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PAPER

The course of fear of cancer recurrence: Different patterns by age in breast cancer survivors

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Abstract

Objective: To examine the time course and predictors of fear of cancer recurrence (FCR) in breast cancer survivors over a period of 18 months after initial surgery.

Methods: Breast cancer patients (n = 267) were followed until 18 months after primary breast surgery. Shortly after surgery, participants completed the Life Orientation Test-Revised to measure optimism and the Concerns about Recurrence Scale to measure FCR. Mixed regression analysis was performed with age, optimism, marital status, education, type of surgery, with or without lymphectomy, chemotherapy, hormonal therapy, or radiotherapy, time since surgery, and all interactions with time as predictors of FCR.

Results: The final model included a significant interaction between age and time since surgery and a main effect for optimism.

Conclusion: These results suggest that the course of FCR depends on the age of breast cancer survivors. Younger survivors showed an increase of fear during the first 1.5 years after breast surgery, whereas older survivors showed stable levels during the first 6 months after which it declined. Also, less optimistic survivors reported higher levels of FCR. Health care providers should pay (extra) attention to FCR in younger and less optimistic patients and offer psychological help when needed.

KEYWORDS

breast cancer, fear of cancer recurrence, predictors, time course

1 | BACKGROUND

The continuing improvement of cancer treatments has led to an increasing number of cancer survivors. This survivorship can lead to positive feelings, ie, increased appreciation of life, self-improvement and personal growth, and enhanced meaning in life.[1] However, there are also negative aspects of survivorship such as side effects of medical treatments, physical limitations, and living with the stigma related to cancer.[1] Additionally, a large proportion of cancer survivors (44-73%)[2-5] live with a certain level of fear of cancer recurrence (FCR), which can be defined as "fear, worry, or concern relating to the possibility that cancer will come back or progress."[6] Fear of cancer recurrence is one of the biggest complaints and unmet needs[7] that can result in a lower quality of life[3] in cancer survivors.

Previous studies have examined the course of FCR in cancer survivors by using different methodologies.[2-4,8-15] Cross-sectional studies examining FCR as a function of time since diagnosis in (long-term) cancer survivors suggest stable levels of fear over time.[2,3,8,9] Longitudinal studies, on the other hand, mostly suggest that the highest levels of FCR are reported immediately after diagnosis and during treatment, which is followed by a decrease after treatment and reaching stability after a few months in breast[12-15] and other types of cancer survivors.[4,11,16] However, some studies report stable levels throughout the entire follow-up period in breast cancer survivors.[17-19]

Not only the course of FCR but also its association with patient- and treatment-related characteristics have been examined. Systematic reviews indicate that the most consistent factors contributing to elevated levels of FCR are younger age, experiencing physical symptoms, and low levels of optimism.[5,7,20] The evidence for the contribution of cancer-related factors (cancer type and stage), treatment-related factors (type of surgery and chemotherapy), sociodemographic factors other than age (sex and education), and

social factors (family resources and social support) to levels of FCR is weak or inconclusive.[5,7,20]

So far, most studies have only considered the influence of patient- and treatment-related characteristics on the level of FCR during 1 point in time, while only few studies have examined predictors of changes in FCR. There are some indications that the course of FCR can be affected by the type and stage of cancer,[4,21] receiving adjuvant treatment[4,22] and the outcome of surgery (positive of negative surgical margins after prostatectomy).[22] A psychological factor that may influence the course of FCR in breast cancer survivors is optimism.[23] Persistent FCR in head and neck cancer survivors was most strongly predicted by dispositional optimism, independent from other factors like anxiety or baseline FCR.[24]

To our knowledge, only 1 previous study used a longitudinal design to specifically examine predictors of the course of FCR in breast cancer patients.[25] Higher initial FCR and better physical health predicted a steeper decline in FCR over the course of 6 months. However, no information on the development of FCR during longer follow-up periods after breast cancer surgery is available. The present study therefore explored the influence of patient- and treatment-related characteristics on the level and course of FCR until 18 months following surgery. Women having undergone breast surgery reported on FCR shortly after surgery and 6 and 18 months later. Demographic variables (age, sex, and education), type of surgery (lumpectomy vs mastectomy and lymphectomy), adjuvant treatment (chemotherapy and radiotherapy), and dispositional optimism were tested as predictors of the level and course of FCR. We specifically focused on optimism because previous studies identified it as one of the most consistent psychological influence on FCR. We hypothesized that younger age and low dispositional optimism would be associated with higher overall levels of FCR and less decline in FCR over the course of 18 months. Sex, education, and treatment-related factors were expected to show no or limited associations with the severity and course of FCR.

2 | MATERIALS AND METHODS

2.1 | Study participants

This study was performed on data previously collected for a study on resilience in breast cancer patients.[26] A total number of 284 women with primary breast cancer were recruited at a general hospital in the province of Limburg in Belgium between 2009 and 2013 (treating an average of 150 new breast cancer patients per year). The patients were asked to participate during admittance (1 day prior to surgery) in the hospital for breast surgery. The patients received a diagnosis of breast cancer 1 or 2 weeks prior to this surgery. The participants had to meet the following inclusion criteria: (a) age between 20 and 80 years old, (b) residents of the province of Belgian Limburg, (c) adequate cognitive ability, and (d) able to understand and speak Dutch. Ethical approval for the study was obtained from the ethical committee of Oost-Limburg Hospital (approval #09/001U).

All 284 participants signed informed consent and agreed to participate. Seventeen women did not complete the measurement for FCR at any time point and were excluded from analysis. Motives were that the questionnaire was "forgotten," "too confronting," or "lost." A total sample of 267 participants was used for analysis. All available data from the 267 participants who had completed the measurement for FCR on at least 1 time point were included into the data analysis, using mixed regression for repeated measures (the so-called "direct likelihood" method), which is valid under the same missingness conditions as multiple imputations and somewhat more efficient.

2.2 | Measurements

The *Concerns About Recurrence Scale* (CARS)[2] is a reliable and valid questionnaire to measure FCR in breast cancer survivors. The original questionnaire includes 2 parts: 1 to measure the overall level of FCR and 1 to measure sources of this fear. The current study used a Dutch version[3] of the 4-item overall fear scale. Items were rated on a scale from 1 (not at all) to 6 (extremely). Total scores range between 4 and 24 with higher scores representing more FCR. A validation study in Dutch breast cancer survivors[3] showed good internal consistence (Cronbach α = 0.94), test-retest reliability, and construct validity. Moreover, results confirmed that these questions loaded on one factor representing overall fear.[3]

The Dutch translation of the *Life Orientation Test-Revised* (LOT-R)[27] was used to measure dispositional optimism. This self-report questionnaire contains 10 items rated on a scale from 0 (strongly disagree) to 4 (strongly agree). Six items are used to compute the total score, of which 3 are reversely coded. Total scores range between 0 (low optimism) and 24 (high optimism). Good psychometric properties were described for the LOT-R, and the Dutch version showed good internal reliability (Cronbach α = 0.83).[27,28]

2.3 | Procedure

During the hospital admission procedure for surgical treatment, the breast cancer nurse asked breast cancer patients to participate in this study. This was 5 to 10 days after diagnosis. The baseline measurement included demographic data (ie, age, marital status, and educational level), the CARS, and LOT-R and was completed after surgery but before discharge from the hospital. Follow-up measurements of CARS were completed at 6 and 18 months. The participants received the CARS by mail and were asked to return the completed questionnaire with the attached prepaid envelope. Information concerning the type of surgery (mastectomy or lumpectomy with or without lymphectomy) and follow-up treatment was collected during weekly multidisciplinary meetings among oncologists, radiologists, pathologists, nuclear medicine physician, and breast cancer nurses in the treating hospital.

2.4 | Statistical analyses

The course and predictors of FCR were examined with mixed linear regression modeling by using maximum likelihood estimation in SPSS (version 21.0), to enable inclusion of all available data from patients who dropped out before the last follow-up without requiring multiple imputation or the construction of, eg, a missingness indicator variable. This "direct likelihood" method is valid under the same missingness assumptions as multiple imputation and must be distinguished from

ad hoc methods of handling dropout such as complete cases analysis or last value carried forward, which are known to be biased in general.[29] The mixed regression model had 2 levels: patients and time of measurements (baseline, 6 months, and 18 months). Interindividual patient differences were accommodated by assuming an unstructured variance-covariance matrix for the repeated FCR measurements, which is the most general structure.

The dependent variable in the mixed model was FCR measured with the CARS at baseline, 6 months, and 18 months follow-up. Predictors were age, optimism, marital status (married/living together vs not married/living together), education (using dummy coding for secondary school (yes/no), and for higher education (yes/no) with primary school as reference category), type of surgery (lumpectomy vs mastectomy), lymphectomy (yes/no), chemotherapy (yes/no), radiotherapy (yes/no), hormonal therapy (yes/no), and time since surgery (using dummy coding for 6 months [yes/no] and 18 months [yes/no] follow-up, with baseline as reference time point) as well as interactions of all predictors with time. Marital status was dichotomized as married/living together versus divorced, widow, or single in view of the small frequencies of the latter 3 categories. Age and optimism were centered by subtracting their mean from individual age and optimism to avoid possible collinearity with their interactions with time and to allow interpretation of time effects as average time effects even in the presence of interaction with age or optimism.

Nonsignificant interactions with time were excluded from the model one-by-one, using likelihood ratio testing (with $\alpha = 0.05$), because each interaction was represented by 2 model terms (time was dummy coded) that must be tested jointly. Reported results of the final mixed model are based on restricted maximum likelihood estimation as this gives better estimates of standard errors than maximum likelihood estimation.[29]

3 | RESULTS

3.1 | Participants

The total sample for analysis included those participants that completed the CARS at least once, resulting in a sample of 267 participants. At baseline, 252 participants (94%) completed the questionnaire. Six months later, 201 participants (75%) returned a completed questionnaire and 168 participants (63%) at 18 months follow-up. It was not possible to determine the motives of nonresponders. Table 1 shows demographic and clinical characteristics of complete and partial responders. Table 2 shows mean observed scores of FCR at baseline, 6 months, and 18 months follow-up for the total sample and different age categories.

3.2 | Mixed regression results

Table 3 shows the results of the final mixed regression model, which shows a significant interaction effect between age and 18 months follow-up ($P < .02$ according to the likelihood ratio test of both interaction terms jointly). This interaction suggests that the course of FCR over time depends on the age of the participants. Moreover, the results show a significant main effect for optimism on the level of FCR, indicating that low optimistic participants report higher levels of FCR. No significant main effects on the level of FCR were found for the other predictors.

TABLE 1 Demographic and clinical characteristics of complete responders (completed Concerns About Recurrence Scale [CARS] at all time points, n = 145) and partial responders (missing CARS at 1 or 2 time points, n = 122) at baseline.

	Complete Responders	Partial Responders
Age (years, *M*, SD)	54.31 (10.09)	54.01 (9.63)
Optimism (*M*, SD)	20.21 (5.00)	19.44 (5.16)
Marital status		
Married	112 (78%)	99 (83%)
Not married	32 (22%)	21 (18%)
Education		
Primary school	18 (13%)	30 (25%)
Secondary school	63 (44%)	47 (39%)
Higher education	63 (44%)	43 (36%)
Type of surgery		
Lumpectomy	76 (53%)	68 (56%)
Mastectomy	67 (47%)	54 (44%)
Lymphectomy		
No	78 (55%)	73 (60%)
Yes	65 (46%)	49 (40%)
Chemotherapy		
No	63 (44%)	52 (43%)
Yes	81 (56%)	70 (57%)
Hormonal therapy		
No	17 (12%)	21 (17%)
Yes	127 (88%)	101 (83%)
Radiotherapy		
No	32 (22%)	22 (18%)
Yes	112 (78%)	100 (82%)

The interaction between age and time since surgery was further investigated by plotting mean predicted values of CARS for participants of different ages, while keeping constant all other variables, based on the final regression model (Figure 1). Ages of interest were determined by calculation of the 10th, 25th, 50th, 75th, and 90th percentiles of age at baseline, which were 41, 47, 53, 61, and 66 years, respectively. Table 4 shows the size and significance of the time effects for different ages. It shows that the increase in younger breast cancer survivors is specifically seen 6 months after surgery, while older patients show decreasing FCR after this period. These effects are obtained by running the same final mixed regression model as in Table 3, but now after centering age around the 10th, 25th, 50th, 75th, and 90th percentiles, respectively, noting that the time effects in the final model are the time effects for a person with age 0 after centering.[30]

4 | DISCUSSION

The aim of this study was to investigate the course of FCR and its predictors over a time period of 18 months following surgery in a sample of breast cancer survivors. The results showed that all breast cancer

TABLE 2 Observed means of Concerns About Recurrence Scale (CARS) per time point for different age groups

	Total Sample	Youngest 20% (Age 24-45)	Next 20% (age 46-51)	Middle 20% (age 52-57)	Next 20% (age 58-63)	Oldest 20% (age 64-78)
n	266	54	54	53	55	50
Baseline	12.91	12.74	13,01	13.42	13.10	12.26
Missing n	15 (6%)	0	2 (5%)	3 (6%)	6 (11%)	4 (8%)
6 months	13.42	13.22	13.40	13.81	13.70	12.92
Missing n	66 (25%)	13 (24%)	9 (17%)	16 (30%)	15 (27%)	13 (26%)
18 months	13.20	12.75	15.09	14.81	12.51	10.94
Missing n	99 (37%)	22 (41%)	19 (35%)	21 (40%)	22 (40%)	14 (28%)

Note: The time course of the observed mean per age group is biased by the occurrence of missing values since the sample composition itself then changes over time. The best estimate of the time course of fear of cancer recurrence (FCR) per age group is obtained by the mixed regression analysis, which adjusts for missingness. Results are given in Figure 1 and Table 4.

TABLE 3 Effects of patient and treatment-related characteristics on fear of cancer recurrence (FCR) in the course of 18 months

Variable	*B*	SE	*P*
Intercept	13.10	1.15	<.001
Age	−0.05	0.04	.16
Optimism	−0.45	0.06	<.001
Being single	−0.95	0.70	.18
Secondary school	−0.12	0.85	.89
Higher education	−1.10	0.86	.20
Mastectomy	0.12	0.65	.86
Lymphectomy	0.88	0.61	.16
Chemotherapy	0.18	0.65	.78
Hormonal therapy	−0.35	0.92	.71
Radiotherapy	0.21	0.82	.80
6 months	0.56	0.35	.11
18 months	0.48	0.40	.23
6 months * age	−0.01	0.04	.83
18 months * age	−0.09	0.04	.03

Note: Of all N = 267 participants, n = 14 had a missing value on optimism and were thus excluded from the regression analysis. Repeating the mixed regression without optimism to include all participants confirmed the significance and pattern of age by time interaction as reported here. n = 15 had a missing baseline level of CARS. Repeating the mixed regression with exclusion of these participants confirmed the results as reported here.

Being single = married/living together (0) vs not married/living together, includes widows and divorced women (1).

Secondary school = primary school (0) and higher education (0) vs secondary school (1).

Higher education = primary school (0) and secondary school (0) vs higher education (1).

Mastectomy = lumpectomy (0) vs mastectomy (1).

Lymphectomy = no (0) vs yes (1).

Chemotherapy = no (0) vs yes (1).

Hormonal therapy = no (0) vs yes (1).

Radiotherapy = no (0) vs yes (1).

6 months = baseline measurement (0) and 18 months follow-up (0) vs 6 months follow-up (1).

18 months = baseline measurement (0) and 6 months follow-up (0) vs 18 months follow-up (1).

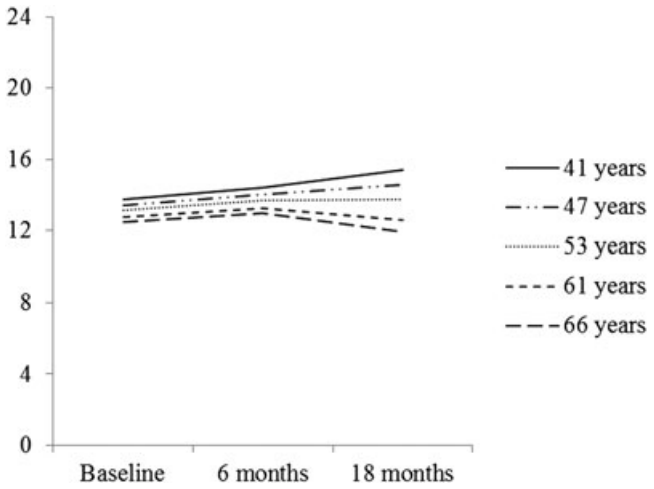

FIGURE 1 Mean predicted values of Concerns About Recurrence Scale (CARS) per time point for individuals with different ages who are married, completed primary school, were treated with a lumpectomy, without lymphectomy or secondary treatment, and scored average on optimism. Time courses for individuals with other characteristics are parallel to these, differing by an additive constant only

survivors reported stable levels of FCR in the first 6 months after surgery. After this period, older breast cancer survivors reported decreasing levels of FCR, which is in line with previous studies showing either stable or decreasing levels in the first period after diagnosis or treatment for breast cancer.[2,3,12-15,17] However, younger patients reported an increase of FCR after this period. This finding is novel. Previous studies did report higher overall levels of FCR in younger cancer patients[5,7,20] but have not examined fear trajectories in relation to age. Our results suggest that especially the time course of FCR is related to age and therefore that whether or not age differences in fear are found depends on the time of assessment of FCR. Immediately after diagnosis or surgery, the difference in FCR for younger and older breast cancer patients may not be so prominent. This difference may increase when time passes.

Different trajectories of FCR in subgroups of patients have been reported before.[21,22] However, this is the first study suggesting an influence of age on the trajectory of FCR. A possible reason for this finding might be that patients feel relieved in the first period after treatment. When time passes, survivors focus more on the future. It could be that younger survivors have more worries for the future than older survivors. Future research is necessary to examine the underlying reasons causing FCR. Also, generalizability to other types of cancer remains to be established.

TABLE 4 Effect of time since surgery (A) and mean predicted values of Concerns About Recurrence Scale (CARS) (B) for individuals with different ages (effect estimates and *P* values obtained as described in the main text)

	41 years		47 years		53 years		61 years		66 years	
	B	*P*	*B*	*P*	*B*	*P*	*B*	*P*	*B*	*P*
A. Effect Estimates										
Change from baseline to 6 months	0.66	.24	0.61	.14	0.57	.11	0.50	.25	0.47	.41
Change from 6 to 18 months	1.01	.03	0.51	.14	0.02	.94	−0.64	.06	−1.05	.02
Change from baseline to 18 months	1.67	.01	1.12	.02	0.59	.15	−0.13	.79	−0.58	.36
B. Mean predicted values										
Baseline	13.75		13.45		13.15		12.76		12.51	
6 months	14.41		14.06		13.72		13.26		12.98	
18 months	16.08		15.18		14.31		13.13		12.40	

Note: These scores are presented for individuals who are married, completed primary school, were treated with a lumpectomy, without lymphectomy or secondary treatment, and scored average on optimism. Time courses for individuals with other characteristics are parallel to these, differing by an additive constant only.

In line with previous systematic reviews,[5,7,20] no associations of FCR with marital status, education, type of surgery, lymphectomy, chemotherapy, hormonal therapy, or radiotherapy were found. Moreover, our results replicated previous findings for an association between optimism and the overall level of FCR in breast[23,31] and other types of cancer survivors.[5,7,9,20] High optimistic survivors reported lower fear compared with less optimistic survivors across all time points. This association can be explained by the way that optimism, a trait-like or dispositional characteristic, influences coping with illness. More optimistic individuals are more often active copers who accept their illness in an early stage.[31] Additionally, a recent paper providing an overview of various theoretical frameworks for the persistence of FCR identified risk perception and worrying as core elements in most of these frameworks.[32] Dispositional optimism may be a key protective factor against heightened risk perception and maladaptive coping strategies such as worrying.

It remains relevant to look into factors that are related to a higher level of FCR in survivors of cancer because high fear is associated with distress and decreased quality of life[3] and may lead to higher health costs.[33] Early interventions for patients at risk of increasing FCR levels may reduce patients′ as well as societal burden. Our results suggest that especially younger patients could profit from such interventions. In the last years, several interventions have been developed that were shown to be effective in reducing FCR. This includes psycho-educational interventions,[34] cognitive behavioral interventions,[35] cognitive-existential therapy,[36] and mindfulness-based stress reduction.[37] Recently, a comprehensive therapy has been developed encompassing multiple theory-grounded components, which is now being tested for efficacy in patients with breast and colorectal cancer.[38] For patients with low levels of optimism, addressing their negative beliefs about the future and changing these for more realistic beliefs may be especially helpful.

4.1 | Study limitations

The current study has several strengths and limitations. Strengths are the longitudinal design and the fact that we examined predictors of the course of FCR instead of only for the level of fear at 1 time point. However, there are several limitations. First, the timing and type of measurements used in this study. The participants completed the baseline measurement while they were recovering from surgery. It is possible that this specific time point was related to lower FCR scores compared with fear just before or 1 week after surgery. A previous review indicated that levels of FCR differed based on the timing of the assessment: prior to or after a follow-up visit.[39] The current study did not collect data on follow-up meetings, so the influence of this factor is unknown. Additionally, FCR was measured with the overall fear scale of the CARS instead of the complete CARS to limit patients′ burden. Cut-off scores for clinical levels of FCR are missing for this scale. Therefore, clinical relevance could not be determined. Many different instruments to assess FCR exist, and there is no consensus on what should be considered as the gold standard.[5] Future studies could use an instrument allowing for more extensive assessment of different aspects of fear like the Fear of Cancer Recurrence Inventory.[40] Also, the generalizability of the results to other breast cancer survivors could be questioned since the current sample only included Belgian breast cancer patients treated in 1 hospital.

Another study limitation is the observational nature of the study. Although the effects of all demographic and treatment variables on FCR were adjusted for confounding by each other by using regression analysis, we cannot rule out bias by some unmeasured confounder. In addition, no information is available on actual cancer recurrence. This could potentially impact on the results. However, cancer recurrence in breast cancer survivors in the given time frame is rare. Another possible bias might in principle arise from the attrition (25%) at the last time point. However, all available measurements from all participants were included into the analysis by using mixed regression with maximum likelihood estimation, which takes into account the correlation between repeated measures. This method prevents bias arising from so-called missing at random missingness (ie, missingness related to predictors or preceding FCR measurements) in the same way as multiple imputation does and is much better than popular methods for missing data such as complete cases analysis or last value carried forward.[29]

A last limitation is the fact that we tested 9 interactions of time with a demographic or treatment variable, and so the finding of age by time interaction can be a type I error due to multiple testing even though its *P* value was between .01 and .02 (likelihood ratio test). Replication is therefore recommendable.

4.2 | Clinical implications

This study showed that FCR remained stable until 6 months after surgery, after which it declined in older breast cancer survivors, while it increased in younger survivors. If the time by age interaction can be replicated, then this implies that health care providers should pay (extra) attention to FCR in young breast cancer survivors. Even if they do not show clinical levels of FCR shortly after surgery, these may develop when time passes. Therefore, the course of FCR should be monitored regularly. In addition, we found optimism to be negatively associated with FCR in breast cancer survivors. Less optimistic patients may be especially vulnerable to develop maladaptive beliefs regarding their illness and to show unhelpful coping responses. Interventions aiming to instill more realistic beliefs and to promote adaptive coping behaviors may therefore be especially promising. Future studies should test the efficacy of such interventions and explore whether changing pessimistic beliefs could mediate the beneficial effects of these interventions on FCR.

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