Title: FATIGUE IN GYNAECOLOGICAL CANCER PATIENTS DURING AND AFTER ANTI-CANCER TREATMENT

Article Type: Original Article

Keywords: fatigue; neoplasm; gynaecological; symptoms; adult

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01 October 2008

Dear Editor in Chief,

Re: FATIGUE IN GYNAECOLOGICAL CANCER PATIENTS DURING AND AFTER ANTI-CANCER TREATMENT

Following your recommendation we have merged the original submissions to you journal and have now submitted the manuscript on the above topic via the online submission system for your consideration.

All authors have read and approved both manuscripts. I would be most grateful if you could copy all correspondence to my co-authors: Dr Fiona Cramp; fiona.cramp@uwe.ac.uk and Dr Jacqueline Gracey; jh.gracey@ulster.ac.uk as I am currently on maternity leave and may not be able to access my emails on a regular basis.

I hope that you will consider the enclosed manuscript for publication in the Journal of Pain and Symptom Management and look forward to receiving your response.

Yours Sincerely

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FATIGUE IN GYNAECOLOGICAL CANCER PATIENTS DURING AND AFTER ANTI-CANCER TREATMENT

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Abstract

This longitudinal survey aimed to analyse the fatigue experienced over 12 months by a gynaecological cancer population, to determine if the fatigue was more severe than that reported by females without cancer and to identify variables associated with cancer related fatigue (CRF). Data was collected over a 12 month period before, during and after anti-cancer treatment. Fatigue was assessed using the Multidimensional Fatigue Symptom Inventory-Short Form. Participants with cancer also completed the Rotterdam Symptom Checklist (RSCL). Sixty-five cancer patients (mean age = 57.4, SD 13.9) and 60 control subjects (mean age 55.4, SD 13.6) participated. Descriptive analysis indicated that the pattern of CRF differed depending on cancer treatment received. Regarding fatigue severity, the cancer participants reported worse fatigue than the non-cancer individuals. The pattern of fatigue over time also appeared to vary between the two groups. Repeated Measurements Modeling (RMM) confirmed that females with cancer had significantly greater fatigue than females with no cancer history at all time points (p < 0.001) and that the level of fatigue changed with time (p = 0.02). Individuals with gynaecological cancer experienced significantly worse fatigue than non-cancer females during and after treatment, and fatigue persisted long after treatment was complete. A forward stepwise regression demonstrated that psychological distress level was the only independent predictor of CRF during anti-cancer treatment (p < 0.00), explaining 44% of the variance in fatigue. After treatment, both psychological distress level (p < 0.00) and physical symptom distress (p = 0.03) were independent predictors of fatigue, accounting for 81% of the variance. Psychological distress level is an important indicator of CRF in
gynaecological cancer. Interventions focused on the reduction of psychological distress may help alleviate CRF.

**Keywords:** fatigue; neoplasm; gynaecological; symptoms; adult.

**Running title:** Fatigue in gynaecological cancer
**Introduction**

Cancer-related fatigue (CRF) is an almost universal symptom in patients receiving anti-cancer therapy (1). CRF can have a phenomenal impact on a patient’s life (2) and can hinder the chance of remission or even cure, owing to the direct influence it can have on the individuals desire to continue with treatment (3). Research has indicated that individuals with gynaecological cancer experience more severe fatigue than those with other cancer diagnoses (4). In a UK multi-centre survey of 576 cancer patients with varying diagnoses, half of which were currently receiving anti-cancer treatment, over 50% reported fatigue as their biggest problem. It was concluded that fatigue had a much greater effect on individuals with cancer than any other physical or mental consequence of the disease or its treatment (5). Furthermore, a pilot study indicated that fatigue is a significant problem for females with gynaecological cancer at various stages of their disease and treatment process (6). It was therefore deemed appropriate and necessary to further examine fatigue in gynaecological cancer.

A number of methodological limitations have been highlighted in the research to date (7-9). Three main problems have been emphasized, firstly, there is a degree of uncertainty surrounding the best approach for CRF assessment, thus a variety of self-report measures exist. Many of these measures are single item, which are therefore inadequate to measure fatigue, a multidimensional construct. The most appropriate and valid approach would be to use a multidimensional measure (8). Secondly, a number of investigations are cross-sectional in design which has restricted the conclusions that can be drawn with regard to fatigue as an ongoing symptom. A more methodologically sound approach is to
undertake a longitudinal survey, to enable fatigue to be charted accurately over time. Fatigue is also a common complaint among the general population which must be taken into consideration when reporting the prevalence of symptoms among cancer patients (9).

The most effective approach for the management of a symptom such as fatigue is to identify and treat the source of the symptom (10). It has been suggested that CRF is linked with tumour and/or treatment related variables. In a baseline assessment before anti-cancer therapy lung cancer produced significantly higher fatigue prevalence than breast or prostate cancer (11). In a chemotherapy study of breast and ovarian cancer patients, those with a diagnosis of ovarian cancer experienced worse fatigue (4). It is plausible that fatigue severity increases with advancing stage of the disease (10), however CRF has also been shown to be unrelated to disease stage (12). Fatigue is frequently reported as a common side effect of most chemotherapy regimes; nevertheless there have been some conflicting findings in this area (13). It has been reported that patients receiving radiotherapy complain of fatigue which may be influenced by factors that are unique to radiotherapy such as radiation dose, target field and radiation quality (14). However, fatigue has also been shown to be unrelated to radiotherapy (15).

Many authors have postulated anemia as a cause of CRF (3,10,16-18) either related to the disease itself or due to the anti-neoplastic therapy. Once more however a disagreement exists in the literature (19).
As a result of an interaction between the tumour and the host’s defense system (18) cytokines are released in greater amounts in cancer patients. It has previously been suggested that cytokines such as TNF can alter central serotonin levels and hence the perception of fatigue (3). This serotonin dysregulation may help explain the development of CRF although the issue of cytokine release contributing to CRF remains controversial (10).

Psychosocial factors may have a role to play in the development of CRF. CRF has been associated with mood disturbance (20), anxiety, depression and difficulty sleeping (17). Furthermore, it has been reported that personality type and stress can also lead to a greater perception of fatigue severity (16). In contrast it has been reported that an increase in the level of fatigue does not relate to a concurrent increase in anxiety and depression or sleep quality (21).

The conflict and controversies present in the literature have left the etiology of CRF unclear. It is important to understand the factors associated with CRF as without this understanding, the prevention and management of the condition becomes very complex.

Aims

The study aimed to analyse prospectively the onset and pattern of fatigue, if any, experienced over a 12 month period by a gynaecological cancer population, and determine if the fatigue experienced was more severe than the fatigue experienced by matched non-cancer volunteers. The study also aimed to explore the variables associated
with CRF during and after anti-cancer treatment and identify those associated with more severe fatigue in gynaecological cancer.
Methods

Ethical approval was obtained from the Central Office of Research Ethics Committees (COREC) (January 2005).

Participants

Information was obtained from gynaecological cancer patients from the Belfast City Hospital, Southampton General Hospital and United Bristol Healthcare Trust. Data for comparison purposes was collected from a group of age matched females, with no history of cancer. Participants in the non-cancer group were recruited via a peer nomination process (22,23). When the cancer subject could not nominate a suitable match a control was assigned to them from a list of eligible volunteers created before the commencement of the survey.

Inclusion/exclusion criteria

Included cancer subjects were newly diagnosed with gynaecological cancer having received no treatment, except surgery, for their disease to date, with no previous diagnosis of cancer. They had to be fully informed of their diagnosis, be 18 years or older, be English speaking and have provided informed consent. Individuals attending a clinical psychologist or psychiatrist, with cognitive impairment or incompetence, with a chronic disease in which fatigue was a prominent symptom or those with a serious underlying medical condition were excluded.

Included non-cancer females were 18 years or older and within 5 years of their matched cancer subject. They had to be English speaking and have provided fully informed
written consent. The exclusion criteria were as for the cancer participants; in addition the cancer participant’s primary carer was excluded.

Procedure

Cancer participants

Data was collected at predetermined intervals over a twelve-month period. This commenced following surgery, prior to anti-cancer treatment. At baseline participants were asked to complete a demographic questionnaire. Data on fatigue was obtained using the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). The cancer participants were invited to complete the MFSI-SF weekly during their anti-cancer treatment for a maximum of twelve weeks. Once a participant had completed treatment or reached the twelve-week cut off point, they moved on to monthly completion of the MFSI-SF thus reducing patient questionnaire burden. The Rotterdam Symptom Checklist (RSCL) was completed by the cancer participants on a monthly basis for the twelve months.

Non-cancer volunteers

The non-cancer comparison group was required to complete the initial demographic questionnaire and the MFSI-SF. The fatigue questionnaire was completed on a monthly basis for the twelve-month duration.

Any individual that did not wish to participate or withdrew was invited to score their fatigue verbally on a Numerical Rating Scale (1 – 10) (NRS-F) as a one off record.
Outcome Measures

Demographics

Information on age, marital status, number of dependents, employment status and normal activity levels was obtained. Relevant medical data was acquired from participant medical records.

MFSI-SF

The 30 item MFSI-SF has five subscales: general (GF), physical (PF), emotional (EF) and mental fatigue (MF) and vigor (V). The respondent indicates the extent to which they have experienced each symptom during the preceding week (0 = not at all; 4 = extremely) (24). Ratings are summed to obtain scores for each of the subscales detailed previously. In addition, a total fatigue (TF) score can be generated by summing the four fatigue subscales and subtracting the vigor subscale (24).

RSCL

This is a well established (25), cancer-specific tool designed to assess physical and psychological distress over the past week, on a 30 item, four point Likert scale (26). It appears to be a feasible measure of quality of life (27). This provided a more comprehensive picture of each participant’s cancer experience and helped to monitor activity levels through the generation of an activity level score.
**Statistical analysis**

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) Version 11 for Windows.

**Sample size**

A previous study provided MFSI-SF scores for cancer participants and non-cancer controls (28). Based on the difference of scores on the general fatigue subscale between these two groups a power calculation was conducted and it was determined that for 90% power a sample of 114 was necessary. It was planned to recruit a sample of 125 to allow for attrition.

After 12 months of recruitment at three cancer centres 65 individuals with a diagnosis of gynaecological cancer had consented to participate. At this stage, having sought statistical advice there were logical reasons to look at the data (slow accrual and limited resources for extended data collection) (29). It was therefore decided to conduct an interim analysis to determine whether stopping recruitment at this stage could be justified. At the interim analysis stage, due to the issue of multiplicity, normal statistical approaches could not be used. However, analysis procedures are available to permit repeated statistical analysis to be performed on accumulating data. This involved the adjustment of the alpha level. This type of analysis allowed the stopping of recruitment if the information was sufficient to conclude (30). The value of the alpha was determined according to the total number of analyses planned (30). For this investigation, the one
interim analysis created two planned analyses. The O’Brien-Fleming method of using an alpha of 0.005 at the interim analyses and 0.048 at the final analysis stage was used (31). This is favourable as it uses a low p value at the interim analysis stage, thus the stopping criteria is quite conservative, and preserves almost the entire intended alpha for the final analysis stage (29).

Interim analysis

A summary statistic was calculated for each cancer participant to indicate the change in PF from baseline to four weeks and baseline to twelve weeks post initiation of anti-cancer treatment. This was calculated from the repeated weekly administration of the MFSI-SF. A one sample t-test was conducted to determine if recruitment could be stopped.

Final analyses

A univariate analysis (t-test) was used to compare the difference in fatigue scores as measured by the NRS-F in those who agreed to participate and those who did not, to detect the presence of selection bias. A similar analysis was carried out for those who dropped out and those who did not.

Repeated Measurements Modelling (RMM) was conducted to examine the change in fatigue with time and to determine whether or not those with gynaecological cancer had more severe fatigue than females with no history of cancer. RMM computes estimated marginal means (EMM) of the dependent variable. It is important to note that these show the effect being studied without the error, not the actual observed means (32). Time and
group, which is cancer and non-cancer, were entered as factors. If time was not significant as a factor, it was entered as a covariate. The RMM was chosen as it can be used to describe the temporal changes of a dependent variable in a dataset with missing data and it is capable of treating time as a categorical variable or a continuous variable (33).

A forward stepwise regression with baseline Total Fatigue (TF) as measured by the MFSI-SF as the dependent variable was also conducted. Initially, a univariate analysis was undertaken to identify the individual predictors of the dependent variable. Independent variables included were tumour-related, treatment-related and demographic. Those that were identified as significant were entered into a forward stepwise regression with baseline TF as the dependent variable. Independent variables were entered and removed until the independent variables that remained in the model were all significant in the presence of each other.

This analysis was repeated two times with month 2 TF (during treatment) and month 12 TF (end of follow up) as the dependent variables.
Results

Gynaecological cancer participants

Over the course of 12 months 92 individuals were identified as being eligible to participate. Twenty seven of the 92 declined involvement. There was no significant difference in NRS-F scores for participants (Mean = 4.13, SD 2.49) and non-participants (Mean = 3.44, SD 3.65; t = 0.886, p = 0.38).

The demographic characteristics of the 65 participants are summarized in Table 1. The mean age of the cancer group was 57.4 years (SD 13.9), ranging from 23 – 86 years. The majority of participants were married (n = 35, 54%), not working (n = 57, 88%) with 28 (49%) citing their cancer as their reason for not working, the majority of respondents had a low activity level (n = 46, 71%).

Medical oncology data are summarized in Table 2. The most common malignancy was ovarian cancer (n = 35, 54%), with most tumours being stage 1 (n = 27, 42%). The sample was heterogeneous regarding antineoplastic treatment received. There was no significant difference in fatigue between those who had undergone surgery prior to baseline (Mean = 7.00, SD 15.81) and those who had not (Mean = 9.57, SD 19.97; t = -0.394, p = 0.70).
Non-cancer participants

Over the twelve months, sixty females with no history of cancer were recruited. Demographic characteristics are summarized in Table 1. The mean age of this cohort was 55.4 (SD 13.6), ranging from 24 – 86. The majority were married (n = 39, 65%), currently working (n = 38, 63%), and had a subjectively low activity level (n = 34, 57%). There was no significant difference in age (p = 0.43) or marital status (p = 0.26) of those who had cancer and those who did not (p = 0.43).

Completion rates

Of the 65 individuals with gynaecological cancer that agreed to participate, 15 withdrew over the course of the twelve months. The most common reasons given were that they no longer wished to participate as they had finished treatment (n = 5), and disease progression (n = 7). A further 25 failed to complete the final 12 month questionnaire. Of this 25, eight had died, six had disease progression and two had been admitted to hospital. Consequently only 25 individuals completed the final questionnaire. A comparison of the final NRS-F for those who completed the study, and the last available NRS-F for those who dropped out indicated that there was no significant difference in NRS-F scores between those who completed (Mean = 4.57, SD 2.12) and those who did not (Mean = 5.64, SD 2.41; t = -1.82, p = 0.07). Forty two of the sixty healthy volunteers completed the study.
Summary Statistics for Cancer Participants

Interim analysis

There was a statistically significant change in PF from baseline to four weeks (p = 0.001) and twelve weeks (p = 0.004). As these p values are less than 0.005, it was justified to stop recruitment.

Final Analysis

At the end of the study, the summary statistics were repeated. As a result of the interim analysis, for the change to be significant, the p value had to be less than or equal to 0.048 (31). There was a statistically significant increase in PF scores from baseline (mean = 2.18, SD 2.98) to the mean of four weeks (mean = 4.62, SD 4.34; t = -5.03, p < 0.001). For those who received at least twelve weeks of anti-cancer treatment (n = 35) there was a statistically significant increase in PF scores from baseline (mean = 2.37, SD 2.95) to the mean of the first twelve weeks of treatment (mean = 5.32, SD 3.86; t = -5.18, p < 0.001).

Fatigue

Cancer participants

The mean scores for the cancer participants for each subscale of the MFSI-SF at each separate time-point are presented in Table 3 for weekly questionnaire completion and Table 4 for monthly questionnaire completion. A wide range of TF scores can be seen at each time-point.
The change in fatigue over time is summarised in Figures 1a – 1f. The level of GF and PF peaked during treatment and returned to approximately baseline level by the twelve month endpoint. The level of EF declined with time, and V improved with time. The level of MF remained relatively stable. Similar to GF and PF, TF peaked during treatment and gradually declined after anti-cancer treatment. The first and last TF measurements were similar. As a heterogeneous sample with regards to tumour site and anti-cancer treatment was recruited, it was possible to compare descriptively the impact of tumour site and treatment received on the pattern of fatigue during and after therapy. As can be noted from Figures 2a – 2c, during chemotherapy, a peak in TF was apparent at the time of infusion. However, during radiotherapy, there was a gradual increase in the level of CRF with time. After treatment, in both chemotherapy and radiotherapy, a drop in the level of TF was noted. The pattern of fatigue over time for ovarian and endometrial tumours is reflective of the patterns noted during chemotherapy and radiotherapy respectively. As with chemotherapy, those with a diagnosis of ovarian cancer peak TF was higher than the peak in TF of those with endometrial cancer. (Figure 3)

Non-cancer participants

The mean scores for the non-cancer participants for each subscale of the MFSI-SF at each separate time-point are presented in Table 5. The scores for the non-cancer participants were much lower than those reported by the individuals with gynaecological cancer, indicating the females with gynaecological cancer suffered a higher level of fatigue. Over the course of the twelve months, the mean subscale scores for the non-cancer respondents
remained relatively stable. The mean TF score fluctuated around zero. A negative score was frequently reported, indicating that those with no history of cancer were not suffering from fatigue.

*Repeated Measurements Modelling (RMM)*

The RMM addressed three questions: did the cancer patients have more severe fatigue than the non-cancer volunteers; how did the profile of fatigue change with time and was there a group by timepoint interaction?

There was a significant difference in GF, PF, EF, MF, V and TF scores between those who had cancer and those who did not, those with cancer had significantly higher fatigue (p < 0.00). The profile or change in fatigue with time differed for different subscales; for GF (p = 0.038) and PF (p < 0.00) time was significant as a factor, which indicated that there were peaks and/or troughs in fatigue with time. Time was significant as a covariate for EF and TF (p = 0.03; p = 0.02 respectively) which was indicative of a linear downward trend, i.e. an improvement in fatigue levels with time. The level of both MF and V remained constant at all timepoints as time was not significant as a factor or a covariate. For PF a group by time-point interaction was noted. The presence of a group by time-point interaction indicated that at any given time-point, the two groups (that is cancer and non-cancer) were behaving differently.
**Associated Variables**

**Before anti-cancer treatment (Baseline TF)**

The independent variables included in the univariate analysis were: diagnosis, tumour stage, receiving surgery, marital status, age, and indications of baseline psychological distress level, baseline physical symptom distress level, baseline overall valuation of life and baseline activity level as measured by the RSCL. Significant variables were subsequently included in a forward stepwise regression with baseline TF as the dependent variable. These were baseline psychological distress level ($t = 7.83, p < 0.00$), baseline overall valuation of life ($t = 6.62, p < 0.00$), baseline physical symptom distress level ($t = 8.15, p < 0.00$), and baseline activity level ($t = 2.21, p = 0.03$).

The first two variables entered concurrently were baseline psychological distress level and baseline physical symptom distress level. Both independent variables remained significant in the model when entered together (baseline psychological distress level ($t = 4.50, p < 0.00$), baseline physical symptom distress level ($t = 4.87, p < 0.00$)). As a result of this, baseline overall valuation of life was added to the model. All three remained significant in the presence of each other (baseline psychological distress level ($t = 4.68, p < 0.00$), baseline physical symptom distress level ($t = 2.81, p = 0.01$), baseline overall valuation of life ($t = 3.32, p < 0.00$)). Baseline activity level was subsequently entered into the model with the other independent variables. However in the presence of baseline psychological distress level, baseline physical symptom distress level and baseline overall valuation of life, baseline activity level was no longer significant ($t = -1.09, p = 0.28$). Therefore it was concluded that baseline psychological distress level, baseline
physical symptom distress level and baseline overall valuation of life were the three independent predictors of baseline TF, explaining 68% (adjusted r square) of the variance.

*During anti-cancer treatment (Month 2 TF)*

The independent variables considered in the univariate analysis were: Baseline TF, treatment combination, diagnosis, tumour stage, receiving surgery, whether or not the participant had chemotherapy, chemotherapy regime, whether or not the participant had radiotherapy, radiotherapy dose, the demographic characteristics of marital status and age, and indications of month 2 psychological distress level, month 2 physical symptom distress level, month 2 overall valuation of life and month 2 activity level as measured by the RSCL. The variables that were significant and thus included in the forward stepwise regression were baseline fatigue ($t = 3.78, p < 0.00$), month 2 psychological distress level ($t = 6.19, p < 0.00$), month 2 overall valuation of life ($t = 3.26, p < 0.00$), month 2 physical symptom distress level ($t = 3.30, p < 0.00$), and month 2 activity level ($t = 2.08, p = 0.04$).

These variables were entered into a forward stepwise regression. The first two variables entered (with month 2 TF as the dependent variable) were baseline TF and month 2 psychological distress level. With the two variables entered into the model concurrently, month 2 psychological distress level remained significant ($t = 4.87, p < 0.00$), but baseline TF was no longer significant ($t = 1.58, p = 0.12$). Therefore in the presence of
Month 2 psychological distress level, baseline TF was no longer an independent predictor of month 2 TF.

As baseline TF was no longer significant, it was removed from the model, and month 2 overall valuation of life was entered in its place. Again month 2 psychological distress level remained significant ($t = 4.84, p < 0.00$), but in the presence of month 2 psychological distress level, month 2 overall valuation of life was no longer significant ($t = 1.08, p = 0.29$).

Month 2 overall valuation of life was removed from the model. Month 2 physical symptom distress level was included in the model with month 2 psychological distress level. In the presence of month 2 psychological distress level, month 2 physical symptom distress level was no longer significant ($t = 0.88, p = 0.39$).

Finally, month 2 activity level was entered into the model with month 2 psychological distress level, and the non significant month 2 physical symptom distress level was removed. Again month 2 psychological distress level remained significant ($t = 5.44, p < 0.00$), but month 2 activity level became non significant ($t = 0.30, p = 0.76$).

Therefore month 2 psychological distress level as measured by the RSCL was the only independent predictor of month 2 TF, explaining 44% (adjusted r square) of the variance.
After anti-cancer treatment (Month 12 TF)

The independent variables considered in the univariate analysis were: Baseline TF, treatment combination, diagnosis, tumour stage, whether or not the participant had surgery, chemotherapy regime, radiotherapy dose, the demographic characteristics of marital status and age, and indications of month 12 psychological distress level, month 12 physical symptom distress level, month 12 overall valuation of life and month 12 activity level as measured by the RSCL. The variables entered into the forward stepwise regression were baseline TF ($t = 3.24$, $p < 0.00$), month 12 psychological distress level ($t = 8.33$, $p < 0.00$), month 12 overall valuation of life ($t = 4.20$, $p < 0.00$) and month 12 physical symptom distress level ($t = 6.17$, $p < 0.00$).

Initially, baseline TF and month 12 psychological distress level were entered. Month 12 psychological distress level remained significant ($t = 6.32$, $p < 0.00$), but baseline TF became non significant ($t = 0.87$, $p = 0.40$). Baseline TF was then removed from the model, and month 12 overall valuation of life was entered with month 12 psychological distress level. In the presence of month 12 psychological distress level, month 12 overall valuation of life was no longer significant ($t = 2.05$, $p = 0.06$), but month 12 psychological distress remained significant ($t = 5.76$, $p < 0.00$). Month 12 overall valuation of life was therefore removed from the model, and month 12 physical symptom distress level was entered in its place. Both month 12 psychological distress level ($t = 4.28$, $p < 0.00$) and month 12 physical symptom distress level ($t = 2.29$, $p = 0.034$) remained significant in the presence of each other. Thus month 12 psychological distress...
level and month 12 physical symptom distress level were the independent predictors of month 12 TF, explaining 81% (adjusted r square) of the variance.
Discussion

A longitudinal survey accumulating fatigue data from a group of newly diagnosed gynaecological cancer patients before, during and after anti-cancer treatment was conducted. The methodology permitted the investigation of the pattern of fatigue both during and after treatment and facilitated this level of fatigue to be compared to that reported by females with no history of cancer. Without this comparison it would be unknown what proportion of the fatigue experienced by the individuals with cancer was a result of having cancer and receiving cancer treatment.

The gynaecological cancer participants included in the study had more severe fatigue than the non-cancer females. This greater level of CRF was also apparent after treatment was complete. These findings are reflected in the CRF literature. It has frequently been reported that the fatigue experienced during anti-cancer treatment is more severe than non-cancer fatigue (34-37). After anti-cancer treatment, similar findings have been noted (35,38-43).

Raised levels of fatigue compared to the cancer-free participants were also noted before the commencement of anti-cancer treatment. This could be attributed to undergoing surgery, that is, the effects of a general anesthetic and the trauma of surgery (35). However, in this sample, there was no significant difference in the level of fatigue reported by those who had undergone surgery and those who had not, therefore other factor(s) must have been responsible for the increased level of fatigue. It has been proposed that the increase in baseline fatigue could be due to the effects of the tumour
itself and the psychological impact of receiving a cancer diagnosis (35). To investigate this issue further, it would be useful to assess fatigue levels before surgery. However, as demonstrated in an earlier pilot study, it is difficult to obtain fatigue scores at this stage, as the individual may not be emotionally fit to participate and may be unaware of their diagnosis (6).

In some subscales of the MFSI-SF the level of fatigue changed with time, indicating a complex pattern of CRF. This was particularly apparent in the GF and PF subscales where time-point was significant as a factor, indicating that fatigue fluctuated over time. Banthia and colleagues (2006) recommended that it was important to identify which dimensions of CRF were problematic and more sensitive to change over time in order to effectively guide treatment interventions (44). In this survey, the level of GF and PF reported by the cancer participants changed over the course of the 12 months, and was highest during anti-cancer treatment. In comparison, the MF subscale remained at a constant level over the course of the 12 months. The different profiles of the MFSI-SF subscales over time underscores the importance of measuring the different dimensions of fatigue, as it would appear that each dimension behaves differently over time. A number of studies have reported that CRF increases significantly during treatment (12,34,45-51), but this is not verified by all investigations (19,52,53). This inconsistency could be the result of methodological flaws, such as fatigue not being assessed frequently enough to detect fluctuations.
**Interpretation of MFSI-SF scores**

Although the change in MFSI-SF scores over time was statistically significant, the increase in fatigue may not have been substantial enough to have a negative impact on quality of life. ‘Clinical significance’ is a term used to signify whether or not the change in the variable of interest is meaningful to the individual (54). Including the non-cancer group of females provided an indication that the fatigue was worse than the ‘norm’, but a more suitable method for determining clinical significance is the use of Minimal Clinically Important Differences (MCIDs) (54). Unfortunately there are currently no MCIDs available for the MFSI-SF. The National Comprehensive Cancer Network (NCCN) recommendations for the management of CRF suggest that anyone scoring 4 or more on an NRS should have their fatigue investigated further (1). In this survey, the overall mean NRS score for the all of the cancer participants was 4.6. This would suggest that the majority of gynaecological cancer patients in this study had fatigue that was severe enough to warrant further investigation.

**Predictors of fatigue**

**Fatigue before anti-cancer treatment**

The regression analysis suggested that surgery was not associated with having fatigue; furthermore tumour related variables such as tumour site and stage were not related to fatigue. This suggests that the tumour site or stage for gynaecological cancer patients had no influence on the level of baseline fatigue reported. Increased psychological distress level was associated with raised fatigue at baseline, which is likely to be a result of receiving a diagnosis of cancer and feeling anxious about starting anti-cancer treatment.
Reduced quality of life and a raised physical symptom distress level were also related to fatigue, indicating that suffering other symptoms lead to an increase in fatigue.

*Fatigue during anti-cancer treatment*

During treatment, psychological distress level was the sole independent predictor of CRF. A strong relationship has been noted in the literature between CRF during treatment and anxiety and depression (5,9,22,34,49,50,53-67). In this longitudinal survey demographic variables and factors associated with the tumour and anti-cancer treatment were unrelated to the fatigue. A large body of evidence exists to support the finding that CRF during anti-cancer treatment is not associated with tumour stage (12,22,23,46,51,56,60,68-70) or any demographic (12,22,23,34,49,55,56,60,62,64,66-71) or treatment-related variables (12,22,23,46,51,53,55,60,64,68-72). In contrast, two studies have reported that females experience more fatigue than males (62,73), three have demonstrated an association between increasing age and lower fatigue (12,34,53), one between marital status and fatigue, with divorced women experiencing the most fatigue (74), two between working and raised fatigue (12,75), and one between living alone and fatigue (12). In contrast to the current findings the following treatment related variables have been linked to higher fatigue levels: receiving chemotherapy (34) and drug regime (34,74,75).

*Fatigue after anti-cancer treatment*

After treatment, psychological distress level was again an independent predictor of fatigue as was physical symptom distress level. Tumour and treatment related variables were not associated with the persistence of fatigue after anti-cancer therapy. Previous
research has also indicated strong relationships between anxiety and depression and CRF in cancer survivors (34,38-40,42,76-90). In agreement with the current findings the majority of previous research has found no relationship between diagnosis and fatigue (35,40,42,43,76-88,91-93). Studies investigating CRF in survivors of cancer have also reported no association between treatment related variables and fatigue (35,38,39,41-43,76-82,84-88,90,92-95) which concurs with the current findings. These findings, in conjunction with the outcome of this longitudinal survey, leads to the conclusion that in cancer survivors, psychological factors are related to CRF whereas tumour and treatment factors are not. The literature remains ambiguous with regard to an association between demographic variables and fatigue. In agreement with the current findings a number of studies have concluded that no association exists (34,42,76,78-80,83,85,87,90-96). In contrast, two studies reported that females experienced more fatigue than males (80,92), two reported that married individuals had higher fatigue than those who were not married (96,97). A relationship has also been reported between age and fatigue in cancer survivors (34,39,41,83,93,96-98). This finding is complicated by an inconsistency that exists between the direction of the association. For example, with testicular cancer patients (34,38) and participants with a hematological malignancy (87,96), the older the subject the more fatigue reported, whereas with breast cancer patients the younger participants reported more fatigue (90,98). In the current survey, no association with age was noted. The apparent conflict of opinion that exists in this area may be due to the difficulties in the accurate assessment of CRF.
Psychological distress level was an independent predictor of fatigue before, during and after anti-cancer treatment. As has been demonstrated throughout this survey, fatigue is a symptom of cancer, but it is also reported to be a symptom of depressive disorders (99). The symptoms associated with fatigue are similar to the symptoms reported by individuals with depression (100). As a result of this some items included in an assessment scale for CRF, would be incorporated into an assessment scale for psychological impairment. It would be acceptable to assume some level of correlation between the two phenomena, and thus they would appear related in a regression analysis. A relationship between depression and fatigue was frequently reported in the literature. However, there is evidence that CRF may increase over time with no concurrent increase in anxiety and depression (19,21,56,101). Furthermore Jacobsen and colleagues (2003) reported a correlation between fatigue and depression that remained even when items included in both assessment scales were removed. This indicated that a relationship might exist that was not due to the overlap in the two assessment scales (99). The causal relationship between the two phenomena remains to be determined.

In an attempt to combat the overlap in measurement, a clinical syndrome approach has been suggested as a more appropriate method of assessing CRF (99,100). Cella and colleagues (1998) developed a set of four diagnostic criteria for the International Classification of Diseases – 10 (ICD-10) (102). Firstly, they proposed eleven symptoms that could be associated with CRF. To meet the first diagnostic criteria, six of the eleven symptoms must be present almost every day for two weeks over the period of one month. One of the symptoms must be ‘significant fatigue, diminished energy, or an increased
need to rest, disproportionate to any recent change in activity levels’ (102). The second and third criteria suggest that the fatigue must interfere with usual functioning and be linked to cancer or cancer treatment (102). The fourth criteria states that the fatigue symptoms must not be a result of a psychiatric disorder and thus aims to distinguish CRF from psychological disorders (99).

**Limitations**

Only 25 of the original 65 cancer participants completed the final assessment. However, the comparison of the fatigue levels, as measured by the NRS-F, of those who completed the study and those who dropped out demonstrated that there was no difference in the level of fatigue between the two at the time of withdrawal. It cannot however be presumed that the level of fatigue reported by those who withdrew stayed at a similar level as those who completed the study. Every attempt was made to minimise the attrition rate, however due to the nature of the disease and the severity of treatment, drop-outs, as in many studies, were inevitable (103).

Not all cancer participants had a matched control, largely due to the fact that they were elderly participants, and it was difficult to source a match that met the inclusion/exclusion criteria. The omission of five non-cancer participants may have influenced the outcome of the survey. However, the fact that over 90% of cancer participants were matched would indicate that the results are more than likely the true outcome.
The data on CRF was only recorded up to 12 months from baseline. At the 12 month cut
off point, the fatigue reported by the cancer participants had decreased from the level
reported during anti-cancer treatment, but it was still significantly higher than the fatigue
reported by the non-cancer comparison group. It is therefore unknown how long CRF
persists for in survivors of gynaecological cancer. Future research should focus on
investigating this fatigue persistence.

**Implications for practice**

Clinicians should be aware that females with a diagnosis of gynaecological cancer might
experience a raised level of fatigue before they commence treatment regardless of
whether or not they have undergone surgery. This fatigue is likely to last throughout
treatment, and may remain after treatment. To fulfill the National Institute of Health and
Clinical Excellence (NICE) recommendations that all patients should be offered optimal
symptom control should they require it (104), gynaecological cancer individuals should
be screened for high fatigue levels before commencement of anti-cancer treatment. This
screening should continue for the duration of their treatment, and they should be
reassessed at regular intervals once treatment is complete. Frequent assessment will help
to ensure that appropriate interventions are made available to the patient as soon as they
require them.

It is important to encourage the assessment of CRF clinically to ensure that fatigue is
managed appropriately. The outcomes of this longitudinal survey demonstrate that the
various dimensions of CRF behave differently; GF and PF peaked during treatment
whereas MF remained at a constant level over the twelve months. This confirms that the ideal approach for the measurement of CRF is with a multidimensional assessment tool. Clinically however it is acknowledged that it may not be possible for each individual to complete a multidimensional fatigue questionnaire. Where this is not achievable, it is suggested that individuals are screened with a single item scale such as a NRS-F, to identify those that require more comprehensive CRF assessment. The in depth assessment should measure CRF multidimensionally in an attempt to identify the source of the CRF so the fatigue can be managed appropriately. This recommendation has been discussed further by the NCCN (1).

The apparent association between CRF in individuals with gynaecological cancer and psychological distress would indicate that management strategies aimed at reducing this distress may alleviate fatigue. Anti-depressants have been used for fatigue that is related to depression, but there is currently minimal research evidence to support their use (105,106). Psychosocial interventions such as support groups, psychotherapy, relaxation therapy, cognitive behavioral therapy and distraction techniques such as reading and listening to music have also been investigated (10,106-109). The management of CRF through exercise has received the most attention in the literature (10,105,106). In this longitudinal survey activity level as measured by the RSCL was a univariate predictor of CRF. However, in the presence of psychological distress level, activity level was not an independent predictor of CRF. Despite this exercise has been suggested as an effective intervention to reduce CRF both during and after treatment (110)
Conclusions

Fatigue is a problem for gynaecological cancer patients both during and after anti-cancer treatment. From this longitudinal survey it would appear that tumour and treatment related variables are not associated with CRF in gynaecological cancer. This suggests that all females with a diagnosis of gynaecological cancer, regardless of their tumour site, tumour stage or treatment regime should be informed that they may experience CRF during their treatment and that it may persist for many months once their treatment is complete (111). This would enable the individual to provide fully informed consent to treatments such as chemotherapy. Research has also suggested that if an individual is told what to expect, they are not as likely to experience the stress of unexpected problems (10). Furthermore, individuals with gynaecological cancer should be reassured that the experience of severe fatigue is not indicative of disease progression (1). They should be offered education regarding effective fatigue management, for example energy conservation techniques such as delegation, pacing and prioritising, as recommended by the NCCN (1). The strong association presented between CRF and psychological distress in gynaecological cancer indicates that interventions focused on the amelioration of psychological distress may reduce the perception of CRF in this patient population. Future research should focus on the investigation of the optimum management strategy for CRF in gynaecological cancer.

Acknowledgements:

Statistical advice was provided by Dr Ian Bradbury. Financial support was provided by the Northern Ireland Cancer Recognized Research Group.
References


90. 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.


Table 1
Cancer and non-cancer participant demographics

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* Totals 63 as two participants did not consider themselves to be an active person
** Does not total 60 as six participants did not consider themselves to be an active person
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Table 3
Cancer participants mean weekly MFSI-SF scores

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Table 4
Cancer participants mean monthly MFSI-SF scores

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Table 5

Mean MFSI-SF scores for non-cancer participants (n = 60)

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<th>GF mean (SD)</th>
<th>PF mean (SD)</th>
<th>EF mean (SD)</th>
<th>MF mean (SD)</th>
<th>V mean (SD)</th>
<th>TF mean (SD)</th>
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<tr>
<td>Baseline</td>
<td>4.32 (3.24)</td>
<td>1.95 (2.63)</td>
<td>2.81 (4.06)</td>
<td>3.14 (2.57)</td>
<td>13.49 (4.16)</td>
<td>-1.21 (10.69)</td>
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<tr>
<td>Month 1</td>
<td>4.71 (4.00)</td>
<td>2.20 (2.90)</td>
<td>2.96 (3.46)</td>
<td>3.02 (2.70)</td>
<td>12.45 (5.79)</td>
<td>0.44 (13.97)</td>
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<td>Month 2</td>
<td>3.98 (3.58)</td>
<td>2.60 (3.65)</td>
<td>2.31 (2.76)</td>
<td>3.27 (3.00)</td>
<td>12.53 (5.24)</td>
<td>-0.63 (13.09)</td>
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<td>Month 3</td>
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<td>2.60 (3.74)</td>
<td>2.53 (3.20)</td>
<td>3.13 (2.64)</td>
<td>12.15 (4.50)</td>
<td>-0.17 (13.78)</td>
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<td>Month 4</td>
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<td>2.15 (2.71)</td>
<td>3.17 (3.76)</td>
<td>2.65 (2.56)</td>
<td>11.60 (5.87)</td>
<td>0.13 (14.06)</td>
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<td>Month 5</td>
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<td>2.30 (3.51)</td>
<td>3.35 (4.86)</td>
<td>3.18 (2.93)</td>
<td>11.88 (5.07)</td>
<td>0.65 (15.36)</td>
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<td>Month 6</td>
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<td>2.30 (3.25)</td>
<td>2.54 (3.89)</td>
<td>3.00 (2.60)</td>
<td>12.58 (4.86)</td>
<td>-0.58 (14.51)</td>
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<td>Month 7</td>
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<td>2.07 (2.46)</td>
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<td>-3.04 (12.14)</td>
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<td>-2.06 (13.75)</td>
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<td>0.12 (16.05)</td>
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<td>2.93 (4.10)</td>
<td>2.86 (2.67)</td>
<td>11.24 (95.56)</td>
<td>0.19 (13.64)</td>
</tr>
</tbody>
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Figure 1a
Monthly GF for cancer participants

Figure 1b
Monthly PF for cancer participants
Figure 1c
Monthly EF for cancer participants

Figure 1d
Monthly MF for cancer participants
Figure 1e
Monthly V for cancer participants

Figure 1f
Monthly TF for cancer participants
Figure 2a
Mean weekly TF scores during the first three cycles of chemotherapy

Figure 2b
Mean TF score during and after chemotherapy

Figure 2c
Mean TF score during and after radiotherapy
Figure 3
Mean TF score before, during and after anti-cancer treatment for ovarian (n = 35) and endometrial (n = 16) cancer