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A comparison of the characteristics of disease-free breast cancer survivors with or without cancer-related fatigue syndrome

S. Alexander[a], *O. Minton*[a], *P. Andrews*[b], *P. Stone*[a,*]

[a]*Division of Mental Health, St George's University of London, 6th Floor Hunter Wing, Cranmer Terrace, London SW17 ORE, United Kingdom*
[b]*Division of Basic Medical Science, St George's University of London, Cranmer Terrace, London SW17 ORE, United Kingdom*

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ABSTRACT

Purpose: To determine the prevalence of cancer-related fatigue syndrome (CRFS) in a population of disease-free breast cancer survivors and to investigate the relationship between CRFS and clinical variables.

Patients and methods: Women (200) were recruited. All participants were between 3 months and 2 years after completion of primary therapy for breast cancer and were disease free. Subjects completed a diagnostic interview for CRFS and structured psychiatric interview. Participants also completed quality of life, mood and fatigue questionnaires, and provided a blood sample for haematological and biochemical analysis and a 24-h urine specimen for cortisol estimation. Subjects wore a wrist actigraph for 7 days to measure activity and sleep.

Results: Sixty women (30% of participants) were found to fulfil the criteria for CRFS. There were statistically significant differences between fatigued and non-fatigued women with respect to fatigue severity ($p < 0.01$), mood ($p < 0.01$) and quality of life scores ($p < 0.05$). There were significant differences in blood variables including raised total white cell count and lower sodium (all $p < 0.02$). There was no difference in the 24 h urinary free cortisol levels. Actigraphic data demonstrated significant differences in sleep quality and disturbance, but not in overall levels of daytime activity or circadian rhythm.

Conclusion: CRFS affects 30% of women after breast cancer treatment and has significant effects on quality of life and mood. There is some evidence that CRFS is related to sleep disturbance or to a persistent inflammatory or immune response.

1. Introduction

Cancer-related fatigue (CRF) is a common symptom that can occur both in patients during treatment for breast cancer[1] and in disease-free survivors.[2] However, the prevalence of fatigue can vary with how it is measured.[3,4] In an effort to standardise the classification of fatigue, Cella and colleagues have developed a set of diagnostic criteria that must be fulfilled for an individual to be considered a 'case' of CRF.[5] To fulfil these diagnostic criteria the subject must have experienced at least 6 of 11 fatigue-related symptoms on most days or every day for 2 weeks in the previous month. At least one of these symptoms must have been 'significant fatigue, lack of energy, or an increased need to rest'. The fatigue needs to be sufficiently severe to have had an impact on daily life. There must be evidence from the history, physical examination or laboratory findings that the symptoms are a consequence of cancer or cancer therapy. Finally, the fatigue should not be 'primarily a

* *Corresponding author:* Tel.: +44 (0)2087250145; fax: +44 (0)2087253538.
E-mail address: pstone@sgul.ac.uk (P. Stone).
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consequence of co-morbid psychiatric disorders such as major depression, somatisation disorder or delirium'. Most of these criteria can be assessed using Cella and colleagues' short diagnostic interview.[5] However, in order to systematically assess patients with co-morbid psychiatric disorders it is necessary to also perform a psychiatric assessment using an instrument such as the structured clinical interview for the diagnostic and statistical manual of mental disorders (SCID). This approach to defining 'cases' of CRF syndrome is similar to the approach used to diagnose cases of chronic fatigue syndrome (CFS),[6] which potentially has some similarities with CRF in this population.[7] The diagnostic criteria permit patients to have both cancer-related fatigue syndrome (CRFS) and a co-morbid psychiatric diagnosis[8] provided that the fatigue is not primarily due to the psychiatric disorder. It has been suggested that a decision can be made about the causation of the fatigue based upon the timing of the onset of the symptom and the presence or absence of other fatigue-related attributes (e.g. diurnal variation, strength of cognitive symptoms). However, in practice it can be extremely difficult to determine whether the fatigue should primarily be attributed to the psychiatric disorder or to the cancer diagnosis/treatment.

The diagnostic criteria for CRF syndrome have been used successfully in previous studies of breast cancer patients. A small study by Young et al.[9] examined patients ($n = 69$) for an average of 6 months after breast cancer treatment. The prevalence of CRF syndrome was 19%. Those who met the criteria had significantly more fatigue-related symptoms, mood disturbance and quality of life disruption than those who did not. However, patients in this study did not undergo a rigorous psychiatric assessment, making it unclear whether some of the patients with CRF syndrome actually had a co-morbid psychiatric disorder. Andrykowski et al.[10] conducted a much larger study ($n = 288$) to examine the reliability of the CRF criteria in an on-treatment breast cancer population and included the SCID interview to assess psychiatric morbidity. This study demonstrated an increase in the prevalence of CRF syndrome from 10% at baseline to 26% post treatment. This post-treatment prevalence included patients with psychiatric co-morbidities including major depression.

A limitation of both these previous studies is that while they examined a number of subjective symptoms and demographic data neither study attempted to correlate CRF with biological variables or objective measure of activity. The prevalence of CRF syndrome in disease-free women months to years after completion of therapy has not been reported previously.

A recent systematic review by Prue and colleagues[3] demonstrated not only wide variation in the measurement of CRF but also limited evidence of its association with mood disturbance and other quality of life co-variables. This is in part due to the lack of an agreed definition of fatigue and the subjective nature of its measurement.

Despite extensive research on patho-physiological causes of CRF, the causes are poorly understood.[11] Anaemia is frequently considered to be a cause of fatigue in cancer patients,[12] and there is evidence that correction of anaemia leads to improvement in fatigue among patients undergoing chemotherapy.[13] There is a dearth of studies to investigate the relationship between fatigue and other biochemical or inflammatory markers. It has been suggested that there may be similarities between the mechanisms of fatigue in patients with CRF syndrome and patients with CFS.[7] Physical deconditioning has been proposed as one of the key factors in perpetuating fatigue in patients with CFS.[14] It has been suggested that fatigue in cancer patients similarly may be due to deconditioning following a period of inactivity,[12–15] but very few studies have specifically tested this hypothesis. There is some evidence to suggest that patients with CFS demonstrate a disruption of the hypothalamic pituitary adrenal axis (HPA).[16,17] However, very few studies have investigated whether similar defects exist in patients with CRF.

This current study examines the hypotheses that CRFS in this population is related to disruption of the HPA axis and reduced physical activity. We hypothesised that patients with CRFS would have alterations in 24-h urinary free cortisol and objective evidence of decreased physical activity and disrupted sleep (as measured by actigraphy). In order to evaluate the hypotheses that fatigue in cancer survivors is due to anaemia, metabolic disturbances (such as renal or liver impairment) or sub-clinical hypothyroidism, we also obtained routine blood samples for analysis. Additional assessments were undertaken to explore the relationship between fatigue severity and the severity of other symptoms (such as pain, nausea or psychological distress).

The specific aims of the study were therefore: (1) to identify the prevalence of CRF syndrome in disease-free breast cancer survivors and (2) to identify clinical, psychosocial, biological and objective activity variables previously hypothesised to be associated with CRF syndrome.

2. Patients and methods

Participants were women with stage I–IIb breast cancer, treated with primary therapy between 3 months and 2 years previously. Clinically disease-free women were recruited at St George's NHS Trust London over a 2-year period by one researcher (S.A.). Inclusion criteria were age at least 18 years; histologically proven breast cancer; completed all treatment modalities at least 3 months and not more than 2 years previously; and concurrent hormone use was allowed. Exclusion criteria included pregnancy; co-existing cancer diagnosis; evidence of recurrent disease and confusion or dementia.

Approval for the study was given by the Wandsworth Research Ethics Committee and by St George's NHS Trust Research and Development Committee.

Eligible women were identified from the clinic list 14 days prior to their appointment and were posted an introductory letter and an information sheet. Women who declined to participate in the study were asked if they would be willing to complete a short fatigue questionnaire.

2.1. *Assessments*

Participants completed the following assessments:

2.1.1. *Blood tests (taken in the clinic at the time of the first appointment)*

Full blood count; urea and electrolytes; liver function tests; bone profile; thyroid function; glucose and C-reactive protein (CRP).

2.1.2. *Urinary collection (completed at home prior to attending the second assessment 1 week later)*
A 24-h collection for estimation of urinary cortisol.

2.1.3. *Actigraphy (completed at home after the initial assessment over a 1 week period)*
Participants were asked to wear a wrist actigraph for a continuous period of 7 days. The actigraph used was the octagonal motion logger™ (Ambulatory Monitoring Incorporated, Ardsley, NY, USA) and associated software (Action W). Actigraphs convert kinetic energy from wrist movements into electrical energy proportional to activity. Information is recorded at one minute epochs and stored within the watch prior to downloading. This technique has been successfully used before in fatigued cancer inpatients.[18] Actigraphic data are analysed during four major intervals: down intervals – the time spent in bed trying to sleep; up intervals – the time between successive down intervals; 0–0 intervals – the time from sleep onset to sleep offset and 24-h intervals – used to determine circadian rhythm.

2.1.4. *Questionnaires (completed in the clinic at the.second assessment 1 week after the initial assessment)*

(1) Functional assessment of cancer therapy – fatigue subscale (FACT F)[19]: This is a 13-item tool validated in cancer patients and used widely in clinical studies for fatigue interventions.[20]
(2) Bidimensional fatigue scale (BFS): This is a 11-item scale with seven items assessing physical fatigue and four items assessing mental fatigue.[21] It was developed for use in community surveys, but has subsequently been successfully used to measure fatigue in cancer populations.[22,23]
(3) Fatigue catastrophising scale (FCS): This is a 10-item scale used in a previous study of breast cancer patients[24] to measure a particular aberrant coping style.
(4) Work and social adjustment scale (WAS): This is a five-item scale which measures the functional impact of fatigue.[25]
(5) Hospital anxiety and depression scale (HADS): This is a 14-item scale with seven items on anxiety and seven items on depression.[26] It is used extensively in clinical trials and has been used by our group previously in fatigue assessment studies.[27]
(6) European Organisation of Research and Treatment of Cancer Quality of Life questionnaire EORTC QLQ 30: This is a 30-item scale with five functional scales, three symptom scales and a global quality of life score.[28]
(7) EORTC breast module (BR 23): This is a 23-item scale which is validated for use in breast cancer patients.[29] It has four dimensions – body image, sexual functioning, sexual satisfaction and future perspective.

2.1.5. *Diagnostic interview for cancer-related fatigue (conducted with SCID by SA in the clinic at the first assessment)*
This interview determines whether the participant meets the four criteria for a diagnosis of CRF syndrome. Criterion A: the presence of significant fatigue for 2 weeks in the preceding month and the presence of at least 5 of 10 other fatigue-related symptoms. Criterion B: the fatigue has a significant effect on work or self-care. Criterion C: the fatigue symptoms are a consequence of cancer or cancer therapy. Criterion D: the symptoms are not primarily a consequence of a co-morbid psychiatric disorder. It should be noted that although the diagnostic criteria permit patients to have a co-existing psychiatric disorder provided it is not judged to be the main cause of the fatigue, we felt that this would introduce an unacceptable level of subjectivity into the diagnosis. For this reason, a robust categorisation was employed and any patients with potentially fatiguing psychiatric disorders (including phobias and anxiety states) were excluded from the diagnosis of CRFS.

2.1.6. *Structured clinical interview for the diagnostic and statistical manual (DSM) – IV (SCID)*
The SCID provides a method for obtaining DSM-IV diagnoses. The procedure has been successfully used in previous studies examining CRF syndrome.[10,30] Training in the use of the SCID was supervised by two consultant psychiatrists. All interviews were conducted by the same person (S.A.).

3. Statistical considerations

The effect size for between-group differences was calculated for a sample of 200 women, and was based on previous research conducted in the CFS population.[31] It was estimated that we would identify 100 women in each category (cases versus controls) and this would allow us to detect an effect size of 0.52 at 95% power (two-sided 5% significance). The power was subsequently revised down to 80% during the study, which still allowed us to examine between-group differences with at least 60 women in each category. The between-group analysis was conducted using Mann–Whitney tests with comparisons between median scores because of the non-normal distribution of the data. The level of significance was set at $p < 0.05$; no adjustment was made for multiple comparisons. This was an exploratory and hypothesis generating study and p-values are reported and interpreted in this context.

4. Results

Women (292) were eligible for participation, with 208 women consenting. The demographics and questionnaire (BFS only) responses of the non-participants ($n = 84$) were recorded, and are shown in Table 1. The main reasons for non-participation included other medical conditions, work commitments and extra visits required. There were no significant differences in treatment regimen, stage at diagnosis between participants and non-participants. However, there was a significant difference in fatigue scores, with non-participants scoring lower on the BFS – indicating less fatigue in this group. Non-participants also had a significantly higher mean age. Eight women did not proceed to interview for a variety of reasons and 200 women completed the full interview process. Subjects had a mean age of 58 years (SD

Table 1 – Demographic data and fatigue scores for participants and non-participants

Variables	Participants		Non-participants		*p*-Value
	Mean	Standard deviation	Mean	Standard deviation	
Age in years (range)	57.96 (29–89)	12.3	66.61 (35–92)	12.5	<0.01*
Time post treatment in months	9.93	5.6	11.13	5.4	0.10
Bidimensional fatigue scale (BFS) score total	13.69	8.6	9.29	7.42	0.009*
BFS score physical	9.51	5.90	6.70	5.19	0.027*
BFS score mental	4.18	3.31	2.58	2.86	0.108

* *p*-Value < 0.05.

Table 2 – Different frequencies of treatment type and lymph node status in cases versus controls

	Controls		Cases of cancer-related fatigue syndrome (CRFS)		*p*-Value
	Frequency	Percent (%)	Frequency	Percent (%)	
Surgical procedure					
Breast conservation (lumpectomy)	55	52.9	31	51.7	0.88
Modified radical mastectomy	35	33.7	21	35	0.86
Mastectomy and reconstruction	14	13.5	8	13.3	0.98
Adjuvant treatment					
Chemotherapy	50	48.1	34	56.7	0.29
Radiotherapy	74	71.2	48	80	0.21
Hormonal therapy	91	87.5	47	78.3	0.12
Lymph node status					
Lymph node negative	69	66.3	39	65	0.86

Table 3 – Comparison of biochemical, haematological and endocrine indices

Variable	Laboratory reference range	Mean control	SD	Mean CRFS	SD	*p*-Value
Haematology data						
Haemoglobin (g/dl)	12–16	13.09	0.94	13.24	0.991	0.510
White cell count (No. $\times 10^9$/L)	4 –11	5.86	1.60	6.64	1.91	0.021*
Neutrophil (No. $\times 10^9$/L)	1.7–8.0	3.67	1.34	4.21	1.66	0.048*
Lymphocyte (No. $\times 10^9$/L)	1.0–4.0	1.57	0.53	1.72	0.64	0.249
Monocyte (No. $\times 10^9$/L)	0.24–1.1	0.45	0.13	0.5	0.15	0.052
Eosinophil (No. $\times 10^9$/L)	1.0–0.8	0.14	0.11	0.16	0.10	0.051
Basophil (No. $\times 10^9$/L)	0.0	0.01	0.03	0.02	0.04	0.041*
Platelet (No. $\times 10^9$/L)	150–450	249	59.68	267	65.36	0.093
Biochemistry data						
Sodium (mmol/L)	135–145	139.97	2.29	139.15	2.41	0.018*
Potassium (mmol/L)	3.5–4.7	4.41	0.43	4.36	0.34	0.744
Urea (mmol/L)	2.5–8.0	4.77	2.00	4.52	1.41	0.650
Creatinine (μm/L)	60–110	74.36	21.81	70.22	15.22	0.225
Glucose (mmol/L)	3.0–6.0	5.27	0.95	5.95	2.67	0.415
C Reactive protein (mg/dL)	0–7.5	2.74	3.55	3.91	4.24	0.015*
Uncorrected calcium (mmol/L)	2.18–2.47	2.36	0.11	2.43	0.40	0.208
Phosphate (mmol/L)	0.75–1.50	1.18	0.16	1.23	0.19	0.062
Alkaline phosphatase (IU/L)	30–100	60.81	19.99	68.48	23.94	0.024*
Alanine transaminase (IU/L)	0–40	23.31	16.89	25.32	12.00	0.016*
Bilirubin (μmol/L)	0–17	11.68	3.39	11.03	3.49	0.104
Albumin (g/L)	35–48	39.41	4.47	38.80	4.70	0.261
GGT (IU/L)	0–30	28.15	14.20	33.46	21.57	0.235
Endocrine data						
TSH (mU/L)	0.4–4.0	2.01	1.17	2.96	7.68	0.753
Free T4 (pmol/L)	12–24	14.82	2.22	15.23	2.94	0.504
Urinary free cortisol (nmol/24 h)	0–290	159.27	95.17	164.32	64.63	0.305

* $p < 0.05$.

Table 4 – Differences in between-group questionnaire data

Variable	Mean controls	SD	Mean CRFS	SD	*p*-Value
Function scales					
Physical functioning	87.37	13.266	65.42	20.807	<0.001*
Role functioning	91.35	15.576	61.02	24.095	<0.001*
Emotional functioning	85.42	13.530	67.23	22.470	<0.001*
Cognitive functioning	84.13	16.808	55.65	28.636	0.36
Social functioning	93.27	13.645	74.01	26.492	<0.001*
Total of FCS	12.46	3.223	17.70	6.939	<0.001*
Total of WAS	3.58	5.182	16.68	10.336	<0.001*
Total of FACT F	46.00	6.65	26.00	10.39	<0.001*
Total of BFS	8.85	6.16	18.97	7.26	<.01*
Symptom scales					
Fatigue	21.47	15.112	54.07	23.187	<0.001*
Nausea/vomiting	3.85	9.916	5.00	11.191	0.18
Pain	12.66	20.179	36.11	36.069	0.19
Dyspnoea	9.29	17.661	26.11	31.944	0.21
Insomnia	25.00	25.757	60.00	30.56	0.003*
Appetite loss	6.41	16.797	15.56	27.078	0.001*
Constipation	10.26	19.195	16.67	27.787	<0.001*
Diarrhoea	4.49	13.185	8.33	20.005	0.12
Financial difficulties	7.05	18.966	19.44	31.469	0.04*
Body image	83.98	19.964	67.08	331.136	0.001*
Sexual functioning	23.79	24.655	11.39	20.237	<0.001*
Sexual enjoyment	60.42	28.893	38.60	31.940	0.001*
Future perspectives	68.93	28.107	53.89	33.102	0.03*
Breast systemic therapy side effects	12.76	10.313	28.10	19.677	0.004*
Breast symptoms	12.54	13.501	24.58	24.036	<0.001*
Arm symptoms	15.86	17.367	25.18	26.819	<0.001*
Upset by hair loss	16.67	21.681	66.67	43.363	0.004*
Mood questionnaires					
HAD-T score	6.74	4.921	12.23	6.487	<0.001*
Total of HAD-D	2.55	2.496	5.58	3.341	<0.001*
Total of HAD-A	4.19	3.315	6.65	15.045	<0.001*
Global health status	81.09	16.797	56.07	22.787	<0.001*

* $p < 0.05$.

12.3; range 29–89) and the majority were white ($n = 163$, 78%). Overall, 60 participants met the criteria for CRF and were deemed cases, 104 did not meet the criteria and were considered to be the 'control group' and 36 participants were deemed to have a co-morbid psychiatric diagnosis that may have resulted in fatigue and were not included in any further analysis in this report.

4.1. *Characteristics of cases versus controls*

4.1.1. *Treatment and demographic variables (Table 2)*

There was no statistical difference in age (controls 57.45 years [SD 12.77], cases 59.17 years [SD 11.52]; $p = 0.94$) or time since treatment (controls 9.99 months [SD 5.92], cases 9.80 months [SD 5.52]; $p = 0.41$). There was also no statistically significant difference in type of surgery, adjuvant treatment regimen or lymph node status between the groups.

4.1.2. *Haematological, biochemical and endocrine indices (Table 3)*

There were significant between-group differences in a number of these investigations. The most notable were the significant differences in total white cell count (controls 5.86 counts $\times 10^9$ [SD 1.6], cases 6.64 $\times 10^9$ [SD 1.91]; $p = 0.021$), sodium (controls 139.97 mmol/L [SD 2.29], cases 139.15 mmol/L [SD 2.41]; $p = 0.018$) and CRP (controls 2.74 mg/dL [SD 3.55], cases 3.91 mg/dL [SD 4.24]; $p = 0.015$). There were also significant differences in some of the liver function tests. No difference was found in thyroid function tests or 24 h urinary free cortisol.

4.1.3. *Questionnaire data (Table 4)*

There were significant differences on all fatigue scales with cases scoring significantly higher than controls. Cases of CRF scored significantly higher on the FCS and on the WAS indicating greater catastrophising about fatigue and a greater impact of fatigue on work and social adjustment. Cases also scored higher on the anxiety and depression subscales of the HADS – indicating greater sub-threshold mood disturbances. There were significant differences on a number of the quality of life domains in both the EORTC QLQ 30 and BR 23. The most important exception to this was a lack of significant difference in cognitive functioning scores on the QLQ 30.

4.1.4. *Actigraphic data (Table 5)*

There were only a few significant differences in actigraphic data between the groups. There was no difference in mean

Table 5 – Between-group actigraphic data differences

Variable	Mean controls	SD	Mean CRFS	SD	*p*-Value
Down activity measurement					
Down activity mean	39.75	26.712	42.33	26.712	0.219
Down activity median	21.48	30.219	23.93	26.159	0.077
Down activity SD	47.01	14.879	50.21	14.948	0.351
Down wake minutes	55.85	49.590	70.89	50.014	0.047*
Down sleep minutes	318.76	107.165	293.07	95.112	0.177
Down % sleep	75.03	17.457	72.40	15.893	0.167
Down sleep efficiency	92.88	5.860	90.05	8.545	0.056
Down sleep latency	26.66	23.216	63.60	36.01	0.052
Up activity measurement					
Up activity mean	174.33	40.214	179.02	38.134	0.521
Up activity median	186.45	51.594	194.63	51.962	0.278
Up activity SD	83.79	13.497	83.51	11.365	0.889
Up wake minutes	637.04	245.729	614.88	211.213	0.800
Up sleep minutes	71.57	111.7	62.23	92.393	0.769
Up % sleep	13.01	11.010	12.48	11.912	0.564
Up activity index	93.35	7.158	93.39	10.01	0.533
Up wake episodes	7.12	8.627	6.14	4.535	0.873
0–0 activity measurement					
0–0 activity mean	35.17	32.10	177.92	1085.293	0.165
0–0 activity median	2.74	9.81	3.47	5.30	0.063
0–0 activity SD	26.06	12.574	27.77	9.021	0.072
0–0 wake minutes	31.35	73.218	35.43	33.714	0.061
0–0 sleep minutes	314.21	108.356	287.67	96.057	0.179
0–0 % sleep	80.53	17.929	79.07	18.445	0.230
0–0 sleep efficiency	92.92	5.877	89.64	9.739	0.051
0–0 wake after sleep	28.62	24.981	40.15	37.582	0.086
0–0 mean wake episodes	4.13	4.321	4.85	0.89	0.009*
0–0 longest Wake episode	11.24	14.272	15.26	12.429	0.013*

* $p < 0.05$.

down time (rest) activity, mean up (awake) activity or 24 h mean activity. There were some statistically significant differences in the sleep period intervals reflecting the quality and nature of actual sleep as opposed to time spent in bed trying to sleep. There were significant differences in mean wake episodes and median longest wake episode occurring during the true sleep period.

5. Discussion

This study provides further evidence to support the usefulness of Cella and colleagues' diagnostic criteria for CRF in a population of breast cancer survivors. There was, however, only one interviewer (SA) and so our study cannot examine any inter-interviewer reliability of the diagnostic criteria. Using a strict application of these criteria, we established the prevalence of CRF syndrome in our sample to be 30%. This figure is in keeping with the data from the only two previous studies to use the diagnostic criteria in breast cancer patients. Andrykowski and colleagues reported a post-treatment prevalence of 26%[10] and White and colleagues a prevalence of 19% in their smaller sample.[9] The figure from our study is higher despite excluding participants with a potentially fatiguing psychiatric co-diagnosis. The women who were studied in our investigation had completed adjuvant therapy up to 2 years previously, and may have experienced longer term treatment toxicities than have been previously described.

While our figure is higher than those of the other two studies to have used the diagnostic criteria, it is more conservative than many prevalence figures reported in the literature.[32,33] Some studies have simply reported prevalence figures for fatigue based on the number of women reporting at least some degree of the symptom.[34,35] Since fatigue is a common symptom in the general (non-cancer) population, this approach is likely to over-estimate the prevalence of clinically significant fatigue. The validity of the diagnostic criteria is supported by the large and significant differences that we found in virtually all the quality of life domains. Women identified as 'cases' of CRFS reported lower levels of functioning and higher levels of symptom severity. The most notable exception to this was on the cognitive function subscale of the EORTC QLQ 30. This is despite a large effect size, and may be because of the limitations of the EORTC cognitive subscale to fully assess cognitive function.[36]

The HADS data demonstrated a higher level of anxiety and depression in the cases, but not at a level required to meet the cut-off for a psychiatric diagnosis. The significance of these results is unclear – while CRF and depression may overlap, they are two separate phenomena in this population.[37,38] It has been demonstrated previously that CRF is associated with greater psychological distress in women treated for breast cancer.[37] It is possible that this distress may manifest itself as a lower symptom threshold in the cases of CRF. In keeping with previous work, we found that women who tended to

'catastrophise' more about their fatigue had a poorer quality of life.[24,34]

We found no evidence to support our hypothesis that women who were cases of CRFS would be less active than controls. Most studies seem to suggest that exercise is beneficial in terms of improving physical performance,[39,40] but there is much less evidence to suggest that exercise actually improves the symptom of subjective fatigue.[39] Three[41–43] previous small studies have all found no correlation between fatigue severity in cancer patients and objective measures of activity. Our current study is by far the largest to have objectively investigated whether patients who complain of subjective fatigue are actually less active than non-fatigued subjects. Our results suggest that physical deconditioning is not the explanation for fatigue in breast cancer survivors. Furthermore, they suggest that any beneficial effects of exercise in reducing subjective fatigue in this group are likely to be 'indirect' (e.g. secondary to the beneficial effects of exercise on mood, immune functioning or sleep).

We found some evidence that women who were cases of CRF syndrome reported more insomnia than controls and this was supported (to some extent) by the objective actigraphic data. Previous actigraphic studies have also reported a correlation between sleep disturbance and fatigue in cancer patients.[41–43] In our study the observed sleep disturbances were relatively mild and cannot explain all the associated CRF symptoms. Savard and colleagues[44] have reported that while cognitive-behavioural therapy is an effective treatment for insomnia in breast cancer patients it does not significantly improve fatigue. The relationship between sleep and fatigue therefore requires further characterisation.

Most of the laboratory variables that we assessed were not significantly different between cases or controls. In particular, the haemoglobin and thyroid function tests (both significant potential causes of fatigue[45,46]) were not significantly different between the cases and the controls. It is important to note that approximately 10% of the participants were anaemic (Hb < 12 g/l) – although none had haemoglobin less than 10 g/l. The total white cell count and CRP were significantly higher in the cases of CRF (although mean levels still fell within the normal range). These results hint at a prolonged immune/inflammatory response in women with persistent fatigue. A previous systematic review has found evidence of raised IL-1, IL-6 and neopterin in fatigued cancer patients.[47] Unfortunately, the resources of this project did not allow a more sophisticated assessment of inflammatory or immune mediators, but this should be the focus of future studies in this area. The clinical significance of the recorded differences in electrolyte and liver function tests remains unclear. These could be attributable to disturbances post chemotherapy, alterations related to drugs (including alcohol intake) or linked to the pathophysiology of fatigue.

Alterations in HPA axis functioning have been identified in a number of studies in patients with CFS.[48] Bower et al.[49] demonstrated a flattening of the diurnal cortisol rhythm, but no gross disruption of the HPA axis, in 13 fatigued women after completion of breast cancer treatment. Bower measured salivary cortisol at three time points over a 48-h period. The different methods make direct comparison difficult. However, our finding that urinary free cortisol was no different between cases and controls is a useful negative and suggests that there is no gross peripheral disruption to the HPA axis in fatigued cancer survivors. However, urinary cortisol estimation is only a measure of basal secretion rates. A fuller assessment of the HPA axis would require the use of stimulation tests which were beyond the resources of the current study.

Our study evaluated a large number of different variables, and caution is required in not allocating too much significance to any given finding. As this was an exploratory study we did not make any adjustment for multiple comparisons in our statistical analysis and our results must be interpreted with this caveat. Our study lacked an age-matched non-cancer control group. This is important as fatigue has a baseline prevalence in the population which increases with age.[21] However, the prevalence of CRF was still significantly higher in this population even after adjusting for a baseline population level.[4] It is worth noting that participants in our study were actually more fatigued than non-participants. Consequently, it is possible that our study has somewhat over-estimated the prevalence of CRFS. This is perhaps surprising as it has often been assumed that women who are more fatigued will be less likely to participate in research. As far as we are aware this is the first study to have assessed the fatigue scores of non-participants.

In conclusion, this study represents a detailed assessment of the prevalence of CRF in breast cancer survivors (without psychiatric co-morbidity). We found that 30% of women were severely affected by fatigue and that this was associated with a significantly worse quality of life, lower self-reported functional abilities and higher symptom severity. We found no evidence to support the hypothesis that CRF syndrome is related to physical deconditioning. We found subtle disturbances in immune and inflammatory markers, overall quality of life, mood and sleep quality in women with CRF syndrome. Future work should focus on further examination of the immune/inflammatory response and HPA axis to identify specific causes of CRF that can be targeted for treatment in clinical practice. The potential overlap of this group with the CFS population may also provide directions for future research and management.

Conflict of interest statement

None declared.

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REFERENCES

1. Roscoe JA, Morrow GR, Hickok JT, et al. Temporal interrelationships among fatigue, circadian rhythm and

depression in breast cancer patients undergoing chemotherapy treatment. *Support Care Cancer* 2002;**10**:329–36.
2. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in long-term breast carcinoma survivors. *Cancer* 2006;**106**:751–8.
3. Prue G, Rankin J, Allen J, et al. Cancer-related fatigue: a critical appraisal. *Eur J Cancer* 2006;**42**:846–63.
4. Minton O, Stone P. How common is fatigue in disease-free breast cancer survivors? A systematic review of the literature. *Breast Cancer Res Treat* 2007. doi:10.1007/s10549-007-9831-1.
5. Cella D, Davis K, Breitbart W, et al. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol* 2001;**19**:3385–91.
6. Fukuda K, Straus S, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Int Med* 1994;**121**:953–9.
7. Servaes P, Prins J, Verhagen S, et al. Fatigue after breast cancer and in chronic fatigue syndrome: similarities and differences. *J Psychosom Res* 2002;**52**:453–9.
8. Cella D, Peterman A, Passik S, et al. Progress toward guidelines for the management of fatigue. *Oncology (Huntington)* 1998;**12**:369–77.
9. Young KE, White CA. The prevalence and moderators of fatigue in people who have been successfully treated for cancer. *J Psychosom Res* 2006;**60**:29–38.
10. Andrykowski MA, Schmidt JE, Salsman JM, et al. Use of a case definition approach to identify cancer-related fatigue in women undergoing adjuvant therapy for breast cancer. *J Clin Oncol* 2005;**23**:6613–22.
11. Andrews P, Morrow G, Hickok J, et al. Mechanisms and models of fatigue associated with cancer and its treatment: evidence of pre-clinical and clinical studies. In: Armes J, Krishnasamy M, Higginson I, editors. *Fatigue in cancer*. Oxford: OUP; 2004. p. 51–87.
12. Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. *Semin Oncol* 1998;**25**:43–6.
13. Minton O, Stone P, Richardson A, et al. Drug therapy for the management of cancer related fatigue. *Cochrane Database Syst Rev* 2008 [Art. No. CD006704]. doi:10.1002/14651858.
14. Wessely S, Hotopf M, Sharpe M. Physical mechanisms of fatigue; fatigue and inactivity. In: Wessely S, Hotopf M, Sharpe M, editors. *Chronic fatigue and its syndromes*. Oxford: OUP; 1998. p. 55–8.
15. Winningham M. Fatigue. In: Groenwald S, Hansen-Frogge M, Goodman M, et al., editors. *Cancer symptom management*. Massachusetts: Jones and Bartlett Publishers; 1996. p. 42–58.
16. Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. *Endocr Rev* 2003;**24**:236–52.
17. Cleare AJ, Blair D, Chambers S, et al. Urinary free cortisol in chronic fatigue syndrome. *Am J Psychiat* 2001;**158**:641–3.
18. Fernades R, Stone P, Andrews P, et al. Comparison between fatigue, sleep disturbance, and circadian rhythm in cancer inpatients and healthy volunteers: evaluation of diagnostic criteria for cancer-related fatigue. *J Pain Symptom Manage* 2006;**32**:245–54.
19. Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the functional assessment of cancer therapy (FACT) measurement system. *J Pain Symptom Manage* 1997;**13**:63–74.
20. Minton O, Stone P, Richardson A, et al. Drug therapy for the management of cancer related fatigue. Cochrane Database Syst Rev 2008;(1) [CD006704.pub2]. doi:10.1002/14651858.
21. David A, Pelosi A, McDonald A, et al. Tired, weak, or in need of rest: fatigue among general practice attenders. *Brit Med J* 1990;**301**:1199–202.
22. Stone P, Richards M, A'Hern R, et al. Fatigue in patients with cancers of the breast or prostate undergoing radical radiotherapy. *J Pain Symptom Manage* 2001;**22**:1007–15.
23. Loge JH, Abrahamsen AF, Ekeberg O, et al. Hodgkin's disease survivors more fatigued than the general population. *J Clin Oncol* 1999;**17**:253–61.
24. Jacobsen PB, Andrykowski MA, Thors CL. Relationship of catastrophizing to fatigue among women receiving treatment for breast cancer. *J Consult Clin Psychol* 2004;**72**:355–61.
25. Mundt JC, Marks IM, Shear MK, et al. The work and social adjustment scale: a simple measure of impairment in functioning. *Brit J Psychiat* 2002;**180**:461–4.
26. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiat Scand* 1983;**67**:361–70.
27. Stone P, Hardy J, Broadley K, et al. Fatigue in advanced cancer: a prospective controlled cross-sectional study. *Brit J Cancer* 1999;**79**:1479–86.
28. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;**85**:365–76.
29. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol* 1996;**14**:2756–68.
30. Sadler IJ, Jacobsen PB, Booth-Jones M, et al. Preliminary evaluation of a clinical syndrome approach to assessing cancer-related fatigue. *J Pain Symptom Manage* 2002;**23**:406–16.
31. Lawrie S, Manders D, Geddes J, et al. A population-based incidence study of chronic fatigue. *Psychol Med* 1997;**27**:343–53.
32. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in breast cancer survivors: occurrence correlates and impact on quality of life. *J Clin Oncol* 2000;**18**:743–53.
33. Servaes P, Gielissen M, Verhagen S, et al. The course of severe fatigue in disease-free breast cancer patients: a longitudinal study. *Psycho-Oncol* 2007;**16**:787–95.
34. Broeckel JA, Jacobsen PB, Horton J, et al. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 1998;**16**:1689–96.
35. Nieboer P, Buijs C, Rodenhuis S, et al. *J Clin Oncol* 2005;**23**:8296–304.
36. McLachlan SA, Devins GM, Goodwin PJ. Validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) as a measure of psychosocial function in breast cancer patients. *Eur J Cancer* 1998;**34**:510–7.
37. Bennett B, Goldstein D, Lloyd A, et al. Fatigue and psychological distress – exploring the relationship in women treated for breast cancer. *Eur J Cancer* 2004;**40**:1689–95.
38. Goldstein D, Bennett B, Friedlander M, Davenport T, Hickie I, Lloyd A. Fatigue states after cancer treatment occur both in association with, and independent of, mood disorder: a longitudinal study. *BMC Cancer* 2006;**6** <http://www.biomedcentral.com/1471-2407/6/240>.
39. Campbell A, Mutrie N, White F, et al. A pilot study of a supervised group exercise programme as a rehabilitation treatment for women with breast cancer receiving adjuvant treatment. *Eur J Oncol Nurs* 2005;**9**:56–63.
40. Dimeo F, Rumberger B, Keul J. Aerobic exercise as therapy for cancer fatigue. *Med Sci Sports Exerc* 1998;**30**:475–8.
41. Berger AM, Farr LA, Kuhn BR, et al. Values of sleep/wake, activity/rest, circadian rhythms, and fatigue prior to adjuvant breast cancer chemotherapy. *J Pain Symptom Manage* 2007;**33**:398–409.
42. Fernades R, Stone P, Andrews P, et al. Comparison between fatigue, sleep disturbance, and circadian rhythm in cancer inpatients and healthy volunteers: evaluation of diagnostic

criteria for cancer-related fatigue. *J Pain Symptom Manage* 2006;**32**:245–54.
43. Ancoli-Israel S, Liu L, Marler MR, et al. Fatigue, sleep, and circadian rhythms prior to chemotherapy for breast cancer. *Support Care Cancer* 2006;**14**:201–9.
44. Savard J, Simard S, Ivers H, et al. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part I: sleep and psychological effects. *J Clin Oncol* 2005;**23**:6083–96.
45. Jacobsen PB, Garland LL, Booth-Jones M, et al. Relationship of hemoglobin levels to fatigue and cognitive functioning among cancer patients receiving chemotherapy. *J Pain Symptom Manage* 2004;**28**:7–18.
46. Kumar N, Allen KA, Riccardi D, et al. Fatigue, weight gain, lethargy and amenorrhea in breast cancer patients on chemotherapy: is subclinical hypothyroidism the culprit? *Breast Cancer Res Treat* 2004;**83**:149–59.
47. Schubert C, Hong S, Natarajan L, et al. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun* 2007;**21**:413–27.
48. Cleare AJ. The HPA axis and the genesis of chronic fatigue syndrome. *Trends Endocrinol Metab* 2004;**15**:55–9.
49. Bower JE, Ganz PA, Dickerson SS, et al. Diurnal cortisol rhythm and fatigue in breast cancer survivors. *Psychoneuroendocrinology* 2005;**30**:92–100.