, cure beliefs and mental health status. Guidance of patients by HCPs is necessary to reduce elevated levels of FoR (70). Overall research into FoR and effective interventions to reduce high levels of FoR is necessary to prevent medical and societal consequences (18, 21, 22).

The results of this study gives researchers and clinicians also insight into the difficulty of predicting FoR with the demographic, tumour and treatment characteristics available in this study. Further research is necessary to identify key predictors of FoR and to identify at-risk groups who have a greater risk of experiencing elevated levels of FoR. This information could be valuable in the development and implementation of effective interventions to reduce FoR.

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Appendices

Appendix A: SHOUT-BC questionnaire

Algemene vragen

1. In welk jaar bent u geboren?

.....

2. Wat is uw burgerlijke staat?

☐ Alleenstaand
☐ Samenwonend / gehuwd
☐ Gescheiden
☐ Weduwe
☐ Anders, nl.: .....

3. Waaruit bestaan momenteel uw voornaamste dagelijkse bezigheden?

☐ Betaalde baan, voor … uur per week (al dan niet in Ziektewet)
☐ WAO / arbeidsongeschikt
☐ AOW / VUT / Pensioen
☐ Vrijwilligerswerk / onbetaalde baan
☐ Huishoudelijke taken
☐ Volgen van studie / opleiding
☐ Anders, nl.: .....

4. Wat is uw hoogst voltooide opleiding?

☐ Geen opleiding (lager onderwijs: niet afgemaakt)
☐ Lager onderwijs (basisschool, speciaal basisonderwijs)
☐ Lager of voorbereidend beroepsonderwijs (zoals LTS, LEAO, LHNO, VMBO)
☐ Middelbaar algemeen voortgezet onderwijs (zoals MAVO, (M)ULO, MBO-kort, VMBO-t)
☐ Middelbaar beroepsonderwijs en beroepsbegeleidend onderwijs (zoals MBO-lang, MTS, MEAO, BOL, BBL, INAS)
☐ Hoger algemeen en voorbereidend wetenschappelijk onderwijs (zoals HAVO, VWO, Atheneum, Gymnasium, HBS, MMS)
☐ Hoger beroepsonderwijs (zoals HBO, HTS, HEAO, HBO-V, kandidaats wetenschappelijk onderwijs)
☐ Wetenschappelijk onderwijs (universiteit)
☐ Anders, nl.: .....

		Nooit	Af en toe	Soms	Vaak	Altijd
5.	Hoe vaak wordt u door iemand geholpen met het lezen van brieven of folders van uw huisarts of van het ziekenhuis?	☐	☐	☐	☐	☐

		Helemaal niet zeker	Een klein beetje zeker	Een beetje zeker	Nogal zeker	Heel erg zeker
6.	Hoe zeker bent u ervan dat u medische formulieren zelf goed invult?	☐	☐	☐	☐	☐

		Nooit	Af en toe	Soms	Vaak	Altijd
7.	Vindt u het moeilijk om meer te weten te komen over uw gezondheid, omdat u geschreven informatie niet goed begrijpt? Zo ja, hoe vaak is dat?	☐	☐	☐	☐	☐

Besluitvorming

De volgende uitspraken gaan over uw ervaringen in het gesprek met uw arts of (verpleegkundig) specialist over de inrichting van uw nacontrole.

Geef alstublieft aan in hoeverre elke uitspraak voor u van toepassing is.

1. Mijn arts / (verpleegkundig) specialist heeft me duidelijk gemaakt dat er een beslissing genomen moet worden over de inrichting van de nacontrole.

helemaal mee oneens	sterk mee oneens	enigszins mee oneens	enigszins mee eens	sterk mee eens	helemaal mee eens
☐	☐	☐	☐	☐	☐

2. Mijn arts / (verpleegkundig) specialist wilde precies van me weten hoe ik betrokken zou willen worden bij het nemen van de beslissing over de inrichting van de nacontrole.

helemaal mee oneens	sterk mee oneens	enigszins mee oneens	enigszins mee eens	sterk mee eens	helemaal mee eens
☐	☐	☐	☐	☐	☐

3. Mijn arts / (verpleegkundig) specialist heeft me verteld dat er voor de inrichting van de nacontrole verschillende mogelijkheden zijn.

helemaal mee oneens	sterk mee oneens	enigszins mee oneens	enigszins mee eens	sterk mee eens	helemaal mee eens
☐	☐	☐	☐	☐	☐

4. Mijn arts / (verpleegkundig) specialist heeft me de voor- en nadelen van de verschillende mogelijkheden voor de inrichting van de nacontrole precies uitgelegd.

helemaal mee oneens	sterk mee oneens	enigszins mee oneens	enigszins mee eens	sterk mee eens	helemaal mee eens
☐	☐	☐	☐	☐	☐

5. Mijn arts / (verpleegkundig) specialist heeft me geholpen alle informatie te begrijpen.

helemaal mee oneens	sterk mee oneens	enigszins mee oneens	enigszins mee eens	sterk mee eens	helemaal mee eens
☐	☐	☐	☐	☐	☐

6. Mijn arts / (verpleegkundig) specialist heeft me gevraagd welke inrichting van de nacontrole mijn voorkeur heeft.

helemaal mee oneens	sterk mee oneens	enigszins mee oneens	enigszins mee eens	sterk mee eens	helemaal mee eens
☐	☐	☐	☐	☐	☐

7. Mijn arts / (verpleegkundig) specialist en ik hebben de verschillende mogelijkheden voor de inrichting van de nacontrole grondig afgewogen.

helemaal mee oneens	sterk mee oneens	enigszins mee oneens	enigszins mee eens	sterk mee eens	helemaal mee eens
☐	☐	☐	☐	☐	☐

8. Mijn arts / (verpleegkundig) specialist en ik hebben samen besloten over hoe we de nacontrole gaan invullen.

helemaal mee oneens	sterk mee oneens	enigszins mee oneens	enigszins mee eens	sterk mee eens	helemaal mee eens
☐	☐	☐	☐	☐	☐

9. Mijn arts / (verpleegkundig) specialist en ik hebben een afspraak gemaakt over het verdere vervolg.

helemaal mee oneens	sterk mee oneens	enigszins mee oneens	enigszins mee eens	sterk mee eens	helemaal mee eens
☐	☐	☐	☐	☐	☐

Gedachten over uw ziekte

We zijn benieuwd hoe u denkt over uw ziekte en behandeling. Kruis alstublieft aan in hoeverre elke uitspraak van toepassing is. Er zijn geen goede of foute antwoorden. Het gaat om uw ervaring.

	Helemaal mee oneens	**Mee oneens**	**Niet mee eens of oneens**	**Mee eens**	**Helemaal mee eens**
1. Door mijn behandeling is mijn borstkanker genezen.	☐	☐	☐	☐	☐
2. Ik heb geen borstkanker meer.	☐	☐	☐	☐	☐
3. Mijn borstkanker is genezen.	☐	☐	☐	☐	☐
4. Ik zie mijzelf nog steeds als borstkankerpatiënt.	☐	☐	☐	☐	☐
5. Er zijn dingen die ik kan doen om te voorkomen dat de borstkanker terugkomt.	☐	☐	☐	☐	☐
6. Wat ik doe, is van invloed op het wel of niet terugkomen van mijn borstkanker.	☐	☐	☐	☐	☐
7. Ik kan zelf niets doen tegen het risico dat de borstkanker terugkomt.	☐	☐	☐	☐	☐
8. Wat ik doe, heeft geen effect op het risico dat de borstkanker terugkomt.	☐	☐	☐	☐	☐

Zorgen over uw ziekte

De volgende vragen gaan over mogelijke zorgen die mensen na de diagnose en behandeling kunnen hebben.

*Geef alstublieft voor elk van de vragen aan hoe vaak u tijdens **de afgelopen maand** deze zorgen heeft gehad.*

	Nooit	**Zelden**	**Soms**	**Bijna altijd**
1. Hoe vaak heeft u gedacht aan uw kans op het (opnieuw) krijgen van borstkanker?	☐	☐	☐	☐
2. Zijn deze gedachten van invloed geweest op uw stemming?	☐	☐	☐	☐
3. Hebben deze gedachten u belemmerd bij het uitvoeren van uw dagelijkse activiteiten?	☐	☐	☐	☐
4. Bent u bezorgd over de mogelijkheid dat u ooit (opnieuw) borstkanker krijgt?	☐	☐	☐	☐
5. Hoe vaak maakt u zich zorgen over het (opnieuw) krijgen van borstkanker?	☐	☐	☐	☐
6. Zijn deze zorgen een probleem voor u?	☐	☐	☐	☐

Risicoperceptie

De volgende vragen gaan over uw inschatting van het risico op terugkeer van borstkanker in dezelfde of de andere borst.

1. Hoe hoog schat u uw risico op terugkeer van borstkanker in dezelfde of de andere borst?

☐ 1 op de 1000
☐ 1 op de 100
☐ 1 op de 50
☐ 1 op de 25
☐ 1 op de 10
☐ 1 op de 5

2. Hoe beoordeelt u uw risico op terugkeer van borstkanker in dezelfde of de andere borst?

Zeer laag	Laag	Niet laag / niet hoog	Hoog	Zeer hoog
☐	☐	☐	☐	☐

3. Hoe schat u uw eigen risico op terugkeer van borstkanker in dezelfde of de andere borst in, in vergelijking met het gemiddelde risico van vrouwen die borstkanker hebben gehad:

☐ Veel lager
☐ Lager
☐ Hetzelfde
☐ Hoger
☐ Veel hoger

Uitkomstinformatie

Indien u beslissingen moet nemen over de nacontrole en nazorg, zou informatie over gevolgen van borstkanker en de behandeling en ervaringen van patiënten in een vergelijkbare situatie u kunnen helpen.

De volgende vragen gaan over de informatie die met u is besproken in het gesprek over uw nacontrole en nazorg.

1. Is er met u gesproken over …	**Ja**	**Nee**	**Ik weet het niet precies**
… mogelijke **fysieke klachten** (bijv. vocht in de arm of bewegingsbeperkingen) als gevolg van borstkanker en de behandeling?	☐	☐	☐
… mogelijke **psychosociale klachten** (bijv. moeite met sociaal contact of terugkeer naar werk) als gevolg van borstkanker en de behandeling?	☐	☐	☐
… mogelijke **emotionele- en stemmingsproblemen** (bijv. angst, depressie, paniek of onzekerheid) als gevolg van borstkanker en de behandeling?	☐	☐	☐
… mogelijke **vermoeidheidsklachten** als gevolg van borstkanker en de behandeling?	☐	☐	☐
… mogelijke **pijnklachten** als gevolg van borstkanker en de behandeling?	☐	☐	☐
… mogelijke problemen met interesse voor **intimiteit en seks** als gevolg van borstkanker en behandeling?	☐	☐	☐
… mogelijke **stress voorafgaand aan periodieke controles?**	☐	☐	☐
… het aantal patiënten dat nog dagelijks **medicijnen** gebruikt (bijv. hormoontherapie)?	☐	☐	☐
… de mate waarin patiënten **bijwerkingen van hormoontherapie** ervaren?	☐	☐	☐
… het **risico op terugkeer** van borstkanker in dezelfde of de andere borst?	☐	☐	☐
… het **risico op overlijden** aan borstkanker?	☐	☐	☐

Welbevinden

Deze vragenlijst gaat over uw standpunten ten aanzien van uw gezondheid. Met behulp van deze gegevens kan worden bijgehouden hoe u zich voelt en hoe goed u in staat bent uw gebruikelijke bezigheden uit te voeren.
Beantwoord elke vraag door één hokje aan te kruisen. Wanneer u twijfelt over de beantwoording van een vraag, kruis dan de best mogelijke optie aan.

1. Hoe zou u over het algemeen uw gezondheid noemen?

Uitstekend	**Zeer goed**	**Goed**	**Matig**	**Slecht**
☐	☐	☐	☐	☐

2. De volgende vragen gaan over de bezigheden die u misschien doet op een doorsnee dag. Wordt u door uw gezondheid op dit moment beperkt bij deze bezigheden? Zo ja, in welke mate?

	Kruis één hokje per vraag aan		
BEZIGHEDEN	**Ja, ernstig beperkt**	**Ja, een beetje beperkt**	**Nee, helemaal niet beperkt**
a. Matige inspanning, zoals een tafel verplaatsen, stofzuigen, zwemmen of fietsen	☐	☐	☐
b. Een paar trappen oplopen	☐	☐	☐

3. Heeft u de afgelopen 4 weken, een van de volgende problemen bij uw werk of andere dagelijkse bezigheden gehad, ten gevolge van **uw lichamelijke gezondheid**?

	Kruis één hokje per vraag aan	
	Ja	**Nee**
a. U heeft minder bereikt dan u zou willen	☐	☐
b. U was beperkt in het soort werk of andere bezigheden	☐	☐

4. Heeft u de afgelopen 4 weken, een van de volgende problemen bij uw werk of andere dagelijkse bezigheden gehad, ten gevolge van **uw emotionele toestand** (zoals depressief voelen)?

	Kruis één hokje per vraag aan	
	Ja	**Nee**
a. U heeft minder bereikt dan u zou willen	☐	☐
b. U deed uw werk of andere bezigheden niet zo zorgvuldig als gewoonlijk	☐	☐

5. In welke mate bent u de afgelopen 4 weken door pijn gehinderd in uw normale werk? Zowel werk buitenshuis als huishoudelijk werk.

Kruis één hokje per vraag aan

Helemaal niet	Een klein beetje	Nogal	Veel	Heel erg veel
☐	☐	☐	☐	☐

6. Deze vragen gaan over hoe u zich voelt en hoe het met u ging in de afgelopen 4 weken. Wilt u a.u.b. bij elke vraag het antwoord geven dat het best benadert hoe u zich voelde. Hoe vaak gedurende de afgelopen 4 weken…

Kruis één hokje per vraag aan

	Altijd	Meestal	Vaak	Soms	Zelden	Nooit
a. Voelde u zich rustig en tevreden?	☐	☐	☐	☐	☐	☐
b. Had u veel energie?	☐	☐	☐	☐	☐	☐
c. Voelde u zich somber en neerslachtig?	☐	☐	☐	☐	☐	☐

7. Hoe vaak hebben uw lichamelijke gezondheid of emotionele problemen u gedurende de afgelopen 4 weken gehinderd bij uw activiteiten (zoals vrienden of familie bezoeken etc.)?

Kruis één hokje per vraag aan

Altijd	Meestal	Soms	Zelden	Nooit
☐	☐	☐	☐	☐

Kennisvragen

Hieronder staan een aantal vragen over borstkanker en de nacontrole bij borstkanker. Deze kunnen juist of onjuist zijn. Geef a.u.b. per uitspraak aan of deze uitspraak volgens u juist of onjuist is. ***Let op!*** *Deze vragen zijn niet bedoeld om u te controleren, maar om te zien of de informatie die u kreeg begrijpelijk en duidelijk genoeg is. Wij willen daarom liever niet dat u de antwoorden opzoekt. Het is niet erg als u een antwoord niet weet.*

	Juist	Onjuist	Weet ik niet
1. Tegenwoordig geneest het merendeel van alle vrouwen van borstkanker.	☐	☐	☐
2. Vroege opsporing van eventuele uitzaaiingen van borstkanker in het lichaam kan de kans op overleving vergroten.	☐	☐	☐
3. Een bloedtest vormt een standaard onderdeel van de periodieke nacontrole bij borstkanker.	☐	☐	☐
4. Bij een mammografie wordt er een röntgenfoto van de borst gemaakt.	☐	☐	☐
5. Het belangrijkste doel van de nacontrole bij borstkanker is om eventuele uitzaaiingen vroeg op te sporen.	☐	☐	☐
6. Het risico op terugkeer van borstkanker is ongeveer even groot voor alle borstkankerpatiënten.	☐	☐	☐
7. Het risico op terugkeer van borstkanker neemt af naarmate het langer geleden is dat de eerste tumor in de borst werd geconstateerd.	☐	☐	☐
8. Het risico op terugkeer van borstkanker is afhankelijk van kenmerken van de tumor en de behandeling die een patiënt heeft gehad.	☐	☐	☐
9. De nacontrole bij borstkanker wordt altijd gedaan door de chirurg.	☐	☐	☐
10. Een MRI-scan is standaard onderdeel van de periodieke nacontrole.	☐	☐	☐

Appendix B: Demographic, tumour and treatment characteristics of the study cohort per profile

Table B1: *Demographic, tumour and treatment characteristics of participants with stable low levels of FoR (N=22), stable high levels of FoR (N=101) and fluctuating levels of FoR (N=51).*

	Stable low levels of FoR		**Stable high levels of FoR**		**Fluctuating levels of FoR**	
Demographic characteristics	Mean (SD)	Min-max	Mean (SD)	Min-max	Mean (SD)	Min-max
Age	63.2 (10.3)	42-80	59.1 (10.1)	29-79	60.1 (8.5)	40-80
	N	%	N	%	N	%
Marital status						
Single	5	22.7	22	21.8	14	27.5
Married/Partnered	17	77.3	79	78.2	37	72.5
Occupation						
Unpaid job	13	59.1	58	57.4	28	54.9
Paid job	9	40.9	43	42.6	23	45.1
Education level						
Low	4	18.2	13	12.9	9	17.6
Moderate	8	36.4	53	52.5	23	45.1
High	10	45.5	35	34.7	19	37.3
Health literacy						
Inadequate	3	13.6	16	15.8	3	5.9
Adequate	19	86.4	85	84.2	48	94.1
Tumour characteristics						
Tumour size						
< 2 centimetres	18	81.8	62	61.4	39	76.5
2-5 centimetres	4	18.2	36	35.6	11	21.6
> 5 centimetres	0	0.0	3	3.0	1	2.0
Nodal involvement						
0	21	95.5	67	66.3	39	76.5
1-3	1	4.5	31	30.7	11	21.6
> 3	0	0.0	2	2.0	1	2.0
NA	0	0.0	1	1.0	0	0.0
Differentiation						
Grade 1	7	31.8	33	32.7	16	31.4
Grade 2	12	54.5	41	40.6	30	58.8
Grade 3	3	13.6	27	26.7	5	9.8
ER-status						
Negative	4	18.2	11	10.9	1	2.0
Positive	18	81.8	90	89.1	49	96.1
NA	0	0.0	0	0.0	1	2.0
PR-status						
Negative	5	22.7	20	19.8	9	17.6
Positive	17	77.3	81	80.2	41	80.4
NA	0	0.0	0	0.0	1	2.0
HER-status						
Negative	19	86.4	94	93.1	48	94.1
Positive	3	13.6	6	5.9	2	3.9
NA	0	0.0	1	1.0	1	2.0
Multi focality						
No	19	86.4	89	88.1	46	90.2
Yes	3	13.6	12	11.9	5	9.8
Treatment characteristics						
Radiotherapy						
No	7	31.8	20	19.8	9	17.6
Yes	15	68.2	81	80.2	42	82.4
Adjuvant chemotherapy						
No	19	86.4	78	77.2	45	88.2
Yes	3	13.6	23	22.8	6	11.8
Hormone therapy						
No	14	63.6	37	36.6	24	47.1
Yes	8	36.4	64	63.4	27	52.9
Type of operation						
Lumpectomy	19	86.4	76	75.2	45	88.2
Mastectomy	3	13.6	25	24.8	6	11.8
	Mean (SD)	Min-max	Mean (SD)	Min-max	Mean (SD)	Min-max
Five-year locoregional recurrence risk percentage	3.09 (1.32)	1.4-6.5	3.56 (2.75)	1.4-20.4	2.92 (1.19)	1.3-6.3

Abbreviations: SD, Standard Deviation; ER, estrogen receptor; PR, progesterone receptor; HER, human epidermal growth receptor

Appendix C: Results of univariate linear regression analyses

***Table C1**: Results of univariate linear regression analyses of the effect of possible predictors on the continuous FoR-score at the three different timepoints.*

	1 year after surgery (t1)		**1.5 years after surgery (t2)**		**2 years after surgery (t3)**	
	β	**p**	**β**	**p**	**β**	**p**
Age	-0.287	**0.000**	-0.210	**0.006**	-0.209	**0.006**
Marital status [Married/Partnered]	0.058	0.453	0.015	0.848	0.064	0.408
Occupation [Unpaid job]	-0.084	0.273	-0.038	0.621	-0.012	0.880
Education level [moderate]	0.136	0.232	0.158	0.163	0.205	0.070
Education level [high]	0.131	0.248	0.067	0.550	0.153	0.176
Health literacy	0.182	**0.017**	0.136	0.075	0.166	**0.030**
Tumour Size	0.100	0.192	0.103	0.180	0.113	0.141
Nodal Involvement [1-3]	0.153	**0.045**	0.074	0.336	0.148	0.053
Nodal Involvement [>3]	0.158	**0.039**	0.151	**0.049**	0.125	0.103
Differentiation [grade 2]	-0.085	0.331	-0.034	0.694	-0.069	0.428
Differentiation [grade 3]	0.102	0.239	0.121	0.165	0.046	0.601
ER-status	-0.050	0.514	-0.059	0.444	-0.033	0.673
PR-status	0.096	0.209	0.010	0.896	0.052	0.503
HER-status	0.023	0.761	0.072	0.349	0.038	0.626
Multi focality	0.014	0.857	0.025	0.745	0.068	0.377
Radio therapy	0.012	0.871	-0.029	0.707	0.029	0.705
Adjuvant chemotherapy	0.094	0.223	0.154	**0.045**	0.097	0.206
Hormone Therapy	0.083	0.278	0.131	0.087	0.105	0.172
Type of operation [mastectomy]	0.173	**0.024**	0.209	**0.006**	0.219	**0.004**
Cure Beliefs	-0.387	**0.000**	-0.369	**0.000**	-0.479	**0.000**
Personal control beliefs	0.083	0.279	0.093	0.225	0.089	0.249
Mental Health Status	-0.466	**0.000**	-0.478	**0.000**	-0.474	**0.000**
Physical Health Status	-0.199	**0.009**	-0.235	**0.002**	-0.208	**0.006**
Patients' knowledge	0.025	0.742	0.023	0.767	0.086	0.264
Patient-reported received information	-0.141	0.066	-0.037	0.631	-0.032	0.681
Patient-reported SDM	-0.168	**0.028**	-0.164	**0.032**	-0.150	**0.050**

Appendix D: Results of univariate multinomial logistic regression analysis

Table D1: *Results of univariate multinomial logistic regression analysis of the effect of possible predictors on the three different FoR-profiles*

	Stable High vs. Stable Low				Fluctuating vs. Stable Low			
	B	**OR**[1]	**95% CI**[2]	**p**	**B**	**OR**[1]	**95% CI**[2]	**p**
Age	-0.045	0.956	0.956-0.909	0.087	-0.033	0.967	0.916-1.022	0.237
Marital status [levels]	No levels were found significant.				No levels were found significant.			
Occupation [levels]	No levels were found significant.				No levels were found significant.			
Education level [levels]	No levels were found significant.				No levels were found significant.			
Health literacy	-0.200	0.819	0.217-3.097	0.769	0.906	2.474	0.458-13.362	0.293
Tumour Size	0.637	1.890	1.011-3.532	**0.046**	0.259	1.295	0.665-2.522	0.447
Nodal Involvement	2.276	9.736	1.277-74.232	**0.028**	1.896	6.662	0.833-53.300	0.074
Differentiation	0.221	1.247	0.647-2.404	0.509	-0.037	0.964	0.472-1.968	0.919
ER-status	0.575	1.778	0.508-6.215	0.368	2.388	10.889	1.140-104.027	**0.038**
PR-status	0.214	1.238	0.406-3.779	0.707	0.293	1.340	0.391-4.588	0.641
HER-status	-0.895	0.409	0.094-1.779	0.233	-1.332	0.264	0.041-1.706	0.162
Multi focality	-0.135	0.874	0.224-3.400	0.845	-0.351	0.704	0.153-3.245	0.704
Radio therapy	0.612	1.843	0.663-5.125	0.241	0.754	2.126	0.672-6.723	0.199
Adjuvant chemotherapy	0.593	1.810	0.490-6.684	0.374	-0.147	0.864	0.195-3.819	0.847
Hormone Therapy	1.119	3.062	1.172-8.001	**0.022**	0.720	2.054	0.732-5.673	0.171
Type of operation	0.761	2.140	0.584-7.846	0.251	-0.147	0.864	0.195-3.819	0.847
Cure Beliefs	-0.417	0.659	0.538-0.808	**0.000**	-0.221	0.801	0.652-0.985	**0.036**
Personal control beliefs	-0.008	0.992	0.864-1.139	0.908	-0.085	0.918	0.790-1.067	0.264
Mental Health Status	-0.165	0.848	0.767-0.937	**0.001**	-0.096	0.908	0.820-1.006	0.066
Physical Health Status	-0.060	0.942	0.885-1.002	0.056	-0.026	0.975	0.912-1.042	0.448
Absolute Risk Perception	1.117	3.056	1.586-5.887	**0.001**	0.825	2.281	1.168-4.456	**0.016**
Recurrence Risk Appraisal	1.946	6.998	3.305-14.818	**0.000**	0.941	2.562	1.254-5.235	**0.010**
Comparative Recurrence Risk	1.096	2.993	1.632-5.486	**0.000**	0.606	1.834	0.991-3.393	0.053
Patients' knowledge	0.034	1.035	0.814-1.315	0.061	0.097	1.102	0.847-1.433	0.470
Patient-reported received information	-0.187	0.829	0.591-1.162	0.277	-0.018	0.982	0.683-1.413	0.922
Patient-reported SDM	-0.008	0.992	0.978-1.007	0.305	-0.009	0.991	0.975-1.007	0.250