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DOI:

[10.1016/j.jpsychores.2020.110127](https://doi.org/10.1016/j.jpsychores.2020.110127)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Hughes, A., Suleman, S., Rimes, K. A., Marsden, J., & Chalder, T. (2020). Cancer-related fatigue and functional impairment: towards an understanding of cognitive and behavioural factors. *Journal of Psychosomatic Research*, 134, [110127]. <https://doi.org/10.1016/j.jpsychores.2020.110127>

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CANCER-RELATED FATIGUE AND FUNCTIONAL IMPAIRMENT – TOWARDS AN UNDERSTANDING OF COGNITIVE AND BEHAVIOURAL FACTORS

Short Title: Cancer-related Fatigue – Cognitive & Behavioural Factors

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ABSTRACT

Objective: Fatigue is a highly prevalent and debilitating problem in women with breast cancer. This study explored the cognitive, behavioural, interpersonal and affective responses associated with fatigue and functional impairment for women with breast cancer undergoing chemotherapy. A nested prospective study examined factors predictive of cancer-related fatigue after three cycles of chemotherapy.

Method: 159 women with breast cancer who were about to begin or undergoing chemotherapy completed a range of measures. Correlational and multiple regression analyses explored associations between fatigue severity, functioning and a range of psychological, behavioural, demographic and clinical variables. Forty-two patients were followed-up prospectively to examine the relationship between psychosocial variables, fatigue and functioning after three cycles of chemotherapy.

Results: A range of cognitive, behavioural and affective variables were associated with increased fatigue severity and poorer functioning. Key cognitive and behavioural correlates included, all-or-nothing behaviour, avoidance behaviour, cancer-related catastrophising, expectation of future fatigue and critical/ punishing responses from others. For the women in the nested prospective study, fatigue significantly increased after three cycles of chemotherapy. Increased fatigue was predicted by increased anxiety before starting chemotherapy.

Conclusions: Behavioural factors and cancer-specific cognitions make important contributions to cancer-related fatigue and associated impairments. Such factors are potentially amenable to change within the context of cognitive behavioural therapy.

BACKGROUND

Fatigue is one of the most common symptoms reported by breast cancer patients and is often reported as the most distressing ^(1, 2). There is increased understanding of underlying biological as well as treatment-related factors (e.g., type of treatment, dose-intensity) mechanisms related to cancer-related fatigue (e.g. immune etc). However this does not account for the considerable variability in the experience of cancer-related fatigue (3), suggesting other factors may have an important role to play. A multidimensional model of cancer-related fatigue includes a range of contributing biological, psychosocial and behavioural factors ⁽⁴⁾.

Research exploring the psychological factors related to fatigue in cancer have predominantly explored mood and affect. Depression and anxiety have frequently been associated with cancer fatigue and functional impairment in cross-sectional and prospective studies ^(3, 5, 6). Other studies have identified a role for specific cognitive and behavioural factors in cancer-related fatigue, such as catastrophizing, symptom-focusing, sleep and physical activity ⁽⁷⁻⁹⁾. In breast cancer patients undergoing chemotherapy, a greater tendency to catastrophise about fatigue was prospectively associated with increased cancer-related fatigue ⁽¹⁰⁾. In breast cancer survivors, focusing on symptoms has also been associated with cancer-related fatigue ⁽⁸⁾. Prospective studies with breast cancer survivors, show that increased symptom focus, avoidant coping styles ⁽⁸⁾ and stronger somatic attributions of fatigue (i.e. attributing the fatigue to the cancer itself and/or cancer treatment) were predictive of persistent fatigue ⁽¹¹⁾. However, some factors theoretically important in the fatigue cycle remain under researched, for example, fear and avoidance of activity ^(12, 13) and the perceived level of social support ⁽¹⁴⁾. Aside from fear of occurrence few studies have explored beliefs specific to the cancer experience.

We were interested in exploring people's beliefs about their disease and treatment trajectory as well as beliefs related to shame of the cancer diagnosis, something observed by clinicians in the clinic.

Whilst studies have explored some of these factors singularly and in different combinations for women at different stages of treatment and remission, we were not aware of any study which had combined these variables in a multifactorial model of cancer-related fatigue (CRF). A multifactorial exploration would help identify key modifiable factors associated with CRF and would help identify important treatment targets. We were interested in specific cognitive and behavioural factors which contribute to fatigue and functioning, over and above the contribution of broader psychological variables of anxiety, depression and sleep (those previously explored in the literature). Identifying specific cognitions and behaviours could help tailor treatments for cancer-related fatigue, improving their efficacy.

Aims and hypothesis

This study explored the psychosocial and behavioural factors associated with fatigue and functional impairment in women undergoing chemotherapy for breast cancer. A nested prospective study explored factors associated with fatigue after 3 cycles of chemotherapy.

In line with previous research we hypothesised that, *depression*, *sleep* and *anxiety* would be associated with increased fatigue severity and poorer functioning. We hypothesised that certain cognitive and behavioural responses to fatigue would also be associated with fatigue and functioning; specifically, increased *symptom focusing*, *catastrophising*, *embarrassment avoidance*, *avoidance behaviour*, *all-or-nothing behaviours*, *general health anxiety*, perceived

soliciting responses from significant other and a higher expectation of future fatigue. We also explored the relationship between fatigue and functioning and cancer specific beliefs; i.e. cancer-related embarrassment avoidance, and predictions about the progress of their treatment.

Finally, we hypothesised that fatigue would significantly increase over the course of three cycles of chemotherapy and this increase in fatigue would be predicted by psychosocial variables present at the start of treatment.

METHODS

Participants and Procedure

Women with a diagnosis of breast cancer ($n=159$) were recruited from the Breast Care Clinic at King's College Hospital in South London between 17/08/2010 – 01/07/2011. Women were eligible if they were treated or due to be treated with a FEC-T (fluorouracil, epirubicin and cyclophosphamide, followed by docetaxel) chemotherapy regimen. For the prospective analysis, women who had not begun treatment at baseline were asked to complete the follow-up questionnaire after 3-cycles of chemotherapy; on average this was 3.2 months after completing the baseline questionnaire ($SD=1.8$; Range 1.3- 8.1 months). The study received approval from the ethics research and audit panel at King's College Hospital, London (ref: CASS AP1003-01) and informed consent was obtained from all participants.

The design of the main study was cross-sectional. An additional prospective study design followed up women ($n=42$) after they received 3 cycles of chemotherapy, when their

chemotherapy drug changed. Only men and those without adequate English language skills were excluded from the study.

Socio-demographic and clinical characteristics were obtained from questionnaires and review of clinical notes. For follow-up measures, all scales were re-administered except for variables presumed to be stable characteristics (e.g. demographics). Cronbach's α was calculated for all subscales to assess reliability, with all reaching the recommended threshold for inclusion of 0.7⁽¹⁵⁾.

Measures

Dependent Variables

Fatigue The primary measure of fatigue was the Chalder Fatigue Questionnaire (CFQ) an 11 item self-report scale for the measurement of subjective fatigue⁽¹⁶⁾. The measure has been used to assess cancer-related fatigue in multiple studies^(17, 18) and was recommended for use in a systematic review for the measurement of cancer-related fatigue^(19, 20). Clinically significant fatigue was defined as a score >4 as per the authors instructions⁽¹⁶⁾. The CFQ items were scored using the binary method (0 or 1) to establish the presence of clinically significant fatigue 'caseness' and a continuous method (0, 1, 2, 3) to assess fatigue severity. Cronbach's alpha in the current study showed excellent internal consistency (.91).

Functioning The Work and Functioning Scale (WSAS)⁽²¹⁾ is a five-item self-report scale used to measure functional impairment. The five items correspond to impairment in work, home management, social activities, private leisure activities and relationships. Cronbach's alpha in the current study showed excellent internal consistency (.91).

Cognitive and Behavioural Variables

The Cognitive and Behavioural Responses to Symptoms Questionnaire (CBRQ) assesses patients' cognitive and behavioural responses to their symptom experience, in this case, fatigue ^(20, 22). Five cognitive subscales measure *catastrophising*, *damage beliefs*, *embarrassment avoidance*, *symptom focusing* and *fear avoidance*. Two behavioural subscales measure *all-or-nothing behaviour* and *avoidance behaviour*. Cronbach's alpha for the 7 CBRQ subscales were .83, .78, .89, .82, .73, .89, .82 respectively, indicating acceptable- good internal consistency.

Two additional subscales were created for the purpose of this study; '*cancer-related embarrassment avoidance*' and '*cancer-specific catastrophising*'. Items were developed in conjunction with staff at the breast cancer clinic and based on the CBRQ. '*Cancer-related embarrassment avoidance*' consisted of six items adapted from the embarrassment avoidance scale to make the context cancer-specific; including items such as "the embarrassing nature of cancer prevents me from doing things" (Appendix A). The '*cancer-related catastrophising*' sub-scale consisted of six items to assess patients' perceptions about their cancer and treatment trajectory. Items were based on the catastrophising subscale of the CBRQ, and made specific to the cancer context; including items such as "I am afraid that my cancer will not be treated successfully" (Appendix B). Higher scores indicate a more pessimistic view of the future. ⁽²²⁾. Confirmatory factor analysis showed both sub-scales had a good model fit ('*cancer-related embarrassment avoidance*' CFI=.98 TLI=.98; *cancer-related catastrophising*', CFI=.90, TLI=.84) and Chronbach's alpha showed acceptable-good internal consistency; .76 and .79 respectively.

A visual analogue scale (VAS) assessed patient expectations of how tired their chemotherapy would make them on a line anchored at each end by the statements 'not at all tired' and 'extremely tired'.

Part II of the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) is a 14-item scale developed to evaluate the patient's perspective of the responses that their significant other might have to their pain and suffering ⁽²³⁾. The scale is divided into three subscales assessing perceived *punishing*, *distracting* and *solicitous* responses. As with previous studies, the instructions on the measure were adapted from pain to cancer terminology, without changing its meaning ⁽²⁴⁾. Participants were asked to rate 14 statements to indicate how often their significant other generally responded to them in that particular way when they were experiencing symptoms related to cancer from 'never' to 'very often'. The Cronbach's alpha for the scales were .82, .78 and .78 respectively.

The Health Anxiety Inventory (HAI) is a reliable and valid measure of preoccupation and worry about health ⁽²⁵⁾. An abbreviated 'very short' 4-item health anxiety measure (VSHAI) was used which reflected different symptoms of health anxiety. Whilst there is currently no published data as to the VSHAI's reliability and validity, it correlates highly ($r = .8$) with the short HAI in clinical populations (P.M. Salkovskis, personal communication) and has been used previously in other studies ⁽²⁶⁾. In this study the Chronbach's alpha showed good internal consistency (.83). *Wider Psychological & Behavioural Variables*

Depression and anxiety were measured using the two subscales of the Hospital Anxiety and Depression Scale (HADS), a 14-item scale assessing psychological distress ⁽²⁷⁾. The Jenkins Sleep Scale (JSS) is a four-item scale that was used for the estimation of sleep problems ⁽²⁸⁾

Statistical Analysis

Power analyses were conducted using nQuery Advisor software (version 4.0). A paper that considered fatigue in physical illness using the CBRQ measure, guided us to seek to explain 20% of variance in a cross-sectional regression analysis ⁽²⁹⁾. Using the 20% figure, where nine variables explained 10% of the variance and were controlled for, a sample size of 98 was calculated to have 80% power to detect an increase in R^2 of 0.1 (i.e. the remaining 10% of variance) due to the impact of one additional clinically important covariate.

Analyses were conducted using SPSS version 25. Due to the number of exploratory correlations and the likelihood that some of the results were significant by chance we divided the family wise error rate (0.05) by the number of tests for significance. For the correlations 0.05 was divided by 17 (n =number of variables) = 0.002. However, although we report all significance levels in the correlation table we have bolded those that reached significance after correction. We selected $p < .01$ as our significance level for the multiple regression analyses. Bonferroni is considered overly conservative when applied to non-independent (i.e. correlated) tests (30, 31). Use of Kolgomorov-Smirnov tests and histograms ensured our dependent variables were normally distributed, allowing for further parametric analyses. Where subscale totals could not be calculated due to missing data, case mean substitution was used to estimate missing data where no more than 20% of the data was missing for that subscale.

Assumptions of linear multiple regression were met for subsequent analyses, including normality of the residuals, linearity, homoscedasticity, no multicollinearity and independence of residuals. Variables were entered into the regression analyses within statistical limitations e.g. that there should be at least ten cases for every variable being entered into a regression model ⁽³²⁾.

Cross-sectional analyses

To identify factors associated with fatigue and functioning at baseline, bivariate analyses incorporating demographic, clinical and psychosocial variables were conducted. Variables significantly correlated at $p < .01$ level were entered into the multivariable models.

Hierarchical multiple regression was chosen in order to determine the psychological and behavioural variables with the most predictive power when accounting for relevant clinical and demographic characteristics. We then explored the extent to which these variables continued to account for variance in the dependent variables after the entry of wider psychological variables, anxiety, depression and sleep (those previously explored in the literature) into the regression equation. Stepwise entry methods were used within each hierarchy level for all analyses, as there was no strong evidence from the research literature to suggest which variables may be of increased theoretical importance. Variance inflation factors were examined for the potential for collinearity and over-fitting ⁽³³⁾.

Prospective analyses

In the prospective analyses, bivariate models were used to identify demographic, clinical, psychosocial and behavioural factors that were significantly associated with fatigue and

functioning after 3-cycles of chemotherapy. Variables significantly associated with fatigue and functioning at $p < .01$ level were included in the multivariable regression models, along with baseline fatigue and functioning scores.

RESULTS

One hundred-fifty-nine women with breast-cancer were recruited. At the time of completing the baseline questionnaire 51.4% (82/159) had not begun receiving chemotherapy, 27.5% (44/159) had one cycle of chemotherapy and 21.1% (33/159) had more than one cycle of chemotherapy. Women who had not begun receiving chemotherapy at the time of completing the first questionnaire (82/159) were asked to complete the follow-up questionnaire after three cycles of chemotherapy. 42/82 women returned the follow-up questionnaire. Table 1 shows the clinical and demographic variables of the samples.

Table 1. Clinical and demographic variables of samples

	<i>Women at various stages of chemotherapy treatment (n=159)</i>	<i>Women after 3-cycles of chemotherapy (n=42)</i>
Age, M (SD)	52.9 (11.54)	49.34 (9.19)
<i>Marital status, N (%)</i>		
Missing	14	3
Married/ living with partner (%)	79 (54.5)	24 (61.5)
Single/ divorced/ widowed	66 (45.5)	15 (38.5)
<i>Highest educational qualification, N (%)</i>		
Missing	18	4

None	11 (7.8)	2 (5.3)
School	42 (29.8)	6 (15.8)
Polytechnic or similar	29 (20.6)	12 (29.3)
Higher (undergraduate)	59 (41.8)	18 (43.9)
<i>Current work status, N (%)</i>		
<i>Missing</i>	17	3
Full-time work	35 (24.6)	10 (25.6)
Part-time work	24 (16.9)	7 (17.9)
Casual work	1 (.07)	1 (2.6)
Student	2 (.1)	0
Unemployed	11 (7.7)	5 (12.8)
Temporary sick	22 (15.4)	7 (17.9)
Permanent sick / disabled	13 (9.1)	3 (7.7)
Retired	27 (18.9)	2 (5.1)
Looking after home	8 (5.6)	4 (10.3)
<i>Ethnicity, N (%)</i>		
<i>Missing</i>	8	3
White and white other	95 (62.9)	27 (64.3)
Mixed or multiple ethnic groups	4 (2.7)	
Asian or Asian British	12 (7.9)	
Black/African/Caribbean/Black British	31 (20.5)	
Other ethnic group	9 (6.0)	
<i>Comorbidities¹, N (%)</i>		
<i>Missing</i>	13	2
No comorbidities	69 (47.3)	13 (32.5)
1-2 comorbidities	53 (36.3)	17 (42.5)
3+ comorbidities	24 (16.4)	10 (24.4)
Comorbid pain (at a clinical complaint level)	16 (51.4)	5 (12.5)
Comorbid diabetes	9 (6.2)	2 (5.0)
Comorbid heart condition/ high cholesterol	23 (15.8)	8 (20.0)
Comorbid orthopaedic condition	14 (9.6)	5 (12.5)
Comorbid other health condition	43 (29.7)	16 (40.0)
<i>Previous treatment, N (%)</i>		
<i>Missing</i>	13	2

¹ Comorbid anxiety/depression was not available from the patient clinical record as it was a record from a physical health system.

None	60 (41.1)	7 (17.5)
Surgery (lumpectomy/ mastectomy)	52 (35.6)	28 (70.0)
Other (radiotherapy/ chemotherapy/ hormone therapy)	4 (2.7)	2 (5.0)
Surgery and other	30 (20.5)	3 (7.5)
<i>Stage of cancer, N (%)</i>		
<i>Missing</i>	13	2
I	13 (8.9)	4 (10.0)
II	90 (61.6)	24 (70.0)
III	31 (21.2)	10 (25.0)
IV	12 (8.2)	2 (5.0)
Fatigue, M, (SD)	15.7 (6.2)	14.7 (6.2)
Fatigue case, N (%)	72 (45.3)	9 (21.4)
Functioning, M, (SD)	16.0 (10.8)	16.6 (9.7)

Preliminary Analyses

Pearson's product-moment correlation test found a moderate correlation between fatigue (CFQ) and functional impairment (WSAS) ($r = .45$, $p < .01$).

One-way analyses of variance (ANOVA) were conducted to consider differences in the scores on the dependent variables between the three points of treatment (pre-chemotherapy, 1 cycle of chemotherapy, more than 1 cycle of chemotherapy) at baseline ($n=159$). No significant differences were found in fatigue [$F(2, 120)=.01$, $p=.40$] or functioning [$F(2, 117)=.38$, $p=.69$] between women at different stages of treatment. Subsequent cross-sectional analyses were conducted on the combined sample of 159 women.

Cross-Sectional Correlations

Table 2 shows cross-sectional correlations (Pearson's product moment correlation) between all of the psychological predictor variables and the dependent variables: fatigue and functioning of women at baseline ($n=159$).

Table 2. Cross-sectional correlations between all psychological variables, fatigue and functioning ($n=159$)

	Fatigue <i>r</i>	Functioning <i>r</i>
<i>Cognitive & Behavioural</i>		
Symptom focusing (CBRQ)	.27**	.29***
Catastrophising (CBRQ)	.17	.35***
Damage beliefs (CBRQ)	.05	.09
Fear avoidance (CBRQ)	.13	.34**
Embarrassment avoidance (CBRQ)	.24**	.23*
Avoidance behaviour (CBRQ)	.29***	.57***
All-or-nothing behaviour (CBRQ)	.30***	.26**
Cancer-related embarrassment avoidance	.23**	.28**
Cancer-related catastrophising	.30***	.29***
Punishing responses from significant other (WHYMPI)	.29**	.35***
Solicitous responses from significant other (WHYMPI)	-.14	.10
Distracting responses from significant other (WHYMPI)	-.19	.004
Health anxiety (VSHAI)	.26**	.38***
Expectation of future fatigue (VAS) related	.30***	.38***
<i>Wider Psychological</i>		
Anxiety (HADS)	.30***	.47***
Depression (HADS)	.30***	.67***
Sleep (JSS)	.34***	.37***

* significant at the .05 level (2 tailed)

** significant at the .01 level (2 tailed)

***** significant at the .001 level (2 tailed): in bold as considered significant after Bonferroni correction**

CBRQ, Cognitive Behavioural Responses Questionnaire; WHYMPI, West Haven-Yale Multidimensional Pain Inventory; VSHAI, Very Short Health Anxiety Inventory; VAS, Visual Analogue Scale; HADS, Hospital Anxiety and Depression Scale; JSS, Jenkins Sleep Scale.

Medium to large correlations were observed for *symptom focusing, catastrophising,, avoidance behaviour, all-or-nothing behaviour, expectation of future fatigue* and *cancer-related catastrophising* were associated with both dependent variables. *Health anxiety and perceived punishing responses from significant other* were associated with poorer functioning. Of the wider psychological variables, *depression, sleep* and *anxiety* were associated with increased fatigue severity and poorer functioning.

Cross-sectional associations for the clinical/demographic variables are not reproduced here but the significant associations are summarised as follows. There were no significant associations between fatigue and any of the clinical (previous treatment, stage of cancer and co-morbidities) or demographic (age, ethnicity, work status, highest education) variables. Poorer functioning was associated with the stage of cancer [$F(3,123)= 4.65, p=.004$]. There were no other significant correlations between demographic or clinical variables and the dependant variables at baseline.

Cross-Sectional Multiple Regression Analyses

Cross-sectional Associations of Fatigue and Functioning

Multiple regression analyses were conducted to determine the most important psychological predictors of fatigue and functional impairment and whether these factors accounted for variance after the contribution of relevant demographic and illness-related factors, in women at baseline ($n=159$).

Clinical, demographic, psychological and behavioural variables that had correlated with fatigue and functioning at a $p < .01$ level were entered, with fatigue and functioning as the

dependent variables. For fatigue, variables entered into step one included symptom focusing, embarrassment avoidance, avoidance behaviour, all-or-nothing behaviour, cancer-related embarrassment avoidance, cancer-related catastrophising, punishing responses from significant other, health anxiety and expectation of future fatigue. In step two, anxiety, depression and sleep were added. As no clinical or demographic variables were significantly associated with fatigue these were not entered into the model.

For functioning, variables entered into step one of the model were stage of cancer, symptom focusing, embarrassment avoidance, avoidance behaviour, all-or-nothing behaviour, cancer-related embarrassment avoidance, cancer-related catastrophising, punishing responses from significant other, health anxiety and expectation of future fatigue. In the second step of the model anxiety, depression and sleep were added.

Using this method, three regression models were obtained for fatigue and four models for functioning. The final models are reproduced in Table 3.

Table 3. Multiple regression models identifying cross-sectional predictors of fatigue and functioning

Step & Variables	<i>B</i>	S.E. <i>B</i>	β
Fatigue			
<i>(1) Cognitive & Behavioural</i>			
Constant	8.92	1.40	
Cancer-related catastrophising	.34	.11	.25**
All-or-nothing behaviour	.41	.12	.28**
Punishing responses from others	.29	.11	.26**
$R^2 = .24$; $F(2,113) = 11.18$; $p < .001$			

(2) Cognitive, Behavioural & Wider Psychological

Constant	8.58	1.38	
Cancer-related catastrophising	.28	.12	.22*
All-or-nothing behaviour	.26	.14	.18
Punishing responses from others	.27	.11	.21*
Sleep	.27	.11	.24*

$\Delta R^2 = .04$; $F(3,112) = 10.26$; $p < .001$

Total $R^2 = 0.29$

Step & Variables	<i>B</i>	S.E. <i>B</i>	β
Functioning			
(1) Clinical, Cognitive & Behavioural			
Constant	-6.33	2.92	
Avoidance behaviour	.85	.13	.48***
Stage of cancer	3.77	.99	.27***
Punishing responses from others	.45	.17	.20**
Cancer-related catastrophising	.40	.17	.17
$R^2 = .49$; $F(4,103) = 25.05$; $p < .001$			
(2) Clinical, Cognitive, Behavioural & Wider Psychological			
Constant	-3.30	2.64	
Avoidance behaviour	.63	.12	.35***
Stage of cancer	2.71	.89	.19**
Punishing responses from others	.33	.15	.14*
Cancer-related catastrophising	-.05	.17	-.02
Depression	1.33	.24	.44***
$\Delta R^2 = .11$; $F(5,102) = 31.49$; $p < .001$			
Total $R^2 = 0.78$			

* significant at the .05 level

** significant at the .01 level

*** significant at the .001 level

For fatigue, *cancer-related catastrophising* entered the regression model first, explaining 12% of the variance, followed by *all-or-nothing behaviour* which explained an additional 8% of the

variance, and *punishing responses from others* which explained another 5%. From the second step in the hierarchy, *sleep* explained a further 4% of the variance in fatigue, resulting in a significant hierarchical stepwise regression equation which explained 29% of the variance in fatigue.

Considering functioning, *avoidance behaviour* entered the regression model first, explaining 58% of the variance in functioning, followed by *stage of cancer which explained an additional 7% of the variance*, *punishing responses from others* which explained an additional 5% and *cancer-related catastrophising* which explained 3%. From the second step in the hierarchy, *depression* explained a further 11% of the variance, resulting in a significant hierarchical stepwise regression equation which explained 78% of the variance in functioning.

Prospective Analyses

There were no significant differences between women who completed the baseline questionnaire ($n=159$) and those who completed the follow-up questionnaire ($n=42$) in terms of baseline clinical and demographic variables (age, ethnicity, stage of cancer, previous treatment, or comorbidities; all $p>.05$) or baseline levels of fatigue [$t(140) = .52, p=.61$] and functioning [$t(122) = -.45, p=.66$]. After three-cycles of chemotherapy 21.4% (9/42) women met the cut-off for clinical 'caseness' of fatigue.

Paired sample t -tests were conducted to compare the change in fatigue severity and functioning for forty-two women after three cycles of chemotherapy. Fatigue significantly increased over the course of three cycles of chemotherapy [$t(35) = 3.85, p<.001$]. There was

no significant change in level of functioning between baseline and after 3-cycles of chemotherapy [$t(34) = 1.01, p = .32$].

Predictive relationship between Psychological Predictors at the beginning of treatment and Fatigue and Functioning after Three Cycles of Chemotherapy

Pearson's correlation assessed the association between fatigue after three cycles of chemotherapy and the cognitive and behavioural and wider psychological variables (see supplementary material Table S1). Variables which correlated with the dependent variables at $p < .01$ level, were entered into further hierarchical multiple regression analyses, controlling for baseline levels of fatigue. Variables entered into the model were baseline level of fatigue, cancer-related embarrassment avoidance, expectation of future fatigue, anxiety, and sleep. Tolerance and variance inflation factor indicated multicollinearity was acceptable for the multifactorial model. The final models are reproduced in table 4.

Table 4. Multiple regression model identifying prospective predictors of fatigue after three cycles of chemotherapy

Variables	<i>B</i>	S.E. <i>B</i>	β
Fatigue			
Constant	9.62	2.20	
Baseline fatigue	.35	.15	.36*
Anxiety	.57	.22	.39*
$R^2 = .64; F(2,31) = 10.71 p < .001$			

* significant at the .05 level

Anxiety was the strongest predictor of fatigue severity after three cycles of chemotherapy.

CONCLUSIONS

These findings were in line with the hypotheses, in that increased fatigue severity and poorer functioning were associated with greater endorsement of a range of unhelpful psychological and behavioural responses to symptoms. *Cancer-related catastrophising*, *all-or-nothing behaviour* and perceived *punishing responses from others* emerged as significant variables in the cross-sectional multiple regression analyses for fatigue. Similar associations were observed for functioning, with *cancer-related catastrophising*, *avoidance behaviour* and perceived *punishing responses from others* emerging as significant variables. These findings support the hypothesis that specific psychological and behavioural responses play a role in perpetuating fatigue and related impairment in women with breast cancer. In line with previous literature, significant associations were also observed for *depression*, *anxiety* and *sleep* and fatigue and functioning. As expected, fatigue increased after three cycles of chemotherapy. In the prospective analysis, *anxiety* predicted fatigue severity.

The important role of *cancer-related catastrophising* in fatigue and functioning suggests that women's perceptions about their cancer and treatment trajectory is important in terms of their current symptom experience. It may be that there is a reciprocal relationship between these variables- i.e. a more pessimistic view of the future may feed into the current experience of symptoms and vice versa. These findings echo those in breast cancer showing dispositional pessimism predicts illness-related disruption of social and recreational activities

(34).

Similarly the association between *catastrophising* about fatigue symptoms and poorer functioning is one that echoes existing findings in the literature from a breast cancer

population⁽⁸⁾. Several studies have suggested that catastrophising about fatigue may be a risk factor for greater fatigue and poor functioning after treatment^(7, 10, 35). The association between *avoidance behaviour* with functional impairment is also not surprising, as avoiding activity and taking excessive rest will reduce one's ability to engage in daily activities as well as potentially resulting in physical deconditioning.

The association between *all-or-nothing behaviour* and fatigue has not previously been reported in cancer-related fatigue. It is understandable that women undergoing chemotherapy may take advantage of periods of relative respite between episodes of worsened fatigue and engage in bursts of activity at these times. However, these results suggest that alternating between resting and doing too much may contribute to cancer-related fatigue.

The current study found a strong association between the perception of *punishing responses from their significant other* with both fatigue severity and functioning. These findings were unexpected as we predicted a relationship for the perception of *solicitous responses from their significant other* instead, on the basis of previous literature⁽³⁶⁾. One possibility is that distress experienced by the significant other may impact on their ability to provide appropriate social support and could manifest as critical or punishing responses for the patient. Alternatively, this measure may be reflecting pre-morbid relationship difficulties, or a tendency to experience others' responses as punishing, that contributes to ongoing distress and impairments. These possibilities require further research.

To our knowledge, this is the first time that many of these specific beliefs and behaviours have been found to play a role in the severity of fatigue and impairment experienced by cancer patients and to potentially contribute to the development of fatigue and functional impairment during chemotherapy. The beliefs and behavioural responses outlined above continued to show significant associations with fatigue and functional impairment in the presence of clinical/demographic characteristics and broader psychological variables such as depression and anxiety. These findings support the tenet that the beliefs and behaviours considered in this study are an appropriate, helpful and informative way of describing an experience that can get lost in umbrella terms like 'depression' and 'anxiety'. Furthermore, such psychological variables are more amenable to change than demographic and illness-related factors ⁽⁴⁾.

Study Limitations

Whilst there was adequate statistical power for all analyses reported, the number of variables that could be entered in multiple regression analyses for the prospective data was limited by the sample size. Analyses in this study were exploratory; much larger sample sizes are required in the future to have confidence in the results. Future studies should include larger sample sizes to accommodate a wide range of variables at different stages of the cancer experience in a prospective design. There may also have been a selection bias in relying on one clinic, although our sample was fairly heterogeneous in terms of the demographics being measured. Nevertheless, this study does help to shed some light on the complexity of fatigue and illustrates a role for our explanatory variables.

Clinical implications

This study contributes to our understanding of psychological and behavioural factors that may be associated with CRF and related functional impairment in women undergoing chemotherapy for breast cancer. Whilst there is increasing evidence for the use of cognitive behavioural therapy in addressing CRF, the content of these interventions has tended to rely on the application of more general cognitive behavioural principles without addressing issues that may be particular to CRF. By addressing this gap in the literature, this study can inform the development of an integrative cognitive behavioural model of cancer-related fatigue and more appropriately targeted cognitive behavioural interventions. Key cognitive variables that may need to be specifically addressed in these interventions include future expectations, both in terms of the cancer and treatment trajectory and expectations of future fatigue, as well as catastrophising tendencies. Key behavioural variables to target include, all-or-nothing and avoidance behaviours, whilst maintaining a broader focus on depression and sleep issues. Women with breast cancer may also benefit from support with interpersonal issues such as perceived punishing responses from their significant others.

This study helps to shed some light on the complexity of fatigue and illustrates a role for a range of cognitive, behavioural psychosocial explanatory variables.

ACKNOWLEDGEMENTS

TC acknowledges the financial support from the Department of Health via the National Institute for Health Research (NIHR) Specialist Biomedical Research Centre for Mental Health award to South London and Maudsley NHS Foundation Trust (SLaM) and the Institute of Psychiatry at King's College London. All authors also thank James Gwinnutt and Eleanor Schiavone for their assistance with data collection.

CONFLICT OF INTERESTS STATEMENT

TC receives royalties for self-help books on chronic fatigue. The authors have no other competing interests to report.

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Appendix A.

Cancer- related embarrassment avoidance sub-scale

Views about your symptoms	Strongly agree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The embarrassing nature of having cancer prevents me from doing things					
I avoid social situations because of my illness					
I am embarrassed about having cancer					
I am ashamed of having cancer					
I am embarrassed about changes in my physical appearance					
I accept that changes in my physical appearance are part of the treatment process					
There is no point in worrying about changes in my physical appearance					

Appendix B.

Cancer- related catastrophising sub-scale

Views about your symptoms	Strongly agree	Disagree	Neither agree nor disagree	Agree	Strongly agree
I am afraid that my cancer will not be treated successfully					
I feel optimistic about the future					
I am worried that my cancer will spread					
The unpredictability of my cancer means that I cannot plan for the future					
It is very likely that the cancer will be treated successfully					
I will make a full recovery					

Supplementary material

Table S1. Prospective correlations between all psychological variables, fatigue and functioning

	Fatigue <i>r</i>	Functioning <i>r</i>
<i>Cognitive & Behavioural</i>		
Symptom focusing	.29	.19
Catastrophising	.31	.50**
Damage beliefs	.10	-.02
Fear avoidance	.08	.28
Embarrassment avoidance	.35*	.05
Avoidance behaviour	.14	.41**
All-or-nothing behaviour	.07	.07
Cancer-related embarrassment avoidance	.47**	.20
Cancer-specific beliefs	.36*	.12
Punishing responses from significant other	.17	.31
Solicitous responses from significant other	-.13	.15
Distracting responses from significant other	-.21	-.18
Health anxiety	.03	.09
Expectation of future fatigue (Visual analogue scale)	.41**	.63***
<i>Wider Psychological</i>		
Anxiety (HADS)	.55***	.33
Depression (HADS)	.22	.30
Sleep	.42**	.32

* significant at the .05 level (2 tailed)

** significant at the .01 level (2 tailed)

*** significant at the .001 level (2 tailed)