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Contributing Factors to the Experience of Cancer-Related Fatigue (CRF) Before and After Treatment with Chemotherapy

A thesis submitted to
The University of Dublin, Trinity College
for the degree of
Doctor of Philosophy

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2013

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Summary

Cancer and cancer treatment can have substantial and long-lasting physical, psychological and social repercussions that can significantly diminish quality of life (QOL). This thesis focussed on cancer-related fatigue (CRF), an important and often overlooked aspect of cancer survivorship. Although CRF is the most common side-effect of cancer, its causes are not adequately understood. This thesis examined a range of psychological, biological, behavioural and cognitive contributing factors to CRF.

Chapter 1 described the problem of CRF and outlined why further research on this ambiguous and complex condition is necessary. The emerging evidence for the role of cognitive contributing factors to CRF was considered and the suitability of using a cognitive-behavioural model for examining the causes of CRF was discussed. Chapter 2 examined the role of cognitions in CRF by adapting the Illness Perception Questionnaire (IPQ) for use in this population. The scale was validated in a sample of fatigued cancer patients and survivors (n = 155). Confirmatory factor analysis indicated that the scale's factor structure was in line with the Common Sense Model (CSM) on which it is based, and the resulting subscales exhibited good internal consistency and adequate test–retest reliability. Consequently, the scale was recommended for assessing patients' perceptions of CRF and analysis of change in cognitions over time.

Chapter 3 outlined the cognitive-behavioural model of CRF in greater detail; existing evidence for the clinical and demographic, biological, psychological, sleep-related, social, behavioural and cognitive contributing factors that are thought to play a role in the aetiology of CRF were evaluated. Chapter 4 assessed the contribution of a range of pretreatment psychosocial predictors to fatigue both before and after treatment. Nearly 40% of the sample (n = 100) experienced fatigue at baseline, and psychological distress and sleep disturbance played a key role in fatigue at this time. Patients who experienced greater fatigue pretreatment were at increased risk of heightened fatigue after treatment; however, no other demographic, clinical, psychological or behavioural factors at baseline predicted fatigue outcomes post-treatment.

Chapter 5 examined the role of cognitive factors in post-cancer fatigue by testing the causal pathways of the CSM; assessing the role of beliefs within a wider cognitive-behavioural model of CRF; and exploring whether changes in cognitions and coping were related to changes in fatigue. Cognitive representations of CRF, and consequence beliefs in particular, predicted fatigue severity; furthermore, this relationship was partially mediated by psychological distress and focussing on

symptoms. Negative beliefs about CRF were strongly associated with psychosocial correlates of fatigue and predicted fatigue directly and indirectly in multivariate models. Support for a relationship between changes in cognitions and changes in fatigue was limited; however, change scores in fatigue were strongly related to changes in psychological factors. Chapter 6 detailed a longitudinal study that examined inter- and intra-individual differences in the trajectory of fatigue, from before chemotherapy to approximately nine months after treatment, based on a range of proposed psychological, sleep-related and behavioural contributors. Depression, activity levels, stress, and sleep-disturbances predicted interindividual differences in fatigue. Changes in fatigue over time were associated with changes in depression and physical activity. Furthermore, the presence of comorbidities and self-reported activity levels had a significant impact on the rate of change in fatigue over time. Close links between changes in fatigue and changes in QOL were also observed.

Chapter 7 examined whether inflammation and kynurerine pathway (KP) activation are implicated in breast cancer patients' (n = 61) experiences of fatigue and depression. Levels of the inflammatory marker C-reactive protein predicted fatigue independently of depression prior to chemotherapy. There was no evidence that increased KP activation played a role. Nevertheless, kynurenine levels and post-treatment concentrations of the inflammatory cytokine interleukin-6 were associated with changes in depressive symptoms. Chapter 8 examined whether dysregulation of hypothalamic-pituitary-adrenal axis functioning plays a role in CRF by investigating the association between cortisol levels and fatigue severity. There was no evidence that lower levels of morning cortisol, a less pronounced awakening cortisol response, and flatter diurnal cortisol rhythms were associated with fatigue post-treatment (n = 68).

Chapter 9 used the 'additional comments' left by participants (n = 73) at the end of a quantitative questionnaire to gain insight into patients' lived experiences of CRF. Thematic analysis indicated that dominant discourses of cancer and illness can shape these experiences, and that individual narratives are often lost when they deviate from or oppose established conceptualisations of survivorship and recovery. The dominance of such discourses thus overshadows and/or inhibits the emergence of a discourse of CRF that acknowledges the potentially lingering presence of cancer in people's lives.

Chapter 10 integrated the empirical findings presented in this thesis and discussed the implications for understanding the development of CRF. Limitations of the research were considered and directions for further research were suggested.

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Publications arising from this work

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Chapter 1: General Introduction

"I liken Cancer to a Tsumani. It hits you like a wave and then you're left with all this debris afterwards. You have to pick up the pieces - like fatigue." – Monica

1.1 Cancer Trends in Ireland

Advancements in cancer treatments, more efficient and effective screening programmes, as well as an aging population have contributed to significant increases in the incidence of cancer and the life expectancy of cancer patients (National Cancer Registry, 2011). The average number of new cancer cases per year recorded in Ireland from 2007-2009 was 29,745, a 12% increase from the annual average in the previous three year period (2004-2006), and approximately 50% higher than the figures collected in 1994 when the National Cancer Registry was first established. Mortality figures show the opposite trend with a 15% decline during the same time-frame; the overall 5-year survival rate for invasive cancers (excluding non melanoma skin cancer) diagnosed between 1994-1997 was 55% compared to 40% for those diagnosed between 2003-2007 (National Cancer Registry, 2011). As a result, more people are living longer after cancer treatment and this trend is likely to continue in the future. Although there are no complete prevalence figures available in Ireland, it is known that 90,750 people who were diagnosed with invasive cancer between 1994 and 2008 were still alive at the end of 2008 (National Cancer Registry, 2011). Consequently, cancer survivorship issues, such as the long-term side-effects of cancer treatment and their impact on quality of life (QOL), are becoming increasingly important in the Irish health care system and for our research agenda.

1.2 Cancer-Related Fatigue

Fatigue is reported to be the most distressing side-effect of cancer treatment, even more so than other symptoms more commonly associated with cancer treatment, such as pain, nausea, and vomiting (Blohmer et al., 2005; Vogelzang et al., 1997). Cancer-related fatigue (CRF) is multidimensional; it is characterized by a persistent and subjective sense of exhaustion that can affect patients on physical, emotional, and cognitive levels (Morrow, 2007; National Comprehensive Cancer Network, 2012a). Furthermore, CRF can severely limit patients' social functioning and their ability to carry out everyday tasks of daily living (Hofman, Ryan, Figueroa-Moseley, Jean-Pierre, & Morrow, 2007). Unlike fatigue experienced by other populations, CRF is disproportionate to levels of activity and is unresponsive to sleep or rest (Jean-Pierre et al., 2007). Thus, it presents a significant burden for both patients and their caregivers

that can have extremely devastating and long-term effects on quality of life. Patients with severe and persistent CRF may be forced to go on lengthy or permanent sick leave (Curt et al., 2000; Gupta, Lis, & Grutsch, 2007). Level of fatigue has been found to be predictive of length of sick leave (Spelten et al., 2003), while clinically meaningful reductions in fatigue have been associated with gains in productive time, decreases in the amount of assistance needed from caregivers, and improvements in the ability to perform usual activities and family responsibilities (Berndt et al., 2005).

CRF is also one of the most common side-effects of cancer treatment; between 50-90% of cancer patients experience fatigue (Campos, Hassan, Riechelmann, & del Giglio, 2011b), and 19%-38% of patients continue to report severe persistent CRF for months or even years after completing treatment (Prue, Rankin, Allen, Gracey, & Cramp, 2006). However, despite its prevalence and impact, CRF continues to be under-reported, under-diagnosed, and under-treated (Campos et al., 2011b; National Comprehensive Cancer Network, 2012a). Although there is emerging evidence for a variety of different treatment approaches for this side-effect (Kangas, Bovbjerg, & Montgomery, 2008; Minton, Richardson, Sharpe, Hotopf, & Stone, 2008; Mustian et al., 2007), the precise mechanisms underlying the development and maintenance of persistent CRF are still not clear and, therefore, it is difficult to establish a scientific basis for effective prevention and targeted treatment.

1.3 Theoretical Framework for the Thesis

The causes of CRF are complex and involve a number of interrelated factors rather than any single mechanism (Wang, 2008). Research has linked numerous biological, psychological, social, behavioural, and cognitive contributing factors with CRF (Oh & Seo, 2011; Payne, 2004). The factors that have received the greatest attention in the literature include treatment-related variables, hypothalamic-pituitary-adrenal (HPA)-axis and circadian rhythm disruption, alterations in the level and functioning of inflammatory cytokines, sleep disturbances, reduced activity levels, and psychological factors, such as depression and anxiety (Stone & Minton, 2008; Wang, 2008). In addition, the role of cognitive factors, such as fatigue catastrophising and low perceived control, are increasingly being acknowledged (e.g., Andrykowski, Donovan, Laronga, & Jacobsen, 2010; Donovan, Small, Andrykowski, Munster, & Jacobsen, 2007; Servaes, Gielissen, Verhagen, & Bleijenberg, 2007). These different contributing factors may help to bring on fatigue during treatment or help to prolong fatigue after treatment has been completed (Rotonda, Guillemin, Bonnetain, & Conroy, 2011), and

different types of contributing factors are likely to have different degrees of influence depending on a patient's position in the treatment trajectory. For example, clinical and biological factors, such as cancer type and severity, treatment type and intensity, and treatment-related side-effects, such as endocrine dysregulation and anaemia, may initially cause fatigue; however, other psychological and behavioural factors may help to exacerbate and maintain fatigue once cancer treatment has been completed and/or the physiological impact of treatment has subsided. Furthermore, as many of the contributing factors identified are themselves interrelated (Ryan et al., 2007), this could result in a circular process of influence, whereby different factors associated with CRF help to perpetuate one other, and thereby fatigue over time. This is similar to Beck's cognitive behavioural model of emotional distress, which distinguishes between predisposing and precipitating factors and a self-maintaining cycle of cognitive, affective, behavioural and physiological perpetuating factors (Beck, 1976; Deary, Chalder, & Sharpe, 2007). This cycle is autopoietic, whereby the interactions between the different perpetuating factors help to maintain one another and the processes which produced them.

The cognitive-behavioural model of perpetuation has been successfully applied to a variety of conditions with complex and multifactorial aetiologies, such as chronic fatigue syndrome (CFS) and irritable bowel syndrome (Deary et al., 2007; Knoop, Prins, Moss-Morris, & Bleijenberg, 2010). Its suitability for CRF is supported by a number of lines of evidence. Firstly, the model accounts for the multitude of different factors that have been associated with the development of CRF, and the often conflicting findings that have emerged from studies based around different treatment timepoints. For example, while the prevalence and severity of fatigue in cancer patients is greater than in the general population (Fernandes, Stone, Andrews, Morgan, & Sharma, 2006; Jacobsen, Hann, et al., 1999), supporting the role of cancer and cancer-treatments in initiating CRF, relationships between post-treatment CRF and time since diagnosis or treatment, disease stage, or type or extent of treatment are not supported by most studies (Andrykowski, Curran, & Lightner, 1998; Okuyama et al., 2000; Servaes, Verhagen, & Bleijenberg, 2002c). However, findings do suggest that other factors, such as poor sleep quality and sleep disturbances (e.g., Alexander, Minton, Andrews, & Stone, 2009), depression (e.g., Bower et al., 2006), anxiety (e.g., Servaes, van der Werf, Prins, Verhagen, & Bleijenberg, 2001), physical activity (e.g., Servaes, Verhagen, et al., 2002c), and catastrophising in response to fatigue (e.g., Donovan et al., 2007), are

related to persistent CRF. In addition, some longitudinal studies have started to emerge that support the role of biological/treatment-related factors in precipitating CRF and the role of cognitive and behavioural factors in perpetuating CRF (e.g., Andrykowski et al., 2010; Donovan et al., 2007).

Secondly, the cognitive-behavioural model allows a unique perpetuating cycle of cognitive, behavioural, affective, and physiological factors for each individual (Deary et al., 2007), which further helps to explain the conflicting evidence for the involvement of different factors in the aetiology of CRF. For example, while depression is one of the strongest predictors of CRF, not all patients with CRF also have significant levels of depression. Sugawara (2005) reported that a significant number of cancer survivors, who did not suffer from clinical depression, still experienced fatigue, and findings from other studies suggest only about a third of patients with severe CRF also have depression (Kim et al., 2008; Servaes, Verhagen, et al., 2002c). Thus, depression may be a common, but by no means necessary, element of the CRF perpetuating cycle.

Finally, evidence suggests that cognitive-behavioural therapy (CBT) interventions that focus on disrupting the cycle of influence between dysfunctional cognitions, unhelpful coping strategies, and psychological distress are effective in reducing CRF. For example, Giellesen et al. (2007; 2006) reported that a personalised CBT-based intervention directed at proposed perpetuating factors of CRF was effective in reducing fatigue in a sample of disease-free cancer survivors relative to a waiting-list control sample.

A cognitive-behavioural model therefore appears to be a suitable framework for the aetiology of CRF; however, more longitudinal research is necessary to test whether this model can account for changes in CRF severity over time. The majority of studies to date have been cross-sectional and have focused on a small number of hypothesised contributing factors in isolation. Longitudinal studies that track the development of CRF from before treatment and assess a broad spectrum of psychosocial and physiological predictors across the cancer trajectory are required to understand the factors that precipitate CRF and the interplay of factors that help to perpetuate CRF post-treatment. Furthermore, although the effectiveness of CBT interventions supports the role of patients' illness beliefs in the aetiology of CRF, and cognitive factors, such as low perceived control and catastrophising, have been linked to CRF severity, the role of illness perceptions has not been adequately explored, and there is little evidence that

changes in such beliefs actually mediate reductions in fatigue. Finally, while some cognitive factors, such as control perceptions, have been assessed in the context of CRF there is no standard measure of patients' illness beliefs regarding CRF.

1.4 Aims of the Thesis

The aim of this thesis was to elucidate the mechanisms underlying the development of CRF and to test the appropriateness of a cognitive-behavioural framework for understanding the interplay of different contributing factors to CRF over time. The research is presented in three sections. The aim of the first section, described in Chapter 2, was to adapt the Illness Perception Questionnaire (Moss-Morris et al., 2002; Weinman, Petrie, Moss-Morris, & Horne, 1996) for assessing the illness beliefs of people with CRF. The availability of a scale for quantitatively assessing how people with CRF conceptualise their fatigue is necessary for examining whether representations of CRF change over time, and for exploring whether such representations can influence psychological and behavioural responses to symptoms and symptom outcomes. Furthermore, the importance of developing condition- and culture-specific measures of illness representations has been noted (Moss-Morris et al., 2002).

The second section of this thesis investigated the contributing factors to CRF. Chapter 3 reviews the existing literature on the aetiology of CRF, and Chapters 4 to 8 analyse findings from a longitudinal study that explored the trajectory of fatigue in a mixed sample of cancer patients. The aim of these chapters was to examine the role of a variety of proposed clinical-demographic, biological, behavioural, psychological, and cognitive predictors in CRF, from before chemotherapy treatment to approximately nine months post-treatment. Furthermore, in line with the cognitive-behavioural model, interrelationships between various contributing factors at different points along this trajectory were investigated.

Finally, the third section of this thesis, presented in Chapter 9, consists of a qualitative study that explored the experiences of patients with CRF based on the 'additional comments' they left at the end of quantitative questionnaires. Although the aetiology of CRF is conceptualised within a biopsychosocial model of illness, the sociocultural influences that form part of the social dimension also need to be considered. The environment and cultural context in which people perceive and respond to symptoms impose certain expectations regarding illness and recovery. Exploring people's own accounts of a symptom can give insight into such sociocultural

factors, and can provide a context for the observed beliefs and the interplay between cognitions and psychological and behavioural responses. The final empirical chapter thus examines the sociocultural context of CRF, and considers how it can inform our understanding and management of this symptom. In addition, to further contextualise the findings in this thesis and to set the scene for each subsection, a quote from a participant is presented at the start of each chapter.

Chapter 2: Assessing Patients' Beliefs About Their Cancer-Related Fatigue: Validation of an Adapted Version of the Illness Perception Questionnaire.

"I think part of my fatigue is from side effects from taking the chemo drug Taxotere. ... The radiation damaged my bone marrow "factory" so I have low red & white blood cells. There isn't anything thing they can do. That is the most frustrating part." – Niamh

2.1 Introduction

Cancer-related fatigue (CRF) is a common and distressing side-effect of cancer treatment that impacts negatively on patients' quality of life (Hofman et al., 2007). Up to a third of cancer survivors continue to experience CRF long after completing treatment (Prue et al., 2006); however, the causes of persistent fatigue are not clear. While chemotherapy and radiation therapy are known to cause the fatigue experienced by almost all patients during active treatment, the development of persistent CRF in some cancer survivors is likely to involve complex interactions between biological, psychological, social, and behavioural factors (Bower, 2005; Ryan et al., 2007). Patients' own beliefs about their CRF may also help to maintain this side-effect. For example, the belief that physical activity is harmful for fatigue (Young & White, 2006), low perceived control over fatigue (e.g., Servaes et al., 2007), and somatic and psychological causal attributions (e.g., Servaes, Verhagen, et al., 2002c) have all been associated with severe CRF in cancer survivors. Furthermore, such beliefs may also exacerbate some proposed contributing factors to CRF, such as anxiety, depression, sleeping problems, and activity avoidance.

Leventhal's common sense model (CSM, Leventhal, Nerenz, & Steele, 1984) outlines how patients create representations of an illness to understand and respond appropriately to their condition. These representations comprise different dimensions (Weinman et al., 1996). *Identity* refers to patients' beliefs about the nature of their illness and the symptoms associated with it. *Cause* relates to beliefs about the factor(s) that caused their illness. *Time-line* is concerned with the patient's perception of how long their illness will last. *Consequences* refer to the perceived severity of the illness and its likely impact. Finally, *cure/controllability* is concerned with the extent to which the patient believes their illness can be controlled or cured through their own actions or through treatment.

The illness dimensions outlined in the CSM have been measured using the Illness Perception Questionnaire (IPQ; Weinman et al., 1996) or its revised version, the IPQ-R (Moss-Morris et al., 2002). Research suggests that the structure of patients'

illness beliefs are stable across a diverse range of chronic and acute conditions (Hagger & Orbell, 2003) including coronary heart disease (e.g., French, Lewin, Watson, & Thompson, 2005), chronic fatigue syndrome (CFS; e.g., Gray & Rutter, 2007) and rheumatoid arthritis (e.g., Graves, Scott, Lempp, & Weinman, 2009). The structural validity of the IPQ dimensions has been supported using both exploratory (EFA; Hagger & Orbell, 2003) and confirmatory factor analysis (CFA; e.g., Hagger & Orbell, 2005). Illness representations are powerful predictors of health outcomes, such as social and physical functioning, psychological well-being, and vitality (Hagger & Orbell, 2003), sometimes even more so than objective clinical measures (e.g., Carlisle, John, Fife-Schaw, & Lloyd, 2005). Furthermore, changes in beliefs have been associated with significant changes in illness outcomes; for example, significant reductions in fatigue and disability in CFS patients were associated with changes in perceived control and illness identity (Moss-Morris, Sharon, Tobin, & Baldi, 2005).

Patients' illness representations are based on their own beliefs and experiences, and thus may not be consistent with medical facts (Diefenbach & Leventhal, 1996). This model is therefore particularly suitable for understanding how patients make sense of and cope with CRF because doctors frequently fail to adequately discuss CRF with patients and may give them little or no information about how to manage fatigue (Curt et al., 2000; Donovan, Hartenbach, & Method, 2005; Donovan & Ward, 2005; Piredda et al., 2007; Ream, Browne, Glaus, Knipping, & Frei, 2003). Thus, patients are often left with their own representations of CRF and their own strategies for managing it (Barsevick, Whitmer, & Walker, 2001). The appropriateness of the model is also supported by qualitative research, which found that patients' statements during a focus group on CRF could be directly mapped onto the representation, coping and appraisal components of the CSM (Barsevick et al., 2001).

The aim of the current study was to develop an adapted version the IPQ-R suitable for assessing cancer patients' own representations of the nature and perceived causes of their fatigue. Such a measure could be used in clinical practise to identify whether patients have an inadequate or inaccurate conception of CRF that may be contributing to inappropriate coping strategies and/or increased symptom burden (Barsevick et al., 2001). An IPQ measure for CRF may be useful for identifying cognitive predictors of persistent fatigue in cancer patients. In addition, such a scale would help to capture how beliefs regarding CRF change over time as patients move from active treatment, to post-treatment, to post-cancer stages of recovery, and whether

such cognitions influence fatigue severity across these stages. Changes in fatigue-related cognitions have been proposed as a likely mediator for cognitive-behavioural therapy (CBT) intervention effects (Goedendorp et al., 2010). CBT attempts to improve fatigue by challenging unhelpful thoughts and maladaptive coping strategies (e.g., Armes, Chalder, Addington-Hall, Richardson, & Hotopf, 2007; Cohen & Fried, 2007; Gielissen et al., 2006; Goedendorp et al., 2010). However, evaluation of such interventions has focused on outcome measures of fatigue and psychological wellbeing; no empirical evaluation has examined whether patients' beliefs were actually changed and if such changes could explain reductions in fatigue, either directly or through coping. Consequently, a scale for assessing CRF-specific beliefs that captures many of the existing targets of CBT-interventions (e.g., perceived lack of control over CRF and unhelpful causal attributions; Gielissen et al., 2006) could be extremely useful.

The importance of beliefs in CRF has been recognised with some belief-based measures emerging that assess symptom burden from the patient's perspective. Baro et al. (2009) developed the 'Perform Questionnaire' to assess patient perceptions of CRF for use in clinical practice. However, this measure does not capture patients' beliefs about *the nature* of fatigue; rather, it assesses the impact and consequences of fatigue (Baro et al., 2009). While the 'Symptom Representation Questionnaire' (SRQ; Donovan, Ward, Sherwood, & Serlin, 2008) does focus on illness representations, it was developed to assess patients' beliefs about all cancer-related symptoms and not fatigue specially; thus, it does not fully capture the complexity of CRF, especially regarding the range of possible causal attributions patients may have. Furthermore, the dimensional structure of the SRQ is not theoretically consistent with the CSM. Thus, at present a theoretically consistent and psychometrically robust measure for assessing patients' representations of CRF is lacking.

The aims of this study were to (1) adapt the IPQ-R for use with patients who have CRF, (2) to assess the factorial validity of the adapted scale using CFA, and (3) to test the psychometric properties of the scale. The approach described by Clark and Watson (1995) was used to guide scale development and psychometric evaluation. Clark and Watson highlight three components of construct validity: substantive (the conceptualisation and development of an item pool), structural (item selection and evaluation) and external validity (evaluation of whether the test or measures are related to external constructs in the theorized way). As the CSM provides a hypothesised structure for the scale items, CFA was used to evaluate whether the adapted IPQ for

CRF is structurally equivalent to the original version of the scale (Fleming, Martin, Miles, & Atkinson, 2009). CFA has been used previously to evaluate adaptations of the IPQ (e.g., Cabassa, Lagomasino, Dwight-Johnson, Hansen, & Xie, 2008; Chen, Tsai, & Lee, 2008).

2.2 Method

2.2.1 Questionnaire development.

2.2.1.1 The original IPQ-R scale. The IPQ-R (Moss-Morris et al., 2002) is divided into three sections. Section A assesses illness identity and asks respondents to report (a) whether they have experienced each of a list of 14 commonly experienced core symptoms and (b) whether they believe each of these symptoms is specifically related to their illness using a *yes/no* response format. The sum of the yes-responses to part (b) is used as the identity subscale score. Section B contains 38 items that assess the timeline acute/chronic, timeline cyclical, consequences, personal control, treatment control, illness coherence, and emotional representation dimensions. These items consist of statements (e.g., "My illness will last a long time") that are rated on 5-point Likert scales ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). The mean of the subscale items measures that illness dimension. Section C is concerned with the causes dimension. Respondents indicate whether they believe each of a list of items (e.g., stress) caused their illness using the same 5-point Likert scale.

2.2.1.2 Scale modifications. Modifications were made to adapt the IPQ-R for CRF. The instructions for completing the scale were modified by replacing the phrase "your illness" with "your cancer-related fatigue". In Section A, the list of symptoms included in the identity dimension was tailored to CRF by including 12 symptoms (diminished energy or increased need to rest, diminished concentration or attention, sleep difficulties or increased sleepiness, problems with short-term memory, a need to struggle to overcome inactivity, difficulty completing daily tasks, unrefreshing or nonrestorative sleep, decreased motivation or loss of interest, significant distress or impairment in social or occupational functioning, general weakness or limb heaviness, marked emotional response [e.g., sadness, frustration, or irritability], and fatigue after physical activity that last several hours) specifically associated with this condition (Moss-Morris et al., 2002; Weinman et al., 1996) based on the CRF diagnostic criteria (Cella, Davis, Breitbart, & Curt, 2001; Cella, Peterman, Passik, Jacobsen, & Breitbart, 1998). Six generic symptoms were also retained from the IPQ-R (pain, headaches, dizziness, stiff joints, sore eyes, and upset stomach) so that the identity dimension

would also include some symptoms not specifically related to CRF. Patients with chronic conditions often attribute common symptoms to their illness and the belief that many symptoms are due to an illness has been related to adherence, the use of avoidance coping and emotional expression coping strategies, psychological adaptation and disability (Edwards, Suresh, Lynch, Clarkson, & Stanley, 2001; Kaptein et al., 2008; Moss-Morris & Chalder, 2003). Patients with chronic fatigue syndrome (CFS) in particular often attribute a high number of common symptoms to their illness and engage in symptom focussed coping (Moss-Morris & Chalder, 2003). As CRF has similar diagnostic criteria to CFS and may involve some of the same illness mechanisms (Bennett, Goldstein, Friedlander, Hickie, & Lloyd, 2007) cognitive factors related to symptom attributions and focussing may also be important for CRF.

The structure and response format of Section B were retained; however, the phrase "my illness" was replaced with "my fatigue". The wording of two items was also modified slightly; the item "My treatment can control my illness" was changed to "Treatment can control my fatigue" because patients with CRF often do not receive any treatments specifically for this condition (National Comprehensive Cancer Network, 2010). Furthermore, the item "The symptoms of my illness change a great deal from day to day" was changed to "The severity of my fatigue changes from day to day" because fatigue itself may be seen as a symptom during cancer treatment and this may have led to confusion. No other changes were made to Section B before pilot testing.

Finally, in Section C, items were added to the causes dimension to reflect the contributing factors to CRF outlined by the NCCN (National Comprehensive Cancer Network, 2010). In addition, in the instructions for this section respondents were instructed to think about the "causes and contributing factors to your fatigue" rather than just "the cause of your illness". This change was made because although cancer and/or cancer treatments are thought to initiate the onset of CRF, other factors are thought to contribute to the persistence of fatigue after treatment. Previous research has illustrated that recognising the role of other possible contributing factors, such as psychological attributions, is associated with fatigue severity (e.g., Servaes, Verhagen, et al., 2002c). For this reason, the instructions for Section C also refer to "fatigue" rather than "cancer-related fatigue"; so that respondents also think about possible non-cancer-related contributing factors to their current level of fatigue.

2.2.1.3 Piloting of the adapted IPQ-R. The original item pool was modified based on a pilot study in line with Clark and Watson's (1995) description of the

iterative process of scale development. A small pilot study was carried out to the check the clarity of the items in the adapted IPQ-R and to help reduce the number of the items in the final scale. Twelve post-treatment cancer survivors who self-reported CRF to their oncology care team and had no other medical conditions associated with fatigue were asked to complete the entire adapted IPQ-R and then to provide feedback to the researcher afterwards. Feedback about item clarity and appropriateness was used to guide item selection. For example, the item "My fatigue has had serious economic and financial consequences" was eliminated because participants in the pilot study reported that they did not consider this when asked about the consequences of their CRF. In addition, the range and distribution of correlations between the items intended to measure a particular subscale were examined to address scale homogeneity (Clark & Watson, 1995). Items that did not correlate with the other subscale items or items that performed contrary to theory were eliminated. For example, the item "My actions will have no effect on the outcomes of my fatigue" was eliminated because it did not correlate with any of the other items intended to measure the personal control subscale. A clinical psychologist experienced in the treatment of CRF was asked to check the appropriateness of the remaining items. After piloting the final scale, the IPQ-CRF, consisted of 18 identity items in Section A, 21 items in the Section B (with 3 items for each subscale) and 19 causal items in Section C (see Appendix 1).

2.2.2 Additional measures. Demographic (age, gender, marital and employment status) and medical information (cancer type, treatment, time of diagnosis and treatment, comorbid medical conditions) was obtained through a questionnaire.

2.2.2.1 Fatigue. The Functional Assessment of Cancer Therapy Fatigue (FACT-F) subscale (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997) assessed fatigue severity. The 13-item FACT-F is a unidimensional scale with excellent psychometric properties that has been widely used in a range of cancer populations (Alexander, Minton, & Stone, 2009; Minton & Stone, 2009). A lower score indicates greater fatigue, whereby a score of below 36 indicates significant fatigue.

2.2.3 Procedure. Following receipt of ethical approval (see Appendix 2), participants were recruited through cancer associations and support groups in Ireland and the United Kingdom or through their oncology care team. The study was also advertised on cancer association websites. Cancer patients and survivors who self-reported fatigue were eligible to participate. After giving informed consent (see Appendix 3), participants completed questionnaires on-line or in hard-copy and

returned them using stamped-addressed envelopes. Participants were asked to complete the questionnaires twice so that test-retest reliability could be assessed; those agreeing to the follow-up were either posted questionnaires or e-mailed a link to an on-line version a week after their initial participation. The inclusion criteria were: 1) being at least 18 years of age, 2) previously undergoing or currently undergoing treatment for cancer (excluding non-invasive skin cancer), 3) currently experiencing "significant cancer-related fatigue" (determined by self-report). Individuals who reported fatigue that was attributable to another medical condition were excluded from participation.

Table 2.1 *Demographic characteristics of participants*

Variable	Category	*n* (%)
Method of participation	Online	89 (57%)
	Hard-copy	66 (43%)
Gender	Female	128 (83%)
	Male	27 (17%)
Marital status	Single	36 (24%)
	Married/Long-term partner	112 (73%)
	Widowed	4 (3%)
Employment status	Employed full-time	50 (33%)
	Employed part-time	14 (9%)
	Unemployed	13 (9%)
	Student	5 (3%)
	Housewife	16 (10%)
	Retired	27 (18%)
	Resigned/off work due to illness	27 (18%)
Cancer Type	Breast cancer	44 (28.5%)
	Lymphoma	35 (23%)
	Gynaecological cancer	35 (23%)
	Leukaemia	20 (13%)
	Genitourinary cancer	7 (4.5%)
	Gastrointestinal cancer	5 (3%)
	Other (sarcoma, lung, thyroid, bone, brain tumour)	8 (5%)
Treatment received[a]	Surgery	100 (65%)
	Chemotherapy	120 (78%)
	Radiation therapy	53 (35%)
	Stem cell transplant	6 (4%)
Time since treatment	Active treatment	48 (31%)
	<1 years post-treatment	46 (30%)
	1-2 years post-treatment	22 (14%)
	>2 years post-treatment	39 (25%)
Comorbid medical condition	None	85 (59%)
	1 comorbid condition	31 (22%)
	2-3 comorbid conditions	24 (17%)
	4-5 comorbid conditions	3 (2%)

[a] For this category numbers and percentages represent the total number of people who received each treatment.

2.2.4 Participants. One hundred and fifty-five patients with a variety of cancer diagnoses participated; 12 participants were recruited through an oncology care team, 54 were recruited through cancer support groups, and 89 were recruited through cancer association websites. Table 2.1 describes the sample demographic characteristics. The first 22 participants were not asked to complete follow-up assessments[1]. Of the remaining 133, 97 returned the follow-up questionnaires, 9 had requested not to be re-contacted and 27 did not complete the follow-up giving a response rate of 78%. The mean age was 50 years (*SD* = 12.34 years); the mean time since diagnosis was 2 years and 11 months (*SD* = 43.34 months, *Median* = 19 months). Forty percent of the sample (n = 58) suffered from an additional medical condition. The most common types of conditions reported were high blood pressure (n = 11), asthma (n = 10), hypothyroidism (n = 8), and arthritis, cardiac problems, cholesterol and diabetes (all with n = 5). All other conditions were reported by less than five participants.

2.2.5 Analysis.

2.2.5.1 Structural validity of the IPQ-CRF. The hypothesised factor structure of Section B of the IPQ-CRF at both Time 1 and 2 was tested with CFA using AMOS 7 (SPSS Inc., Chicago, Illinois 60606, US). The hypothesised CFA model specified the items purported to measure timeline acute/chronic and cyclical, consequences, personal and treatment control, illness coherence and emotional representation as indicators of latent factors representing the theoretical illness dimensions. As the chi-square index is an inadequate stand alone fit index, because of its sensitivity to small and large sample sizes (Bentler & Bonett, 1980), different fit indices were used to evaluate the model. The standardised root mean square residual (SRMR), which quantifies the mean absolute value of the correlation residuals, is reported; lower values indicate better model fit, with values below .05 indicating good fit. Model fit was also examined using the comparative fit index (CFI), which approaches 1 for a perfect model fit. Values exceeding .95 indicate a good fit of the model to the data (Hu & Bentler, 1999); however, values greater than .90 are acceptable (Bentler, 1990). Finally, the root mean square error of approximation (RMSEA), a parsimony adjusted index that corrects for model complexity, was examined. Values close to or lower than .05 indicate a close approximate fit (Hu & Bentler, 1999). In addition, configual and metric factorial invariance over time was tested using the steps described by Horn and McArdle (1992).

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[1] due to an administrative error.

Causal attributions can represent a number of different sub-factors, which can vary across different conditions (Moss-Morris et al., 2002). Therefore, in line with previous research (e.g., Moss-Morris et al., 2002), the factor structure underlying Section B of the IPQ-CRF, the causes items, was explored separately using principal components analysis (PCA) with a Varimax rotation. The number of factors was determined by examining the Eigenvalues and the scree plot; item loadings greater than 0.5 were taken to represent a factor.

Section A of the IPQ-CRF, the identity items, was not included in the CFA or PCA because this scale is calculated in a different manner to the other subscales. Psychometric testing of this section is described below.

2.2.5.2 Psychometric properties of the IPQ-CRF identity subscale. The validity and reliability of the identity scale were tested using methods described by Moss-Morris et al. (2002). A paired samples *t* test was used to compare the number of experienced symptoms with the number of symptoms associated with CRF in order to support a conceptual distinction between symptom experience and illness identity. The internal reliability of the identity scale was evaluated using Cronbach's alpha. Finally, the frequency with which each symptom was included in participants' illness identity was investigated as an indicator of the content validity of the symptom list.

2.2.5.3 Psychometric properties of the IPQ-CRF Section B and C subscales. The internal reliability of the subscales was evaluated using Cronbach's alpha for Time 1 and 2. Pearson correlations were used to examine the test re-test reliability of the mean subscale scores across the two timepoints. Correlation coefficients between .40 and .59 were considered fair, between .60 and .74 were considered good, and between .75 and 1.00 were considered excellent (Cicchetti, 1994). Pearson correlations investigated the interrelations among the IPQ-CRF subscales and between the IPQ-CRF subscales and fatigue severity at Time 1 to assess whether these relationships were theoretically consistent. These analyses were used as an indicator of concurrent validity. Regression analysis assessed whether the Time 1 and 2 IPQ-CRF dimensions predicted fatigue severity in line with the CSM, and whether the cognitive representations of CRF could explain the variance in emotional representations (Moss-Morris et al., 2002). Two items (diminished energy and fatigue after physical activity) were dropped from the identity subscale for these analyses to avoid confounding the predictor and outcome variables.

Finally, to examine aspects of external validity, discriminative validity was evaluated using the known-groups method; firstly, by comparing participants on active treatment to cancer survivors who had completed treatment at least one year previously, and secondly, by comparing participants with the most severe fatigue (score ≤10 on the FACT-F) to participants with nonclinical levels of fatigue (score >35 on the FACT-F) on the IPQ-CRF dimensions at Time 1 using independent samples *t* tests. Based on the CSM, participants with severe fatigue were expected to have more negative CRF representations than those with nonclinical levels of fatigue. In line with previous research (e.g., comparison of acute and chronic pain patients; Moss-Morris et al., 2002), cancer survivors with persistent fatigue were expected to have more negative CRF representations than participants still on active treatment. However, no differences were expected between cancer survivors and patients on active treatment on the control dimensions or the treatment-related causal attributions. As fatigue is a widely recognised side-effect of cancer treatment and patients generally expect to experience this symptom during treatment (Hofman et al., 2007), it was hypothesised that participants on active treatment would attribute their fatigue to treatment-related factors and would therefore also report that they have little control over CRF. In line with previous studies, it was expected that fatigued cancer survivors in this study would also endorse treatment-related causal attributions (Gielissen, Verhagen, et al., 2007) and have low control perceptions (e.g, Servaes et al., 2007).

2.3 Results

2.3.1 Structural validity and internal reliability.

2.3.1.1 CFA of the IPQ-CRF Section B subscales. CFA of the IPQ-CRF items at both Time 1 and 2 showed that a seven-factor solution fit the data adequately. For Time 1, although the $\chi^2(168) = 256.27$, $p < .001$ was statistically significant, the goodness of fit indexes indicated satisfactory fit (CFI = 0.94; RMSEA = 0.059; 95% CI: 044-.073) and the average of the residuals was small (SRMR = .07). Similarly, the Time 2 $\chi^2(168) = 239.53$, $p < .001$ was statistically significant; however, the goodness of fit indexes indicated satisfactory fit (CFI = 0.94 RMSEA = 0.061; 95% CI: .046-.076) and the average of the residuals was small (SRMR = .09). The standardised factor loadings at Time 1 and 2 are displayed in Table 2.2 with the internal reliability of each latent factor.

To test for factorial invariance across time, a model in which the loadings (factor loadings, factor variances, factor covariances, and error variances) for

corresponding items at Time 1 and 2 were constrained to be equal was compared with an unconstrained model, in which loadings were freely estimated. The two models were not statistically different, χ^2 difference (41*df*) = 41.55, *p* = ns, supporting configual and metric factorial invariance (Byrne, 2009; Horn & McArdle, 1992).

Table 2.2 *Standardized factor loadings of the IPQ-CRF items and internal reliabilities of the subscales for Time 1 and Time 2*

IPQ-CRF items and subscales	Time 1 β	Time 2 β
Time line (T1 Cronbach α= .83; T2 Cronbach α= 86)		
My fatigue is likely to be permanent rather than temporary	.78	.85
My fatigue will last a long time	.76	.79
My fatigue will improve in time (r)	-.80	-.83
Timeline Cyclical (T1 Cronbach α= .79; T2 Cronbach α= .77)		
The severity of my fatigue changes from day to day	.72	.96
My fatigue is unpredictable	.73	.72
I go through cycles in which my fatigue gets better and worse	.80	.66
Consequences (T1 Cronbach α= .71; T2 Cronbach α= .82)		
My fatigue is a serious condition	.83	.75
My fatigue has had major consequences for my life	.78	.90
My fatigue causes difficulties for those who are close to me	.53	.59
Personal Control (T1 Cronbach α= .78; T2 Cronbach α= .77)		
What I do can determine whether my fatigue gets better or worse	.63	.65
The course of my fatigue depends on me	.88	.96
I have the power to influence my fatigue	.86	.78
Treatment Control (T1 Cronbach α= .74; T2 Cronbach α= .74)		
The negative effects of my fatigue can be prevented by treatment	.90	.92
Treatment can control my fatigue	.94	.90
There is nothing which can help my fatigue (r)	-.56	-.58
Coherence (T1 Cronbach α= .87; T2 Cronbach α= .84)		
My fatigue is a mystery to me (r)	.89	.88
My fatigue doesn't make any sense to me (r)	.92	.95
I have a clear picture or understanding of my fatigue	-.70	-.65
Emotional representation (T1 Cronbach α= .87; T2 Cronbach α= .81)		
I get depressed when I think about my fatigue	.86	.77
When I think about my fatigue I get upset	.93	.84
Having this fatigue makes me anxious	.70	.71

Note. T1 = Time 1, T2 = Time 2, β = Standardised factor loading, (r) = item reverse scored.

2.3.1.2 EFA of the IPQ-CRF causal attributions subscales. As causal attributions can comprise different sub-factors specific to a given illness, the factor structure underlying the causes items was explored separately using PCA. Eight items were excluded because of low factor loadings or because they loaded highly on to more than one factor. The factor analysis of the remaining items produced 4 factors with Eignevalues over 1, which accounted for 67% of the variance (see Table 2.3 for item loadings). The factors were labelled *psychological, behavioural, cancer treatment-related,* and *unchangeable attributions* and they accounted for 23%, 18%, 14%, and 12% of the total rotated variance respectively. The internal reliability of the causal attribution subscales are displayed in Table 2.3.

Table 2.3 *PCA of causal attributions with Varimax rotation and Cronbach's alpha values at Time 1 and Time 2 for the retained causes subscales*

	Component			
	1	2	3	4
Psychological attributions (T1 α= .80; T2 α= .78)				
Stress	**.837**	.029	.032	-.059
Distress (e.g., anxiety or depression)	**.811**	.264	-.059	-.064
Mental attitude (e.g., thinking about life negatively)	**.705**	.195	.003	.123
Family problems or worries	**.656**	.240	-.214	.160
Sleep disturbances	**.584**	-.100	.116	.129
Behavioural attributions (T1 α= .76; T2 α= .67)				
Decreased physical fitness	.026	**.895**	.122	.024
Decreased activity	.108	**.883**	.039	.113
My diet	.296	**.590**	-.142	.060
Cancer treatment attributions (T1 α= .70; T2 α= .68)				
Side-effects from my cancer/my cancer treatment	.056	-.039	**.896**	.017
Cancer Treatment	-.070	.079	**.891**	.038
Unchangeable attributions (T1 α= .58; T2 α= .43)				
Hereditary - it runs in my family	.000	.057	-.033	**.843**
Poor medical care in the past	.167	.095	.087	**.799**

Note. T1 = Time 1, T2 = Time 2.

2.3.1.3 Content validity and internal reliability of the identity subscale. A significant difference was found, $t(125) = 5.40$, $p < .001$, between the number of symptoms experienced ($M = 11.44$, $SD = 4.11$) and the number of symptoms associated with CRF ($M = 10.29$, $SD = 4.23$). The frequency with which each symptom was included in participants' illness identity was investigated as an indicator of the content validity of the symptom list. 'Diminished energy/increased need to rest' was most frequently associated with CRF (93%), followed by 'fatigue after physical activity that

lasts several hours' (74%). The remaining 16 symptoms were endorsed by more than 50% of participants. The internal consistency of the illness identity subscale was .87.

2.3.2 Intercorrelations among the IPQ-CRF subscales and causal attributions. Moderately strong, significant correlations were observed among the IPQ-CRF dimensions and causal attribution (see Table 2.4). Significant, positive correlations were observed among the identity, timeline-acute/chronic, consequences and emotional representations dimensions. Identity was also positively correlated with psychological, treatment, and unchangeable causal attributions. Participants with higher timeline cyclical scores were more likely to perceive severe consequences and have lower illness coherence. Participants who had higher illness coherence were less likely to have negative emotional representations and more likely to have higher personal control beliefs. Treatment control was significantly correlated with personal control and unchangeable causal attributions. Significant, positive correlations were observed among psychological, behavioural and unchangeable casual attributions. Participants who held psychological casual attributions were more likely to have higher perceived personal control but a more negative emotional representation. Behavioural causal attributions were also significantly associated with personal control. Participants who had treatment-related causal attributions were more likely to hold severe consequence beliefs.

2.3.3 Test-retest reliability. Most of the IPQ-CRF dimensions showed good test-retest reliability (see Table 2.4) with correlations ranging from .54 to .78. Treatment control and unchangeable causal attributions were the only dimensions with a test re-test correlation of less than .6.

2.3.4 Relationships between the IPQ-CRF subscales and fatigue. Several IPQ-CRF dimensions had moderate to strong correlations with fatigue severity (see Table 2.4). The strongest correlations were between fatigue and illness identity, consequences and emotional representations. Participants with more severe fatigue were more likely to have a strong illness identity, chronic time-line perceptions, more severe perceived consequences, lower illness coherence, and more negative emotional representations. More severely fatigued participants were also more likely to have psychological, unchangeable and treatment-related causal attributions.

Table 2.4 *Correlations among the IPQ-CRF dimensions and causal attribution subscales at Time 1 and correlations between the IPQ-CRF dimensions and causal attribution subscales over the two timepoints and with fatigue severity*

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10	11.	Test re-test *r*	Fatigue severity
1. Illness identity	-											.78**	-.63**
2. Timeline acute/chronic	.29**	-										.83**	-.32**
3. Timeline cyclical	.17	-.09	-									.61**	-.07
4. Consequences	.50**	.46**	.17*	-								.70**	-.64**
5. Personal control	-.05	-.09	.15	-.16	-							.60**	.14
6. Treatment control	.01	-.06	.03	-.06	.37**	-						.58**	-.06
7. Illness coherence	-.16	.01	-.32**	-.13	.29**	.02	-					.76**	.30**
8. Emotional representation	.48**	.22**	.08	.47**	-.14	.03	-.39**	-				.66**	-.53**
9. Psychological causes	.32**	.16	.03	.03	.18*	.10	-.09	.32**	-			.74**	-.24**
10. Behavioural causes	.08	-.07	.12	.00	.21*	.11	-.01	.07	.38**	-		.60**	-.08
11. Cancer treatment causes	.26**	.09	.06	.20*	-.11	.03	.08	.05	-.08	.01	-	.62**	-.18*
12. Unchangeable causes	.22**	.01	-.01	.12	.13	.25**	-.06	.21*	.35**	.24**	.02	.54**	-.23**

*$p < .05$, **$p < .01$.

The IPQ-CRF dimensions at Time 1 accounted for 64% of the variance in fatigue severity ($F(12, 88) = 15.71, p < .001$) and 54% of the variance in fatigue severity ($F(12, 58) = 7.73, p < .001$) at Time 2. Identity and consequences were significant predictors at both timepoints, and psychological causal attribution was significant at Time 2 (Table 2.5). The IPQ-CRF cognitive dimensions accounted for 37% of the variance in emotional representation ($F(12, 88) = 5.94, p < .001$), whereby coherence and psychological causal attributions made significant contributions to the model (see Table 2.5).

Table 2.5 *Illness representations as predictors of fatigue severity at Time 1 and Time 2 and emotional representation at Time 1*

	Fatigue severity Time 1			Fatigue severity Time 2			Emotional representation		
	B	SE B	Beta	B	SE B	Beta	B	SE B	Beta
Illness identity	-0.75	0.18	-.33***	-0.86	0.26	-.36***	0.04	0.03	.15
Timeline acute/chronic	0.15	0.67	.02	0.92	1.11	.09	-0.09	0.11	-.09
Timeline cyclical	0.49	0.82	.04	1.93	1.33	.16	-0.08	0.13	-.06
Consequences	-5.1	0.95	-.47***	-6.04	1.47	-.53***	0.22	0.17	.17
Personal control	1.00	0.89	.09	1.03	1.29	.09	-0.04	0.14	-.03
Treatment control	-0.87	0.87	-.07	-2.24	1.36	-.16	-0.02	0.14	-.01
Illness coherence	0.52	0.74	.05	0.71	1.05	.07	-0.42	0.11	-.37***
Psychological causes	-1.39	0.70	-.15	-2.78	0.98	-.29*	0.23	0.11	.20*
Behavioural causes	0.75	0.61	.08	-0.38	0.91	-.04	-0.06	0.10	-.05
Cancer treatment causes	-0.40	0.78	-.03	0.01	1.06	.00	-0.01	0.12	-.01
Unchangeable causes	-0.22	0.63	-.02	0.78	0.93	.08	0.08	0.10	.07
Emotional representation	-0.85	0.68	-.10	0.07	0.98	.01	-	-	-
Fatigue severity	-	-	-	-	-	-	-0.02	0.02	-.17

*$p < .05$, **$p < .01$, ***$p < .001$.

2.3.5 Known group validity. Cancer survivors had significantly longer timeline perceptions, more severe perceived consequences, lower illness coherence, and more negative emotional representations than participants still on active treatment (see Table 2.6). The most severely fatigued participants had a significantly higher illness identity, a more chronic timeline perception, more severe perceived consequences, and more negative emotional representations than participants with nonclinical levels of fatigue (see Table 2.6).

Table 2.6 *Comparison between (1) participants on active treatment and cancer survivors and (2) participants with severe fatigue and participants with nonclinical levels of fatigue on the IPQ-CRF subscales*

	1)			2)		
	Active treatment *M (SD) n*=48	Cancer survivors *M (SD) n*=61	*t*	Severe fatigue *M (SD) n*=16	Nonclinical fatigue *M (SD) n*=16	*t*
Illness identity	8.24 (3.69)	9.38 (4.45)	-1.27	11.71 (2.73)	3.25 (3.01)	6.75***
Timeline chronic	2.83 (0.98)	3.35 (0.98)	-2.72**	3.85 (0.84)	2.29 (0.95)	4.79***
Timeline cyclical	3.80 (0.85)	3.88 (0.89)	-0.44	3.54 (0.90)	3.49 (0.74)	0.18
Consequences	3.04 (0.98)	3.68 (0.87)	-3.56***	4.25 (0.86)	2.33 (0.87)	6.08***
Personal control	3.30 (0.87)	3.16 (0.88)	0.86	2.83 (0.73)	3.26 (1.06)	-1.31
Treatment control	3.18 (0.77)	3.05 (0.79)	0.91	3.27 (0.82)	3.14 (0.85)	0.42
Illness coherence	3.62 (1.06)	3.15 (1.03)	2.28*	3.23 (1.02)	3.90 (0.86)	-1.95
Emotional representations	2.84 (1.05)	3.46 (1.08)	-3.00**	3.98 (0.83)	2.19 (1.04)	5.23***
Psychological causes	3.11 (0.99)	3.29 (0.95)	-0.96	3.56 (0.87)	2.77 (1.02)	2.25*
Behavioural causes	3.02 (1.13)	2.81 (1.11)	0.94	2.96 (1.19)	2.42 (0.93)	1.31
Cancer treatment causes	4.47 (0.69)	4.42 (0.82)	0.28	4.50 (0.76)	4.12 (0.71)	1.38
Unchangeable causes	2.57 (1.06)	2.52 (0.93)	0.23	2.89 (0.84)	2.15 (1.34)	1.73

*$p < .05$, **$p < .01$, ***$p < .001$.

2.4 Discussion

The present study developed and evaluated a version of the IPQ suitable for use with patients who suffer from CRF. CFA demonstrated acceptable fit with the data supporting the proposed theoretical structure of the scale. To date few studies have used a CFA approach to test the factor structure of the IPQ and none have adequately adapted the IPQ for CRF; thus, the present findings make an important contribution to the IPQ literature and present a useful and psychometrically robust measure for use in CRF research.

2.4.1 IPQ-CRF dimensions: CFA. The IPQ-CRF items loaded well onto the specified CSM constructs in the CFA; only two items had loadings below .60. It is possible that the item "There is nothing which can help my fatigue" did not load as highly onto the treatment control factor because it does not explicitly address the influence treatment has on fatigue and thus respondents may have considered other non-treatment related strategies that could help CRF. Similarly, the item "My fatigue causes

difficulties for those who are close to me" may not be as appropriate for the consequences subscale because it focuses on the impact of CRF on others and not on one's own life. It is recommended that the suitability of these items be investigated further and that possible alternatives are considered. For example, the items "Treatment can reduce my fatigue" and "My fatigue has not had much effect on my life" may be more consistent with the treatment control and consequences subscales, respectively. Nevertheless, the data support the reliability of the IPQ-CRF; the scale's dimensions demonstrated excellent internal consistency and the test re-test reliability of most of the subscales was satisfactory.

2.4.2 Identity and causal attribution subscales. The findings support the suitability of the amended identity subscale; all of the items formed part of the illness identity of some participants and a significant difference was found between the number of symptoms experienced and illness identity. Support was found for psychological and behavioural causal dimensions similar to those reported previously (Hagger & Orbell, 2005; Moss-Morris et al., 2002; Wittkowski, Richards, Williams, & Main, 2008) and a cancer treatment-related causal attribution dimension emerged. Although a fourth factor ('unchangeable causes') emerged, the reliability coefficients for this construct were low and therefore it should be treated with caution.

2.4.3 Psychometric evaluation of the IPQ-CRF subscales. Correlations among the IPQ-CRF subscales revealed relationships in line with the CSM. As in previous studies (Hagger & Orbell, 2005; Moss-Morris et al., 2002; Wittkowski et al., 2008), emotional representation was strongly related to several cognitive dimensions (e.g., identity, timeline acute/chronic, consequences, and illness coherence) supporting the idea that there is some conceptual overlap between the cognitive and emotional representations of an illness. Nevertheless, the intercorrelations among the IPQ-CRF dimensions support the empirical distinction between these constructs. For example, the distinctions between the personal and treatment control subscales and the timeline acute/chronic and cyclical subscales proposed by Moss-Morris et al. (2002) were upheld. The pattern of correlations among the subscales is also largely in line with previous findings (e.g., Hagger & Orbell, 2005; Moss-Morris et al., 2002). For example, significant positive intercorrelations were found between chronic timeline perceptions, negative perceived consequences and emotional representations, and positive relationships were observed between the attribution subscales and identity.

The validity of the IPQ-CRF was further supported by comparisons between different subgroups of participants. Participants with the most severe fatigue had significantly more negative representations of CRF than participants with nonclinical levels of fatigue suggesting that illness beliefs can discriminate between these subgroups. In line with expectations, cancer survivors had significantly more negative beliefs regarding the timeline, consequences, illness coherence, and emotional representation of CRF than participants still on active treatment. However, no significant differences were observed between these subgroups on the control or the causal attribution dimensions. Although cancer treatments are known to cause fatigue during active treatment, there is little evidence that they continue to play a role in causing persistent CRF post-treatment (Gielissen, Verhagen, et al., 2007) and greater endorsement of such somatic attributions by cancer survivors has been associated with more severe fatigue (Gielissen, Verhagen, et al., 2007; Servaes, Verhagen, et al., 2002c). This association between treatment-related casual attributions and more severe fatigue was also found in the current study. Thus, while treatment-related attributions during cancer treatment are in line with scientific evidence, such attributions can be maladaptive after the completion of treatment. It is also interesting that no overall difference was found in personal control between participants on active treatment, when fatigue is known to be largely attributable to treatment, and those post-treatment, when factors under patients' own control can undoubtedly contribute to fatigue (e.g., sleeping patterns, activity levels).

Many moderately large significant relationships were observed between fatigue severity and other IPQ dimensions, supporting the idea that the way patients think about their fatigue can impact illness outcomes. Specifically, these findings suggest that patients with stronger illness identities, longer timeline perceptions, more serious perceived consequences, lower illness coherence, and higher emotional representations are more likely to have severe fatigue. Overall, participants' illness representations explained a substantial proportion of the variance in fatigue severity and emotional distress regarding CRF. As increasing numbers of people are living with and recovering from cancer, due to earlier detection and more effective treatments, more emphasis needs to be placed on understanding, preventing and treating the long-term consequences of treatment like fatigue. Although fatigue may start as a side-effect of cancer and/or its treatment, it is clear that it can develop into a major health issue in its own right that can have an extremely negative and long-term impact on cancer

survivors' quality of life (National Comprehensive Cancer Network, 2010). The value of investigating belief-systems in order to understand the development of similar psychosomatic conditions, such as CFS, has been illustrated (Hagger & Orbell, 2003). The current study suggests that adopting such a self-regulatory framework to understand the development of CRF, or indeed other chronic conditions that are initiated by medical treatments, would be beneficial. Future longitudinal research should investigate whether representations of CRF before and after cancer treatment can predict the maintenance of CRF post-treatment. If cognitive predictors of persistent CRF can be reliably identified then early targeted interventions can be developed to challenge the formation of maladaptive beliefs, and thereby help to prevent the development of chronic CRF in cancer survivors.

2.4.4 Limitations. The study sample size was small and less than 20% of the sample was male, which limits the generalisability of the findings. As recruitment was carried out on-line and through cancer centres it is possible that there was a sampling bias; those with more problems associated with fatigue may have been more likely to come across the study and participate. Furthermore, participants recruited through cancer support groups may have had different representations of CRF as a result of their involvement in such groups.

Almost a third of the sample was still on active treatment and therefore may not yet have developed concrete representations of their CRF. As beliefs regarding fatigue are likely to play a greater role post-treatment, when the biological effects of treatment are no longer as influential, additional research with greater numbers of cancer survivors is necessary to replicate and expand on these findings. This may also explain why some IPQ dimensions had low test-retest reliability; when participants who were less than a year post-treatment were excluded from the analyses the test-retest reliability improved. Thus, while the IPQ-CRF could still be useful for exploring the illness representations of fatigued cancer patients during and shortly after cancer treatment, these representations may not be as stable as those of persistent CRF sufferers. Furthermore, as this was the first study to examine patients' causal attributions of CRF, and as many causal items did not fall into meaningful categories, the stability of the causal dimensions should also be investigated.

Additional psychometric testing of the IPQ-CRF is warranted. The piloting of the scale was limited as only 12 participants took part in the initial testing of the scale and only one expert was asked to check the appropriateness of the items. Qualitative

respondent feedback from a larger sample and think-aloud protocols would be beneficial to further assess content validity and response process validity. The content validity of the identity scale could also be explored by testing whether respondents routinely report any other symptoms of CRF not included in the current scale. The current study used correlations among the IPR-CRF subscales and between the subscales and fatigue as an indicator of concurrent validity in the absence of another scale that measures the same constructs. Predictive criterion validity could be assessed in future research to test whether beliefs measured by the IPQ-CRF are predictive of fatigue outcomes. Finally, the test-retest interval in the current study was very short. Future research should explore whether the fatigue representations of long-term cancer survivors with fatigue are stable over longer follow-up periods.

All participants in the current study self-reported that they had "cancer-related" fatigue. There are many different clinical or medical factors, such as anaemia, pain, and the presence of comorbidities, that could cause or contribute to the fatigue experienced by cancer patients (National Comprehensive Cancer Network, 2010). Although participants in the current study were asked whether they had any other medical conditions, and some of these were indeed related to fatigue, it was not possible to ascertain whether the fatigue they experienced was caused entirely or in part by such factors. Finally, a measure of depression was not included in the current study to minimise participant burden. However, given the strong association between depression and fatigue, and the potential impact depression might have on cognitions regarding fatigue (Clark, 2001), future CRF studies should explore the relationship between the CSM dimensions and depression.

2.4.5 Conclusion. To effectively address and manage cancer-related fatigue in clinical practise it is important to first of all assess and treat any potential contributing factors, such as anaemia, poor nutrition, pain, and emotional distress (National Comprehensive Cancer Network, 2010). However, this paper argues that it is also of value to ascertain and address patients' own beliefs regarding the nature and causes of their fatigue. The CRF-IPQ was developed for this purpose and the results of the initial psychometric testing of this scale, described in the present study, are promising. As the initial item pool was based on a robust pre-existing measure, the conceptual basis for the subscales is clear. The structural validity of the scale was supported by examining the dimensionality and internal consistency of the items. Confirmatory approaches supported the *a priori* hypothesised factor structure of the scale at two assessment

points. In addition, formal assessment of measurement invariance over time was supported. Finally, the present study provided some evidence of discriminative validity; however, as Clark and Watson (1995) point out, establishing external validity is an ongoing process and further psychometric testing of the CRF-IPQ is necessary.

The CRF-IPQ may be useful clinically to help identify whether patients with CRF have inaccurate or unhelpful representations of their fatigue. Identifying such beliefs is important for understanding the factors that may contribute to inappropriate coping behaviours and the persistence of CRF post-treatment. However, further research is necessary to explore the relationship between patients' representations of their CRF, their coping behaviours, and long-term fatigue outcomes.

Chapter 3: The Development and Persistence of Fatigue in Patients Treated for Cancer: A Review of the Literature.

"The fatigue I am experiencing does not care about positive thinking!! :) I'm too tired to exercise much now because I don't have the energy despite trying to keep going. In short, the fatigue is definitely not just in my mind!" – Laura

Cancer-related fatigue (CRF) is an extremely common and potentially long-term side-effect of cancer treatment, whose aetiology is still not adequately understood. The purpose of this chapter is to review the existing literature on the prevalence of CRF and the trajectory of this side-effect over time, outline the potential causes of CRF, and consider the evidence for proposed contributing factors that may maintain fatigue after cancer treatment. Furthermore, the theoretical framework for the thesis is presented.

3.1 The Prevalence and Severity of Cancer-Related Fatigue over the Cancer Trajectory

Fatigue is the most common side-effect of cancer treatment, affecting virtually all patients treated with multimodel therapies, intense or dose-dense treatment protocols (National Comprehensive Cancer Network, 2010). Studies that assessed fatigue severity during cancer treatment and included a comparison group of healthy controls have consistently reported that cancer patients have significantly higher levels of fatigue during active treatment than the general population (Holzner et al., 2002; Jacobsen, Hann, et al., 1999; Tchen et al., 2003). In addition, research suggests that many patients experience heightened fatigue even before their surgical or adjuvant treatment (Ancoli-Israel et al., 2006; Jacobsen, Hann, et al., 1999; Spichiger et al., 2011). For example, Nieboes et al. (2005) reported that around 20% of the breast cancer patients in their study were fatigued before the start of chemotherapy. Fatigue prior to cancer treatment could be related to the disease itself, prior surgical treatment or psychological distress related to the treatment and diagnosis (Jacobsen, Hann, et al., 1999).

While most studies on fatigue and cancer have focussed on fatigue during treatment, fatigue also remains an important problem for disease-free cancer survivors (Servaes, Verhagen, & Bleijenberg, 2002a). In a review of the literature, Prue et al. (2006) reported that CRF continues to affect between 19 and 38% of patients after treatment has been completed, and research highlights significantly greater levels of fatigue in cancer survivors compared to the general population (Andrykowski et al.,

1998; Fossa, Dahl, & Loge, 2003; Minton & Stone, 2008). Longitudinal studies also support the continued impact of fatigue long after treatment. For example, Bower et al. (2006) found that the prevalence of fatigue in breast cancer survivors remained stable at around 33% between 1-5 years and 5-10 years after diagnosis, whereby 21% of the sample demonstrated a persistent fatigue profile. Some evidence suggests that fatigue can actually worsen over time in cancer survivors; Goedendorp et al. (2011) reported that the severity of fatigue increased during a post-treatment follow-up of between 4 and 42 months for patients treated with chemotherapy.

Although the research carried out to date illustrates that fatigue is an important problem both during and after cancer treatment, the prevalence rates reported in these studies varies widely. For example, according to Prue et al. (2006), fatigue affects between 39% and >90% of patients undergoing cancer treatment while Servaes et al. (2002a) reported rates between 25% and 75%. Variation in such rates may be due to the heterogeneity of the study samples, which differ according to cancer and treatment type, disease stage and assessment times. However, even studies on similar patient groups after the completion of treatment have reported widely different prevalence figures. For example, studies on breast cancer survivors at least one year post-treatment have reported fatigue prevalence rates of 20% (Nieboer et al., 2005), 31% (Lindley, Vasa, Sawyer, & Winer, 1998) 34% (Bower et al., 2006; Cavalli Kluthcovsky et al., 2011), 41% (Meeske et al., 2007) and 56% (Okuyama et al., 2000). While these studies differ to some extent on sample characteristics and follow-up timepoints, variation in the percentage of fatigued patients reported are also likely to be due to factors such as the assessment tools used to measure fatigue and the cut-off values used to define fatigue caseness. Most studies have used self-report scales of fatigue that vary in terms of the dimensions of fatigue they assess and in terms of the quality of their psychometric properties (Minton & Stone, 2009). Diagnostic criteria for CRF have been established (Cella et al., 2001); however, prevalence rates based on these also vary widely due to the lack of consistency in how they are applied (Donovan, McGinty, & Jacobsen, 2012). Differences in measurement of fatigue and sampling between studies thus make it difficult to compare across cross-sectional studies to identify how fatigue severity and prevalence varies across the cancer trajectory and between different treatment protocols and patient groups.

A number of longitudinal studies have documented the severity and/or prevalence of fatigue prospectively from before treatment to post-treatment follow-up.

Nieboer (2005) found no differences in fatigue severity or prevalence (~20%) in patients treated with chemotherapy for breast cancer between assessments before the start of chemotherapy and 1-, 2-, and 3- year follow-ups. Conversely, Andrykowski et al. (2005) reported that the prevalence of CRF increased from 10% before chemotherapy to 26% after treatment, whereby 5% of the sample demonstrated persistent fatigue. In this study a clinical interview was used to determine whether patients met the CRF diagnostic criteria rather than a self-report scale of fatigue. Goldstein (2012) reported fatigue prevalence rates of 24% after surgery, 42% after adjuvant treatment, 19% 6 months post-treatment, 15% one year post-treatment and 21% five years post-treatment in patients treated for early stage breast cancer and assessed using a self-report fatigue scale. CRF was a persistent problem for 11% of participants 6 months after treatment and continued for 6% of the sample 12 months after treatment. Thus, although differences in CRF prevalence rates are still apparent between longitudinal studies, this research design can give insight into changes in fatigue severity and prevalence over the cancer trajectory and help to quantify the problem of persistent CRF in cancer survivors.

3.2 The Causes of Cancer-Related Fatigue

The cause of CRF is complex and is likely to involve a number of different contributing factors rather than any single mechanism. Furthermore, there is a temporal aspect to its development and the factors that play a role may vary between individuals. Research implicates numerous biological, psychological, social, and behavioural factors as well as sleep disturbances in the aetiology of CRF, many of which may also help to exacerbate or perpetuate existing fatigue. Elucidating the precise aetiology of CRF is difficult, not only because of the wide range of factors that may be involved, but also because many of these factors are interrelated themselves and may reciprocally influence one another.

3.2.1 Theoretical models for understanding CRF. A number of different models for understanding CRF have been proposed that identify diverse contributing factors to CRF and act as a guide for variable selection for researchers seeking to investigate the aetiology of fatigue in cancer patients (e.g., see Payne, 2004). The two models that are most frequently cited as theoretical frameworks for empirical studies of CRF are Piper's (1987) integrated fatigue model and Winningham et al.'s (1994) psychobiological-entropy model. The integrated fatigue model identifies many different factors that are thought to contribute to CRF, such as innate host factors, and

patterns relating to psychological factors, social factors, symptoms, treatment, disease, sleep/wake and activity/rest cycles (Piper et al., 1987). The model has been cited as the conceptual framework for many studies on CRF (e.g., Berger et al., 2008; Berger & Walker, 2001; Meeske et al., 2007; Von Ah, Kang, & Carpenter, 2008). However, although it acknowledges the multifactorial nature of CRF and overlap among contributing factors, the model does not infer temporal relationships between concepts and it is unclear how these various factors influence one another and fatigue. Although descriptive models make an important contribution by identifying factors that are pertinent to health outcomes, content specific process models that outline "how things happen" are required to examine the mechanisms underlying such associations (Leventhal, Musumeci, & Contrada, 2007, p. 381).

Winningham et al.'s (1994) psychobiological-entropy model explicitly acknowledges temporal relationships between contributing factors to CRF and provides a framework for understanding how fatigue can develop over time in cancer patients. A combination of pre-existing conditions, environmental influences, cancer and cancer treatments are thought to lead to reductions in physical activity, which results in reduced energy capacity and, subsequently, decreased functional status and fatigue in a self-perpetuating cycle that can ultimately result in disability. Thus, the importance of balancing activity and rest patterns is emphasised; however, crucially, the model explicitly acknowledges that fatigue can be a secondary symptom of cancer that manifests as a result of an individual's responses to cancer and its associated effects. Nevertheless, the model's focus on a select number of predictors and the relationships between them means that it does not fully account for the complex, multifactorial nature of CRF. For example, it does not adequately consider the role of cognitive processes in post-cancer fatigue.

More recently, researchers (e.g., Andrykowski et al., 2010; Servaes et al., 2007) have started to approach CRF from a cognitive-behavioural perspective. For example, Donovan et al. (2007) investigated whether catastrophising as a cognitive factor and physical activity as a behavioural factor could help to perpetuate fatigue following breast cancer treatment. Cognitive-behavioural models have been developed to explain a number of health conditions and symptoms with a multifactorial aetiology, including fatigue in multiple sclerosis (van Kessel & Moss-Morris, 2006) and chronic fatigue syndrome (Deary et al., 2007; Knoop et al., 2010; Wessely, Hotopf, & Sharpe, 1998). The cognitive-behavioural perspective offers a broad theoretical framework that

captures a wide variety of factors that might contribute to an illness or symptoms and, furthermore, outlines how such contributing factors might interact with one another to maintain symptoms over time. While the importance of patients' beliefs and the role that cognitions play in perpetuating symptoms is central to this approach, cognitive-behavioural models also subsume biological, psychological and behavioural contributing factors in an integrated way, helping to structure thinking about the causal mechanisms underlying symptoms. As the roles of different contributing factors in initiating and perpetuating symptoms are explicitly considered, cognitive-behavioural models propose pathways of influence that can be tested empirically.

3.2.1.1 A cognitive-behavioural model of CRF. The cognitive-behavioural model presented in *Figure 3.1* outlines the theoretical framework that was used in the current thesis. The model distinguishes between the factors that may predispose individuals to develop more severe fatigue in response to cancer and/or cancer treatments and the factors that could precipitate and perpetuate fatigue in cancer patients and survivors. This structure is in line with research evidence on the predictors of fatigue at various stages of the cancer treatment trajectory (Wang, 2008) and findings supporting different intervention approaches depending on a patient's treatment status (National Comprehensive Cancer Network, 2012a). The model also incorporates a wide variety of biological, psychological, behavioural and cognitive contributing factors that have been linked to CRF and synthesizes the perspectives of different explanatory models that have been put forward to explain fatigue associated with cancer. Individual characteristics, such as a history of a depressive disorder, the presence of comorbidities, trait anxiety, or high BMI, are thought to predispose patients to experience more severe or persistent fatigue in response to cancer. Such factors are similar to the innate host factors identified in Piper's (1987) fatigue model. Disease-related factors and/or acute treatment effects (e.g., inflammation, HPA-dysregulation, anaemia or pain) are proposed as the initiating factors that trigger the onset of fatigue. Finally, patients' cognitive, behavioural, emotional and physiological responses to symptoms, as well as interactions among these responses, are thought to maintain fatigue in a self-perpetuating cycle after the acute effects of cancer and cancer treatments have subsided. As an example of this, a patient may become physically deconditioned due to treatment-related fatigue and decreased activity levels during treatment. The sensation of fatigue or aches and pains may be distressing and lead to worrying thoughts about disease worsening or the belief that more rest is needed.

Excessive rest and low activity levels may contribute further to physical deconditioning and fatigue and consequently greater distress. Emotional distress might also contribute to sleep disturbances and physiological changes that could also exacerbate fatigue. Thus, after cancer treatment is completed and the impact of cancer/treatment-related causes of fatigue is reduced, these cognitions, emotions, behaviours and physiological responses remain and help to maintain one another as well as the fatigue.

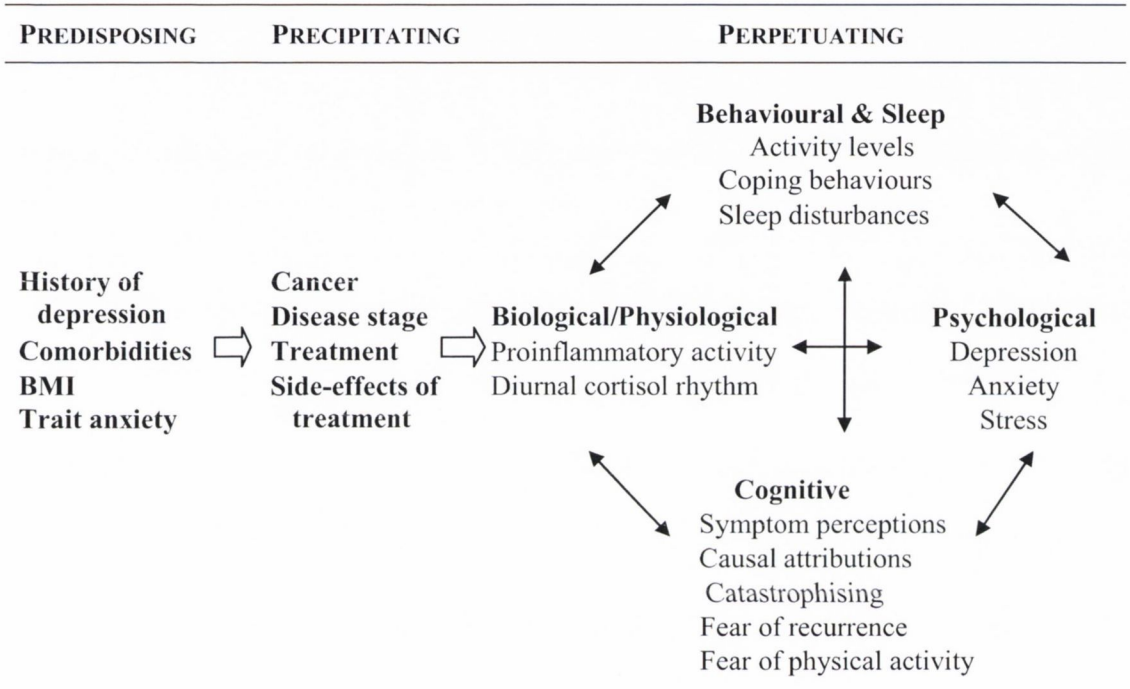

Figure 3.1. Cognitive-behavioural model of CRF with multidimensional and multidirectional contributing factors.

This model of CRF thus integrates the diversity of factors that are identified in Piper's (1987) fatigue model. For example, it acknowledges how activity/rest cycles and psychological response patterns can impact on fatigue while also incorporating potential cancer and treatment-related causes. However, it explicitly considers how such factors might influence one another and fatigue over time by applying a psychological structure that can be used to guide further research and interventions for CRF. Equally, Winningham's proposed system of influences between the factors that could lead to reductions in physical activity, deconditioning, and fatigue can be subsumed under the model. For example, the idea that pre-existing conditions and the effects of cancer and cancer treatments could act in combination to lower activity levels and decrease functional status is consistent with this way of thinking about CRF.

However, the model also allows for alternative pathways through which fatigue might develop and persist that are independent of activity levels. Thus, individual differences in the mechanisms underlying CRF are permitted using this framework; by identifying multiple potential pathways of influence, the model accounts for the finding that not all individuals with CRF experience each of the factors linked to CRF, such as symptoms of depression, sleeping problems and low levels of activity.

The cognitive-behavioural model of CRF accounts for the complexity of the symptom, the multitude of different factors that have been associated with its development and the often conflicting findings that have emerged from studies based around different treatment timepoints and different samples. Although the framework is very broad, it helps to structure the existing research evidence and theories of CRF in an integrated and coherent way and permits the role of new factors to be added and evaluated. The model can thus be used to guide research on how different contributing factors might play a role in CRF based on the proposed system of interrelations.

The current thesis used this integrative cognitive-behavioural model as a conceptual framework for the research and analyses presented. The aim of the thesis was not to test the model presented in *Figure 3.1* in its entirety; however, the studies carried out examined different aspects of the model, made predictions based on its components, and investigated specific pathways within it. The research evidence on which the model is based is reviewed in the remainder of this chapter. For the sake of clarity, findings are presented in different categories of contributing factors; however, as many of the proposed causes may work in combination to influence fatigue, potential interrelationships between contributing factors are identified throughout. It should also be noted that this review does not cover all of the factors that could be involved in the fatigue experienced by cancer patients. It is not feasible to comment on all of the possible contributing factors; however, the main factors that have been linked to CRF that are relevant to the results presented in this thesis are considered.

3.2.2 Contributing factors to CRF.

3.2.2.1 Clinical and demographic contributing factors to CRF. Studies that have examined relationships between CRF and demographic and clinical factors have produced very inconsistent results (Donovan et al., 2012). Demographic factors that have been linked to CRF include age, gender, ethnicity, educational level attained, household income, and number of children (Andrykowski et al., 2010; e.g., Bower et al., 2006; e.g., Gerber et al., 2010; Huang, Zhang, Kang, Song, & Zhao, 2010;

Reinertsen et al., 2010; Schultz et al., 2010; Storey et al., 2011); however, findings from these are inconclusive. For example, it is possible that tolerance for fatigue varies with age and there is some suggestion that younger cancer survivors experience more severe fatigue (e.g., Banthia, Malcarne, Ko, Varni, & Sadler, 2009; Cavalli Kluthcovsky et al., 2011). Younger cancer patients may report greater fatigue because they have greater social and environmental demands and therefore fatigue necessitates bigger lifestyle changes than for older patients who have experienced age-related fatigue (Banthia et al., 2009). However, studies have also found more severe fatigue in older cancer patients compared to younger patients (Butt et al., 2010). A number of studies have reported significant associations between CRF and having/number of children (e.g., Dhruva et al., 2010; Gerber et al., 2010). However, additional research is necessary in order to establish whether such demographic factors are predictive of CRF.

Although the prevalence and severity of fatigue in cancer patients are greater than in the general population (Fernandes et al., 2006; Jacobsen, Hann, et al., 1999), supporting the role of cancer and cancer-treatments in initiating CRF, the relationships between post-treatment CRF and cancer and cancer-treatment related factors are not supported by most studies (e.g., Andrykowski et al., 1998; Hjermstad et al., 2005; Minton, Alexander, & Stone, 2012; Okuyama et al., 2000; Prue et al., 2006; Servaes, Prins, Verhagen, & Bleijenberg, 2002; Servaes, Verhagen, et al., 2002c; Young & White, 2006). Clinical factors that could potentially impact CRF include disease type and stage, time since diagnosis or treatment, type or extent of treatment, physical comorbidities, menopausal status and BMI. However, research on these (e.g., Andrykowski et al., 2010; Bower et al., 2006; Huang et al., 2010; Kim et al., 2008; Reinertsen et al., 2010; Schultz et al., 2010) has also resulted in inconsistent findings and the influence they have on CRF, if any, is not adequately understood. The relationship between CRF and BMI has received the most reliable support (e.g, Andrykowski et al., 2010; Gerber et al., 2010; Huang et al., 2010; Reinertsen et al., 2010; Wratten et al., 2004). In addition, comorbid conditions, such as hypothyroidism, hypertension, and arthritis, as well as treatments for these, are likely to contribute to fatigue (Berger, Gerber, & Mayer, 2012). For example, cardiovascular problems predicted long-term fatigue in breast cancer survivors up to 10 years after diagnosis (Bower et al., 2006). Although it is difficult to isolate the effects of comorbid conditions from the many contributing factors to CRF, the contribution of such factors needs to be carefully considered. Further research is necessary to establish what

clinical factors impact on persistent CRF; however, currently there is little empirical support for the continued effects of cancer and cancer treatment-related factors on persistent CRF post-treatment.

3.2.2.2 Biological contributing factors to CRF. Cancer and cancer treatments, cancer/treatment-related side-effects and comorbidities, such as thyroid and cardiac dysfunction, vomiting, nausea, diarrhoea, weight loss, pain and psychological distress, can result in a variety of biochemical and physiological changes that have been linked to fatigue (Ryan et al., 2007; Wang, 2008). There are thus many different mechanisms through which CRF might develop. Proposed mechanisms include alterations in the level and functioning of proinflammatory cytokines, hypothalamic-pituitary-adrenal (HPA) axis disruption, circadian rhythm deregulation, complications from anaemia, vagal-afferent nerve activation, alterations in muscle and adenosine triphosphate (ATP) metabolism and increased brain serotonin levels (Ryan et al., 2007; Wang, 2008). Many of these proposed biological contributing factors are interrelated and may work in combination to produce fatigue. Furthermore, it is possible that they share a common denominator; for example, a number of researchers have proposed that proinflammatory cytokine activation could be the underlying biological mechanism in the development of CRF (Jager, Sleijfer, & van der Rijt, 2008; Schubert, Hong, Natarajan, Mills, & Dimsdale, 2007; Wang, 2008).

Proinflammatory cytokines. The idea that activation of the proinflammatory cytokine network is central to CRF has become increasingly popular and is supported by several different research strands (Bower & Lamkin, 2012). Experimental animal research and clinical trials of cytokine therapies in patients have shown that the administration of proinflammatory cytokines, namely Interleukin (IL)-1 and tumour necrosis factor-alpha (TNF)-α, can induce "sickness behaviour", such as fatigue, reduced motivation and interest in day-to-day activities, decreased activity levels, weakness, and concentration problems (Kelley et al., 2003). Elevated levels of proinflammatory cytokines have also been linked to chronic fatigue syndrome (CFS; Shor, 2003; Wyller, Eriksen, & Malterud, 2009). Studies on fatigue in cancer patients specifically suggest that there is a positive association between CRF and circulating levels of pro-inflammatory markers such as IL-1ra, IL-6 and neopterin (Schubert et al., 2007). Longitudinal studies on immunogenomic markers and CRF have reported significant relationships between elevated fatigue and high levels of neutrophil/monocyte, IL-1ra, and IL-6 during radiation therapy, high levels of IL-1β

during chemotherapy, and high levels of IL-1β and IL-6 with stress induction (Saligan & Kim, 2012). In addition, research has shown that both pre-chemotherapy and chemotherapy-induced alterations in inflammation are associated with changes in fatigue in response to chemotherapy (Mills, Parker, Dimsdale, Sadler, & Ancoli-Israel, 2005).

There are multiple ways through which proinflammatory cytokines might be increased in cancer patients. Molecular epidemiology research on CRF suggests that cytokine gene variants that play a part in cancer may also affect the experience of cancer- and treatment-related symptoms such as fatigue (Reyes-Gibby et al., 2008). Thus, genetic variations between individuals on cytokine genes may play a role in their symptom expression in response to treatment. In addition, both the disease itself and cancer treatments can contribute to elevated levels of circulating cytokines and cytokine receptors, such as TNF-α, IL-1β and IL-6 (Ryan et al., 2007). Cancer treatments such as chemotherapy and radiation therapy have been linked to increased proinflammatory activity in animal research, in in vitro experiments, and in studies on cancer patients undergoing treatment (Jager et al., 2008; Schubert et al., 2007). For example, the administration of the chemotherapy agent Paclitaxel has been associated with increases in plasma levels of IL-6, IL-8 and IL-10 (Pusztai et al., 2004). Cancer cells can also produce cytokines, which stimulate tumour growth and progression and can cause the immune system to induce the production of other cytokines in a type of "snowball effect" (Kurzrock, 2001). Finally, psychological and behavioural factors may contribute to increased levels of cytokines. For example, research has reported that physical inactivity and BMI, which have been linked to CRF, are correlated with increased inflammatory activity and could therefore impact on fatigue through such pathways (Bower & Lamkin, 2012). Psychological stress and prior or current depression can also contribute to elevated inflammatory processes and associated symptoms of fatigue (Bower & Lamkin, 2012). In addition, sleep disturbances are common in cancer patients (Roscoe et al., 2007) and sleep deprivation has been associated with increases in the production of some cytokines (Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006). The relationship may be also be reciprocal (Irwin, 2002), as proinflammatory cytokines are thought to influence the processes underlying sleep regulation (Guess et al., 2009). A recent study reported that the relationship between IL-6 and fatigue in ovarian cancer patients before surgery may be mediated by poor sleep (Clevenger et al., 2012).

Increased levels of proinflammatory cytokines could contribute to CRF in a number of different ways. However, current understanding of the neural processes that might mediate the effects of inflammation on fatigue are limited (Bower & Lamkin, 2012). As alterations in cytokine activity have been linked to various conditions associated with fatigue, such as anaemia, cachexia, infection and depression (Barsevick, Frost, Zwinderman, Hall, & Halyard, 2010), such conditions may play a role. In addition, dopaminergic pathways have been proposed as underlying mechanisms for inflammation-induced neurovegetative symptoms like fatigue and ahedonic behaviour (Bower & Lamkin, 2012). A chronic pro-inflammatory state could also alter serotonin metabolism and dysregulate the HPA axis, which have been linked to fatigue (Jager et al., 2008).

The HPA axis is the primary neuroendocrine stress axis in humans and regulates the diurnal pattern of cortisol production and the release of cortisol in response to stress (Barsevick et al., 2010; Wang, 2008). Reduced HPA-axis function and low cortisol levels have been associated with fatigue in a number of conditions, such as CFS and rheumatoid arthritis, as well as cancer (Ryan et al., 2007). Although proinflammatory cytokines can stimulate the HPA axis in the short term and lead to increased cortisol levels, a prolonged inflammatory state can lead to reduced HPA axis function and thereby decreased cortisol production and a blunted diurnal cortisol rhythm (Jager et al., 2008). Flattened diurnal cortisol slopes, significantly lower levels of morning serum cortisol, and a blunted cortisol stress response have been reported in breast cancer survivors with prolonged fatigue up to 5 years post-treatment (Bower, Ganz, & Aziz, 2005; Bower, Ganz, Aziz, & Fahey, 2002; Bower, Ganz, Dickerson, et al., 2005).

Although much research on the biological factors underlying fatigue has emerged in the last few years; CRF is multidimensional and its underlying causes are likely to depend at least in part on the individual characteristics of the patient (Bower, 2007). Although cross-sectional studies have demonstrated that CRF has significant, positive, associations with systemic inflammatory markers and signals for immune system response, these significant associations often fail to persist when covariates, such as BMI, ethnicity, educational level or menopausal status, are accounted for in the analysis (Saligan & Kim, 2012). Previous research has also been limited by methodological problems including cross-sectional designs, small sample sizes, failure to obtain baseline biological measures, lack of a working case-definition for CRF, and failure to use standard measures of CRF that can predict clinical significance and assess

the multidimensional nature of CRF (Saligan & Kim, 2012; Schubert et al., 2007). Furthermore, the direction of effects and the interrelationships between proposed contributing factors are not clear. For example, although proinflammatory cytokines can stimulate the HPA axis, the HPA axis can also influence the production of proinflammatory cytokines (Ryan et al., 2007). In addition, changes in both these systems, and their subsequent influence on CRF could be due to comorbid conditions such as sleep disturbances.

While cancer and cancer-treatments undoubtedly play an important role in the initial development of CRF, the causes of persistent fatigue post-treatment are likely to be even more complex. Although several studies support proinflammatory cytokine involvement in persistent CRF (Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006; Schubert et al., 2007), findings are often inconsistent (e.g., Orre et al., 2011) and there is insufficient evidence for the continued effect of these proposed biological causes. For example, although Bower et al. (2002) reported that fatigued breast cancer survivors had higher levels of several markers associated with pro-inflammatory cytokine activity, including IL-1ra, soluble tumor necrosis factor receptor type II (sTNF-RII), and neopterin, than non-fatigued survivors at least one year after diagnosis, the levels of these markers remained within the normal range. Other research found no association between anaemia or inflammatory markers and fatigue in cancer survivors (Dimeo et al., 2004; Knobel et al., 2000; Orre et al., 2011). Thus, while there is mounting evidence for the role of a number of biological factors in the aetiology of CRF, there are still substantial gaps of knowledge that must be addressed (Bower & Lamkin, 2012; Payne, 2011; Saligan & Kim, 2012). Further research is necessary to understand the interrelationships between potential biological mechanisms and how these relate to other comorbid conditions associated with CRF, such as depression and sleep disturbances.

3.2.2.3 Sleep disturbances and CRF. Sleep disturbances, such as poor sleep efficiency, problems falling or staying asleep, and premature wakening, are common in cancer patients (Davidson, MacLean, Brundage, & Schulze, 2002; Roscoe et al., 2007) and several studies have reported associations between CRF and self-reported sleep disturbances at different stages of the cancer trajectory (Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008; Roscoe et al., 2007). Poorer sleep quality and more sleep problems have been associated with a greater likelihood of being fatigued in newly diagnosed breast cancer patients prior to treatment (Fagundes et al., 2012). Greater

sleeping difficulties, including prolonged sleep latency and frequent night-time awakenings, have also been reported in fatigued cancer patients undergoing treatment relative to non-cancer controls (Wu, Davis, Padiyar, & Yarandi, 2011) and sleeping difficulties were found to be predictive of fatigue severity in a large sample of cancer patients during treatment (Stepanski et al., 2009). Finally, research on disease-free cancer survivors, also supports a relationship between CRF and global measures of sleep disturbance and insomnia (Alexander, Minton, Andrews, et al., 2009; Banthia et al., 2009; Cavalli Kluthcovsky et al., 2011; Minton et al., 2012; Schultz et al., 2010).

CRF and sleep disturbances are often reported as part of a symptom cluster with pain, depression and anxiety (Donovan & Jacobsen, 2007; Fiorentino, Rissling, Liu, & Ancoli-Israel, 2011; Kwekkeboom, Cherwin, Lee, & Wanta, 2010), suggesting that CRF and sleep disorders may share common underlying mechanisms (Roscoe et al., 2007; Wu, Davis, & Natavio, 2012). Cancer- and/or treatment- related physiological factors that have been linked to CRF, such as alterations in the function of the HPA-axis and endocrine rhythm disruptions, have also been associated with disturbances in the sleep/wake cycle (Ancoli-Israel, Moore, & Jones, 2001). Furthermore, psychological distress such as worry, rumination, and anxiety and symptoms such as pain can contribute to both sleep difficulties and CRF (Ancoli-Israel et al., 2001; Hu & Silberfarb, 1991).

Despite an overlap in contributing factors and potential mechanisms, CRF and sleep disturbances are nevertheless distinct problems. However, the strong relationship between them suggests that they may reciprocally influence one another. Research suggests that insomnia is a risk factor for experiencing persistent fatigue after cancer treatment (Savard & Morin, 2001). Conversely, the experience of fatigue can contribute to behavioural changes in sleep practices, such as increased daytime napping, going to bed earlier and rising from bed later, which have in turn been associated with night-time sleep disturbances (Ancoli-Israel et al., 2006; Roscoe et al., 2007). Nevertheless, the extent and the mechanisms through which sleep disturbances may play a causal role in precipitating and/or perpetuating CRF are still unclear and there are limited data to support the use of sleep management interventions as a means to reduce fatigue in patients with cancer (Zee & Ancoli-Israel, 2009).

Several studies have used actigraphy to objectively assess sleep in cancer patients and to investigate the relationship between objective measures of sleep and CRF (Ancoli-Israel et al., 2001). Actigraphy is a non-invasive method of measuring

day- and night-time activity levels through motion-sensitive accelerometers worn on the wrist. Actigraphy recordings enable the estimation of sleep/wake parameters (e.g., sleep onset latency, sleep duration, number and length of times awake after sleep onset, and sleep efficiency), activity/rest patterns (e.g., mean daytime activity, duration of daytime wake and sleep periods, and percentage of time spent awake and asleep during the day) and circadian rhythm. Circadian rhythms are 24hr cycles of biological processes such as hormone secretion (e.g., cortisol) and sleep/wake patterns (Ancoli-Israel et al., 2006). Research suggests that cancer treatments can disrupt such biological rhythms and thereby affect fatigue (Ancoli-Israel et al., 2001).

Several studies have reported significant associations between CRF and different objective sleep/wake and circadian rhythm parameters (Roscoe et al., 2007). For example, higher self-reported fatigue has been associated with less daytime activity, more daytime sleep, lower circadian consistency, and more night-time restlessness in breast cancer patients undergoing chemotherapy treatment (Berger & Farr, 1999; Roscoe et al., 2002). Similarly, Berger et al. (2009) reported a consistent relationship between disrupted patterns of circadian activity rhythms and fatigue in breast cancer patients before, during and after chemotherapy. Such research suggests that patients with CRF have less stable and robust circadian rhythms with less differentiation between day- and night-time levels of activity. However, findings on CRF and objective rest/activity and sleep/wake patterns have been mixed, with several studies reporting no observed relationships between actigraphy sleep parameters and CRF; thus, the relationship between sleep and CRF is not yet clear.

Alexander et al. (2009) reported that although fatigued disease-free breast cancer survivors reported more insomnia than non-fatigued controls, these differences were only supported to a limited extent by objective actigraphy data. Moreover, the observed sleep disturbances are relatively mild and could not explain CRF symptoms. Mixed results have also been reported in patients on active treatment. Liu et al. (2012) observed significant associations between fatigue and both subjective sleep ratings and objective actigraphy measures of daytime sleepiness in breast cancer patients undergoing chemotherapy; however, no association was found between fatigue and night-time sleep actigraphy measures. Conversely, Fernandes et al. (2006) found no association between self-reported fatigue severity and any actigraphic variables on sleep or circadian rhythm in a sample of female inpatients with cancer. In addition, although it has been suggested that disrupted sleep prior to cancer treatment might be a risk

factor for CRF, there is limited evidence that objectively-measured sleep disturbances are associated with fatigue at this time. Ancoli-Israel et al. (2006) reported that, although more phase-delayed circadian rhythms were associated with increased functional impairment in women with breast cancer before the start of chemotherapy, no significant correlations were observed between objective day- or night-time sleep variables or circadian rhythm parameters and fatigue. Similarly, Berger et al. (2007) found that while poorer subjective sleep reports were associated with higher levels of fatigue in breast cancer patients prior to adjuvant chemotherapy, there was no correlation between subjective sleep measures and objective sleep reports, which were largely within the normal limits established for healthy individuals.

The finding that self-reported sleep disturbances are more strongly associated with fatigue severity than objective measures of sleep is interesting and has been reported in a number of other studies (Alexander, Minton, Andrews, et al., 2009; Ancoli-Israel et al., 2006). It is possible that patients' own perceptions regarding their sleep - their interpretation or beliefs regarding sleep disturbances and quality - play a larger role in CRF than their actual sleep. This is supported by research on the link between CRF and psychological and cognitive responses such as anxiety and catastrophising. Nevertheless, common method bias could also account for such findings; when self-report measures are used to collect data on both outcomes and hypothesised predictors, factors such as having a common rater, a common measurement context, and a common item context can inflate the association between measures of different constructs (Podsakoff, MacKenzie, Lee, & Podsakoff, 2003). Evidence suggests that common method variance can have a substantial impact on observed relationships (Podsakoff et al., 2003); thus, strong correlations between self-report measures should be interpreted with caution.

3.2.2.4 Psychological distress and CRF.

Depression. The relationship between depression and CRF is one of the most documented findings reported in the literature. Comparisons between fatigued and non-fatigued cancer patients consistently reveal significant differences in measures of depression (Andrykowski et al., 2005; Bower et al., 2002; Bower et al., 2006; Fernandes et al., 2006; Fossa et al., 2003; Loge, Abrahamsen, Ekeberg, & Kaasa, 2000). Such differences can continue long after cancer treatment has been completed. For example, Fossa, Dahl and Loge (2003) reported significantly higher levels of depression among fatigued testicular cancer survivors whose median time since

treatment was 12 years. Depressive symptoms have been associated with the presence and/or severity of fatigue in patients before (Ahlberg, Ekman, Wallgren, & Gaston-Johansson, 2004; Ancoli-Israel et al., 2006), during (Dimeo et al., 1997; Fernandes et al., 2006; Haghighat, Akbari, Holakouei, Rahimi, & Montazeri, 2003) and after cancer treatment (Dimeo et al., 2004; Minton et al., 2012; Servaes et al., 2001), as well as in long-term cancer survivors (Bower et al., 2006; Romito, Cormio, Giotta, Colucci, & Mattioli, 2012). Although fatigue and depression are highly correlated, they are nevertheless distinct conditions. Sugawara (2005) reported that a significant number of cancer survivors, who did not suffer from clinical depression, still experienced fatigue, and findings from other studies suggest only about a third of patients with severe CRF also have depression (Kim et al., 2008; Servaes, Verhagen, et al., 2002c). Nevertheless, depression and fatigue may reciprocally influence one another, and treatments for one may be effective for the other (Donovan & Jacobsen, 2007).

Two systematic reviews on the relationship between depression and CRF have been carried out in recent years; both showed that higher levels of depression were associated with higher levels of fatigue (Brown & Kroenke, 2009; Oh & Seo, 2011). Brown and Kroenke (2009) found an average correlation of .56 (with a range of .16 to .84) between depression and CRF, weighted by sample size across 51 studies. Fatigue shared approximately 31% of variance with depression. Oh and Seo (2011) found a large, significant mean effect size of depression on CRF based on 23 studies. Depression had a stronger association with CRF than anxiety and symptom distress such as pain and nausea/vomiting. Nevertheless, despite the plethora of research reporting a correlation between depression and CRF, the nature of the relationship between these conditions is still not clear. Measurement issues relating to how CRF and depression are assessed and the limited number of longitudinal studies carried out to date mean that interpretation of existing findings is difficult and the direction of causality among these conditions remains uncertain. These issues are addressed in turn.

The relationship between fatigue and depression is especially difficult to investigate because there is substantial overlap between their symptoms; therefore, both conditions may be mistaken for one another in cancer patients and assessing one independently of the other is challenging. For example, symptoms such as decreased motivation or interest to engage in usual activities, decreased energy and difficulty concentrating are included in both the diagnostic criteria for CRF and major depressive disorder and are commonly included in self-report scales of CRF and depression

(Donovan & Jacobsen, 2007). For instance, the Beck Depression Inventory contains questions which specifically address tiredness or fatigue and these are used to calculate the total depression score (Beck, Steer, & Brown, 1996). Thus measurement issues must be carefully considered, as scales that assess the somatic symptoms of depression or the emotional and/or cognitive aspects of CRF can impact on the strength of the observed association between these conditions.

Brown and Kroenke (2009) reported that of the 59 studies included in their review, which used 31 different measures of fatigue and 12 different depression scales, only a few investigators took steps to limit the potential measurement overlap between depression and fatigue. Some researchers chose measures that focussed on the cognitive and affective symptoms of depression from the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) or the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), which do not include physical symptoms of such as lack of energy or sleep disturbances (e.g., Fossa et al., 2003; Roscoe et al., 2002), while others excluded fatigue-related items from depression scales (e.g., Stone, Hardy, Huddart, A'Hern, & Richards, 2000; Stone, Richards, A'Hern, & Hardy, 2000; Stone, Richards, A'Hern, & Hardy, 2001; Visser & Smets, 1998). Nevertheless, strong significant relationships were still observed when such steps were taken. In a review of the evidence for a symptom cluster of fatigue, depression and insomnia, Donovan and Jacobsen (2007) also concluded that the relationship between depression and CRF cannot be accounted for by measurement approaches alone. Nevertheless, care should still be taken in the interpretation of positive associations between fatigue and depression. In addition to potential measurement overlap, the method of assessment and the implications that can be drawn based on these must be considered. As the majority of studies in this area used scores on questionnaires to indicate depression and did not make diagnoses of clinical depression based on the DSM IV criteria (Gielissen, 2007), findings support the association between *depressive mood* and CRF rather than fatigue and clinical depression.

Although strong positive correlations between fatigue and non-somatic symptoms of depression have been found, the nature of the relationship between these conditions is still uncertain. For example, does depression play a causal role in the development of fatigue, is their relationship bidirectional, or are there common mechanisms underlying both conditions? As the majority of studies investigating the relationship between fatigue and depression to date have been cross-sectional in design,

it is difficult to determine whether depression is a cause, consequence, or correlate of fatigue. For example, patients may experience fatigue or lack of energy secondary to depression; similarly, patients who are fatigued may develop feelings of depression in response to the negative impact of fatigue on functioning and quality of life.

Longitudinal studies that have measured both fatigue and depression have reported mixed results and the directional relationship between these conditions is not clear from findings to date. Stone et al. (2001) and Tchekmedyian et al. (2003) reported that changes in fatigue were significantly associated with changes in depression over time. However, both of these studies only assessed fatigue at two timepoints (before and after treatment). The majority of longitudinal studies that assessed fatigue and depression over multiple timepoints report ambiguous findings or do not support a causal relationship between the two conditions (Brown & Kroenke, 2009). For example, Visser and Smets (1998) assessed a mixed sample of cancer patients before and after treatment and at a nine month follow-up; their findings indicated that fatigue and depression did not follow the same course over time. Schumacher et al. (2002) found that fatigue was not consistently correlated with depression in a sample of 101 patients with acute myeloid leukaemia (AML) over 12 treatment timepoints spread over a 3-year period. Finally, Geinitz et al. (2001) reported that although depression was significantly correlated with fatigue in their sample of breast cancer patients before, during, and after radiation therapy, levels of depression and fatigue followed different patterns across time. More specifically, although self-reported levels of fatigue increased from radiation therapy treatment weeks 1-4, depression did not increase during this time. In addition, despite the overlap in symptoms and significant associations, findings from intervention studies illustrate that treatment for one is not necessarily effective for the other. For example, although treatment with antidepressants can improve mood in cancer patients there is little evidence for their effectiveness in reducing fatigue (Morrow et al., 2003).

Findings from longitudinal research illustrate that merely looking at cross-sectional correlations between proposed contributing factors and fatigue can be misleading. However, the nature of the relationship between depression and fatigue may change over the course of the cancer trajectory. The majority of longitudinal studies have relatively short follow-up assessments that are focussed around cancer treatment; it is possible that psychological factors play a more influential role in perpetuating *persistent* CRF after treatment. This is in line with findings from studies

on long-term cancer survivors; for example, Bower et al. (2006) found that level of depressive symptoms 1-5 years after diagnosis of breast cancer predicted the presence of fatigue 5-10 years post-diagnosis. Noal et al. (2011) also reported that depression during radiation therapy treatment for localised breast cancer predicted the presence of long-term fatigue at a one-year follow-up. Thus, rather than causing CRF during and immediately after treatment, depression may help to maintain existing CRF post-treatment either directly or through its relationship with other contributing factors. For example, depression is associated with behavioural changes such as decreased activity and sleep disturbances, which in turn have also been linked to prolonged CRF. Winningham's (1994) psychobiologic-entropy model also proposes that depression and anxiety can mediate the contribution of activity levels to fatigue severity. However, more longitudinal data is necessary to elucidate such potential mediational relationships.

It has also been hypothesised that there may be common mechanisms underlying both depression and fatigue, and that these account for the strong association between them. For example, proinflammatory activity and dysregulation of the HPA axis, which have been associated with CRF, may also play a role in the development of depression (Bower et al., 2002; Howren, Lamkin, & Suls, 2009; Maes, 2008; Maes et al., 2009; Schiepers, Wichers, & Maes, 2005). Thus, both conditions may develop simultaneously because of physiological changes following cancer and/or cancer treatment. However, currently there is insufficient evidence to support this idea. For example, Bower et al. (2011) examined the relationship between proinflammatory activity and both fatigue and depression in breast cancer patients shortly after treatment; their findings indicated that although fatigue and depression were significantly correlated, and fatigue was positivity associated the inflammatory marker soluble tumour necrosis factor receptor type II (sTNF-RII), no association was found between depressive symptoms and inflammatory markers. Thus, they concluded that there was no evidence for a common inflammatory mechanism underlying both symptoms of fatigue and depression at this point in the cancer trajectory. Bower et al. (2002) reported similar findings in a sample of breast cancer survivors who were an average of 5 years post-treatment; although fatigued participants had significantly higher levels of several proinflammatory markers, none of the immune parameters assessed were correlated with scores on depression. Similarly, Orre et al. (2011) reported that fatigue in disease-free breast cancer survivors was significantly and positively associated with

the inflammatory marker C-reactive protein (CRP) whereas depression was not, even though depression accounted for 34% of the variance in fatigue while CRP alone explained only 7%. Such findings suggest that there are distinct biological processes involved in fatigue and depression, and supports the independence of these symptoms. The frequent co-occurrence of both conditions, and the strong correlation between them, nevertheless supports a reciprocal relationship between CRF and depression.

Anxiety. Cancer and cancer treatments understandably rouse feelings of anxiety in many patients. Although a certain level of anxiety is expected and can be adaptive in response to cancer, persistent and disproportionate levels of anxiety can disrupt functioning and be maladaptive in the long term (Stark & House, 2000). Greater levels of anxiety have been associated with the presence and/or severity of fatigue in patients before (Ahlberg et al., 2004) and during cancer treatment (Dimeo et al., 1997; Fernandes et al., 2006; Haghighat et al., 2003), as well as in disease-free cancer survivors (e.g., Fernandes et al., 2006; Fossa et al., 2003; Loge et al., 2000; Minton et al., 2012; Servaes et al., 2001). Brown and Kroenke (2009) reported an average correlation of .46 (with a range of .16 to .73) between anxiety and CRF, weighted by sample size across 33 studies; fatigue shared approximately 23% of variance with anxiety. In their meta-analysis of the correlates of CRF, Oh and Seo (2011) found a large mean effect size of anxiety on CRF based on 11 studies, although the correlation between anxiety and fatigue was lower overall than that reported between fatigue and depression. Despite strong associations between anxiety and fatigue in the literature, as with depression, the precise nature of the relationship between these conditions is not clear. The experience of fatigue, especially persistent fatigue post-treatment, may lead to anxiety and worry. Conversely, anxiety may influence the development, the maintenance and/or the experience of fatigue. It is possible that a dispositional tendency to react with increased anxiety when confronted with a threatening situation may play a role in CRF; trait anxiety assessed before diagnosis was found to predict fatigue six and twelve months after diagnosis in a sample of women with early stage breast cancer (De Vries, Van der Steeg, & Roukema, 2009a). Furthermore, trait anxiety also predicted fatigue six months after diagnosis in women who were subsequently diagnosed with benign breast problems (De Vries, Van der Steeg, & Roukema, 2009b). Thus, individual differences in perceiving and reacting to threats such as cancer and/or fatigue may be important. However, it is unclear how such differences could contribute to variations in fatigue severity. A tendency towards negative affect has been

associated with greater symptom reporting (Watson & Pennebaker, 1989) and thus trait anxiety could result in more subjective complaints of fatigue. However, greater anxiety in response to cancer, cancer treatment, or fatigue could also impact on fatigue directly or indirectly through behavioural changes and maladaptive coping or biological mechanisms. For example, distress and worry about the consequences of cancer treatment, fears of cancer recurrence and chronic uncertainty about the future, referred to as 'Damocles Syndrome' in the literature (Koocher & O'Malley, 1981; Thewes, Butow, Girgis, & Pendlebury, 2004), may lead to poor coping behaviour, decreased activity levels and sleep disturbances, which in turn have also been linked to prolonged CRF. Andersen et al. (2004) reported that a four-month psychological intervention for reducing emotional distress in breast cancer patients significantly lowered fatigue post-intervention in the participants who had high levels of cancer stress before starting adjuvant therapy. This is in line with the idea that anxiety can have a causal influence on CRF.

Psychological distress could also contribute to the aetiology of fatigue through stress-mediated cytokine dysregulation. Psychological stresses can increase the levels of pro-inflammatory cytokines such as IL-1, IL-1ra, IL-10, TNF-α, IL-6 and IFN-gamma (Maes et al., 1998; Seruga, Zhang, Bernstein, & Tannock, 2008). However, few studies have investigated the relationship between proinflammatory markers, anxiety and CRF. Orre et al. (2009) reported that anxiety (and depression) did not alter the observed significant relationship between chronic CRF and IL-1ra and CRP in long-term survivors of testicular cancer, and thus they found no evidence to suggest that the association between inflammatory markers and fatigue was mediated by psychological factors.

Longitudinal studies that have examined changes in both CRF and anxiety support strong relationships between both symptoms. For example Tchekmedyian et al. (2003) found a positive relationship between improvements in fatigue and reductions in anxiety in a study of lung cancer patients. However, as with depression, there is insufficient evidence that CRF and anxiety follow the same trajectories over time (Geinitz et al., 2001; Stone, Hardy, et al., 2000), which suggests that different underlying mechanisms are involved and causal influences, if existent, are not straightforward. Anxiety may play a greater role in persistent post-treatment CRF; a long-term follow-up of the participants in Geinitz et al.'s study found that both fatigue and anxiety scores were higher 2.5 years post-treatment compared to scores two months

post-treatment (Geinitz et al., 2004). Findings from another study suggested that pretreatment distress may not affect the initial onset and severity of cancer treatment-related fatigue but rather how well a patient recovers in the days following treatment (Higgins, Montgomery, Raptis, & Bovbjerg, 2008). This supports the idea that psychological factors may play a greater role in fatigue maintenance post-treatment. However, more longitudinal data are necessary to elucidate the links between psychological distress and CRF and the factors that might mediate these over time.

3.2.2.5 Social contributing factors to CRF. Social support is conceptualised as the perception that one is cared for and loved or esteemed and valued, or a sense of belonging to a network of communication or mutual obligation (Cobb, 1976). Such supportive interactions are thought to be protective against the negative effects and harmful health consequences of stress (Cohen & Wills, 1985). To date little research has examined the impact of social factors on CRF. Findings suggest that patients with post-treatment CRF or more severe fatigue are less likely to be married or in a committed relationship than those without CRF or non-severe fatigue and thus spousal support may be important (e.g., Bower et al., 2002; Donovan et al., 2007). Berger and Walker (2001) found that women who reported less frequent interpersonal relations behaviours experienced higher fatigue at chemotherapy treatments and at cycle midpoints between chemotherapy treatments for breast cancer. Thus, feeling close to and accepted by another may help to reduce the psychological burden associated with treatment and modify perceptions of fatigue. In line with this, Michael et al. (2002) reported that social isolation in women prior to a confirmed diagnosis of breast cancer was significantly associated with post-illness physical functioning and vitality over a four-year follow-up in participants who remained disease-free. The relationships remained significant even when baseline levels of functioning were accounted for and a significant trend was found, with decreasing levels of social connection associated with lower functioning.

Some studies have reported that CRF in breast cancer patients is significantly and negatively associated with measures of subjective social support (Jiang et al., 2011; Li & Yuan, 2011) as well as objective support and utilization of support (Jiang et al., 2011). Kuhnt et al. (2009) found that fatigue was significantly associated with lower social support in large sample of cancer survivors. However, overall findings on social support have been mixed, with a number of studies reporting significant associations but failing to support a predictive relationship between social support and CRF. For

example, De Vries et al. (2009a) reported that, although social support was associated with fatigue before surgery and 12 months post-surgery in women who were diagnosed and treated for cancer, the relationship was no longer significant in a multivariate model when factors such as trait anxiety and extraversion were entered. Similarly, Okuyama et al. (2000) found that satisfaction with confidants was significantly correlated with fatigue severity in disease-free breast cancer survivors but that this indicator of social support was no longer significant in a multivariate analysis that included factors such as depression and insufficient sleep. They thus suggested that social support may indirectly contribute to improvements in fatigue.

Von ah, Kang and Carpenter (2008) also reported that although fatigue severity was associated with some measures of social support before adjuvant therapy for breast cancer, social support did not significantly predict CRF before, during or after adjuvant therapy in a multivariate model. These authors suggest that nonsignificant findings may have been due to the way social support was conceptualised, and that the match between desired and received social support may be more important than the type and extent of actual social support available. In line with this idea, Servaes et al. (2002c) found that breast cancer survivors with severe fatigue reported more negative social interactions and a greater desire for more social support than non-severely fatigued cancer survivors, although the amount of social support received did not differ between the groups. Furthermore, more severely fatigued breast cancer survivors reported less social functioning and greater impairment in social interactions than those with non-severe fatigue. The authors suggest that this may be because the people close to them do not expect cancer survivors to suffer from fatigue more than a year after treatment. Thus, significant others' perceptions and understanding of CRF may have important repercussions for patients' recovery.

3.2.2.6 Behavioural contributing factors to CRF: Reduced physical activity and increased rest. Maladaptive coping strategies, such as excessive rest or napping and activity avoidance, can help to increase fatigue levels and may play a role in the persistence of CRF. As previously discussed in relation to sleep disturbances, less differentiation between day- and night-time levels of activity (e.g., lower levels of daytime activity, more daytime sleep, and more night-time restlessness) has been associated with more severe CRF (Berger & Farr, 1999; Roscoe et al., 2002). More time spent napping during the day has been linked with fewer hours of sleep at night, more difficulty falling asleep, less satisfaction with sleep and more daytime dysfunction

(Ancoli-Israel et al., 2006). In addition, objective measures of time spent napping during the day has been positively associated with fatigue in cancer patients (Liu et al., 2012). This is in line with Winningham et al.'s (1994) model of CRF, whereby a cycle of increased daytime rest, decreased daytime activity, increased night-time restlessness and poor sleep quality, can contribute to progressive physical deconditioning and greater fatigue, which in turn leads to even greater activity avoidance.

Reduced physical activity is recognised as an important contributing factor in the aetiology of CRF and the maintenance of CRF in cancer survivors (National Comprehensive Cancer Network, 2012a; Stone & Minton, 2008; Winningham et al., 1994). Physical activity describes all types of muscular activities that substantially increase energy expenditure (Brown, Trost, Bauman, Mummery, & Owen, 2004). Numerous studies have documented the relationship between physical activity and fatigue. Cross-sectional studies have found significant negative correlations between self-reported levels of physical activity and fatigue before (e.g., Goedendorp, Gielissen, Verhagen, Peters, & Bleijenberg, 2008), during (e.g., Huang et al., 2010) and after cancer treatment (e.g., Gerber et al., 2010; Servaes, Verhagen, et al., 2002c; Struik et al., 2009). However, research has not reported reliable associations between fatigue severity and objective levels of activity measured through actigraphy (Alexander, Minton, Andrews, et al., 2009; Berger et al., 2007; Fernandes et al., 2006; Servaes, Verhagen, & Bleijenberg, 2002b). Nevertheless, studies suggest that cancer survivors who meet the recommended physical activity guidelines have significantly lower fatigue than those who do not (e.g., Hung et al., 2011; Stevinson et al., 2009). In addition, longitudinal studies have reported that physical activity levels can predict fatigue severity at follow-up assessments. For example, Luctkar-Flude et al. (2009) found that physical activity following consultation for cancer treatment predicted fatigue severity three and six months later in a sample of older adults with cancer. Donovan et al. (2007) examined the course of fatigue prospectively in breast cancer patients using growth mixture modelling; their findings indicated that women who were less physically active at the end of treatment were more likely to have higher fatigue across the 6-month follow-up. However, physical activity was no longer a significant predictor in a multivariate analysis in which BMI and catastrophising emerged as significant contributors.

The strongest support for the contribution of physical activity to CRF comes from research on exercise interventions for cancer patients and survivors. Activity

enhancement is identified as a category 1 intervention (based on high-level evidence such as randomised controlled trials and supported with uniform consensus) for patients with CRF on active treatment, post-treatment, and for patients at the end of life in the NCCN guidelines (2010). A Cochrane review on the effectiveness of exercise in the management of CRF concluded that such interventions were statistically more effective than control interventions in reducing fatigue both during and after cancer treatment (Cramp & Daniel, 2008). However, the mechanisms through which exercise interventions lead to improvements in fatigue are not completely clear; greater levels of physical activity may have positive effects on CRF through a number of different ways.

Physical exercise can increase muscle mass and strength, effect haemoglobin concentration, and stimulate the production and release of proinflammatory cytokines, all of which can play a role in CRF (Al-Majid & Gray, 2009). Exercise interventions may also benefit by reducing BMI, which is a predictor of fatigue in cancer patients (Donovan et al., 2007). As prolonged periods of inactivity during cancer treatment can lead to physical deconditioning, the association between physical activity and CRF could also be mediated by functional mechanisms; increasing activity levels can improve physical functioning and functional capacity in cancer patients (Al-Majid & Gray, 2009; Mock et al., 2001). However, studies that found no association between fatigue severity and objective measures of activity do not support this idea (Berger et al., 2007; Fernandes et al., 2006). For example, Alexander et al. (2009) found no evidence that disease-free breast cancer survivors with CRF were less active than those without CRF, which suggests that physical conditioning does not account for fatigue in this population. Instead the authors suggest that the beneficial effects of exercise may be more indirect through mood, immune functioning or sleep.

Both sleep-related and psychological mechanisms have been linked to CRF and could mediate the relationship between fatigue and activity. Research supports the beneficial effects of exercise interventions on sleeping difficulties and suggests that physical activity can help regulate circadian rhythm patterns (Ancoli-Israel et al., 2001; Mock et al., 1997). In addition, physical activity-related improvements in mood and psychological distress have been well documented (Byrne & Byrne, 1993; Fox, 1999; Mock et al., 1997; Mock et al., 2001). For example, Banasik, Williams, Haberman, Blank, and Bendel (2011) reported that an eight week yoga intervention for breast cancer survivors was associated with reduced morning and 5pm salivary cortisol and improved emotional well-being and fatigue in the intervention group relative to the

control group. McAuley et al.(2010) reported that the association between physical activity and CRF in breast cancer survivors was mediated by self-efficacy, which had a direct effect on fatigue and an indirect effect through depressive symptoms.

These findings demonstrate the complex interrelationships between biological, behavioural, and psychological contributors to fatigue, and highlight the importance of investigating these interactions in order to elucidate the causes of CRF. In addition, the role of cognitions regarding physical activity may also be important in mediating such contributing factors and/or in directly influencing levels of fatigue. For example, one study reported that although self-reported levels of activity were not related to the severity of fatigue in disease-free breast cancer survivors, having a negative perception of physical activity and how it relates to fatigue was (Young & White, 2006). Thus, patients with severe fatigue were significantly more likely to believe that engaging in physical activity would be detrimental to their fatigue. These findings and the role of such beliefs and other cognitive factors in the aetiology of CRF are discussed further in the following section. However, some implications of these findings for understanding CRF and for assessing physical activity are first briefly considered here.

Findings from Young and White (2006) suggest that fatigued breast cancer survivors perceived activity to be more harmful, yet their self-reported level of physical activity did not actually differ from those without severe fatigue. In line with this, findings from Servaes et al. (2002b) suggest that severely fatigued breast cancer survivors perceived themselves to be more limited with regard to physical activity than non-severely fatigued survivors and a control group of healthy women although there was no actual difference between these three groups on level of functioning and objective activity assessed through daily self-observation and actigraphy. Servaes et al. (2002b) did not assess Kinesiophobia (fear of movement) as in the study by Young and White (2006); however, their measures of general self-reported activity, the physical activity subscale from the Checklist Individual Strength (CIS; Vercoulen et al., 1994) and the mobility and ambulation items from the Sickness Impact Profile (SIP; Bergner, Bobbitt, Carter, & Gilson, 1981) assessed respondents' perception of their own physical abilities and activity rather than their actual levels of activity. For example, items included 'I don't do much during the day' and 'I have low output' from the CIS and 'I walk shorter distances or stop to rest often' and 'I stay away from home only for brief periods of time' from the SIP. Thus, in this study, fatigue was associated with a low perception of physical functioning rather than actual physical activity. These findings

are therefore also in line with the idea that people's beliefs or cognitions regarding physical activity may play an important role in CRF.

Servaes et al (2002b) offer a number of explanations for their findings. First, it is possible that because physical activity is more effortful for patients who perceive severe fatigue, they may believe themselves to be less physically active than they previously were before their cancer. Second, fatigued survivors may be unsatisfied with their level of activity and thus perceive themselves to be inactive. Finally, low self-reported physical activity could also reflect emotional distress rather than inactivity. This is supported by the finding that emotional distress was significantly correlated with perceived activity levels and not objective activity levels.

These findings highlight the problems inherent to using self-report measures of physical activity. Simple numeric rating scales that ask participants to rate their level of activity are unlikely to reflect actual physical activity levels. Physical activity measures that ask respondents to report the amount of time spent doing various vigorous, moderate and mild types of activities and include activity examples as well as leisure activities and chores may decrease the subjectivity of physical activity self-reports. For example, measures such as the Scottish Physical Activity Questionnaire (SPAQ; Lowther, Mutrie, Loughlan, & McFarlane, 1999), the International Physical Activity Questionnaire (IPAQ, 2005), or the Physical Activity Survey (Paffenbarger, Blair, Lee, & Hyde, 1993) record the time respondents spend doing different activities, which can then be converted into metabolic equivalents (METs). However, such measures still suffer from the inherent problem that respondents find it difficult to accurately recall their behaviour (Scheeres, Knoop, Meer, & Bleijenberg, 2009).

Discrepancies between subjective and objective measures of physical activity underscore the need to include various different ways of assessment where possible (Servaes, Verhagen, et al., 2002b). However, such discrepancies and the finding that fatigue has different relationships with objective and subjective measures are also interesting in and of themselves, and may be an indication of cognitive mechanisms underlying CRF. The pattern of results from both research on physical activity and sleep suggests that associations between CRF are stronger when subjective, general measures of activity and sleep disturbances are used rather than objective measures (Alexander, Minton, Andrews, et al., 2009; Ancoli-Israel et al., 2006; Young & White, 2006). Insight into the potential significance of such findings can be gleaned from studies on patients with CFS, where discrepancies between subjective perceptions of

impairment and actual impairment have also been reported. Such discrepancies are in line with models of perpetuating factors in CFS, which have long since acknowledged the key role of cognitive processes (Knoop et al., 2010). Patients with CFS often have a tendency to overestimate their level of impairment while underestimating their actual performance, supporting the idea that negative beliefs are central to CFS. Indeed, research has found that effective CBT interventions for CFS changed patients' subjective perceptions of impairment rather than their actual performance on neuropsychological tests (Knoop, Prins, Stulemeijer, van der Meer, & Bleijenberg, 2007). Such findings suggest that distorted perceptions of cognitive functioning play a more important role than actual cognitive performance. Similar processes may be at work in patients with CRF, whereby individuals' beliefs and interpretations of their functioning contribute to the maintenance of symptoms. If maladaptive thinking patterns are driving persistent CRF then this would explain the poor relationship that is observed between objective measures of functioning and fatigue severity. Potential cognitive contributing factors to CRF and the mechanisms through which they might influence fatigue severity are discussed in the next section.

3.2.2.7 Cognitive contributing factors and beliefs about CRF. Patients' beliefs regarding a chronic illness can have important repercussions for their health, adjustment and quality of life because such cognitions can influence coping, moderate behaviour and contribute to mood disturbances such as depression (Hagger & Orbell, 2003). Although very little research has investigated the influence of cognitive factors on CRF, the role of illness cognitions and beliefs on health outcomes has received much attention in other illness populations. Such work supports the common sense model (CSM) of health behaviour, otherwise referred to as the 'common-sense model' (Leventhal et al., 1984). The CSM suggests that people make sense of an illness by forming mental representations based around five components that influence behaviour and coping: signs and symptoms associated with the illness (*identity*); the perceived reasons for getting the illness (*causes*); the physical, social, economic, and emotional repercussions of the illness (*consequences*); beliefs concerning whether it can be treated, controlled or cured (*cure/control*); and the perceived duration and course of the illness (*time-line*). Furthermore, two additional dimensions, *illness coherence* (patients' evaluation of how well they understand or comprehend their illnesses) and *emotional representation* (the emotional responses generated by the illness) have also been added (Moss-Morris et al., 2002). Emotional representations are an integral part of the model

because people are thought to generate both cognitive and emotional responses to an illness, which can actively influence one another. Representations of an illness are based on patients' own experience of somatic symptoms, their personal history, and the sociocultural context in which they occur. Such beliefs are increasingly recognized as a critical factor in adjustment to and recovery from CFS (e.g., Moss-Morris & Chalder, 2003) which, like CRF, has a complex aetiology that involves physiological, psychological, social and environmental factors (Ax, Gregg, & Jones, 2001).

The role of patients' illness or symptom perceptions in perpetuating CRF thus also warrants investigation. As factors that are at least partially under a patient's control can contribute to CRF (e.g., activity levels, bedtime habits and sleep patterns), perceived controllability and causal representations regarding fatigue may be especially important. Although few studies to date have explored the role of symptom perceptions or cognitions in CRF, cognitive-behavioural therapy (CBT) has received much support for the treatment of fatigue in cancer populations (National Comprehensive Cancer Network, 2012a). CBT interventions directly acknowledge how an individual's beliefs or cognitions, such as their thoughts about a symptoms' meaning, controllability, and consequences, influence how that symptom is experienced (Kwekkeboom et al., 2010). Thus, research on CBT interventions is in line with the idea that changing the way patients think about their CRF can lead to better symptom-related outcomes and improvements in functional impairment. For example, Giellesen Verhagen, Witjes, and Bleijenberg (2006) reported that a personalized CBT-based intervention was effective in reducing fatigue in a sample of disease-free cancer survivors relative to a waiting-list control sample.

Giellesen et al.'s (2006) CBT intervention was directed at several proposed perpetuating factors of CRF, such as sleep and activity dysregulation, insufficient coping with the experience of cancer, maladaptive beliefs and catastrophising in response to the fatigue, and sought to teach more helpful ways of viewing and coping with the symptom. A central component of the intervention involved challenging dysfunctional cognitions, many of which relate directly to aspects of Leventhal's illness dimensions; for example, patients' perceived lack of control over their fatigue and external medical causal attributions (i.e., believing that the cancer treatment is causing their fatigue). Findings from the study indicated that the patients in the intervention condition reported significantly greater decreases in fatigue severity, functional impairment, and psychological distress following the intervention compared to the

waiting list control group. In addition, a follow-up study of these patients indicated that these positive effects were maintained over time (Gielissen, Verhagen, et al., 2007).

Gielissen et al.'s (2006) findings directly acknowledge the potential role of cognitions in bringing about improvements in CRF. However, the actual mechanisms underlying these improvements are not clear. For example, although the CBT intervention targeted factors such as patients' self-efficacy beliefs regarding symptom control and catastrophising thoughts relating to fatigue, it is not clear whether changes in these factors or changes in other factors actually mediated the improvements in fatigue. Reanalysis of the data provided no evidence that intervention-induced changes in fatigue were mediated by increases in objectively measured physical activity (Gielissen, Wiborg, Verhagen, Knoop, & Bleijenberg, 2011). Another study, which explored the effectiveness of a CBT intervention for patients on active cancer treatment, also supported the effectiveness of CBT for reducing fatigue and also found that improvements were not mediated by changes in physical activity (Goedendorp et al., 2010). Similar findings have been reported by studies on fatigue in multiple sclerosis and CFS patients, where changes in cognitions regarding fatigue and changes in symptom focussing, but not changes in physical activity, mediated the positive effects of CBT and exercise interventions (Knoop, van Kessel, & Moss-Morris, 2012; Moss-Morris et al., 2005; Wiborg, Knoop, Stulemeijer, Prins, & Bleijenberg, 2010). Thus, it is possible that changes in cognitive factors were also key to the improvements in fatigue observed after CBT interventions for CRF; however, changes in cognitions regarding CRF were not monitored over time in Gielissen et al.'s and Goedendorp et al.'s studies. Nevertheless, a number of correlational studies have examined the relationship between CRF and various cognitive factors. These are discussed below.

Catastrophising. Catastrophising in response to fatigue has been associated with more severe fatigue in patients during (Jacobsen, Hann, et al., 1999) and after adjuvant cancer treatment (Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998). Longitudinal studies have also reported that greater catastrophising before treatment is a predictor of fatigue severity and disruptiveness after treatment (Andrykowski et al., 2005; Jacobsen, Andrykowski, & Thors, 2004). For example, each one-point increase in catastrophising before beginning adjuvant treatment was associated with an approximately 20% greater likelihood of meeting the criteria for CRF post-treatment (Andrykowski et al., 2005). Jacobsen et al. (2004) found that although catastrophising prior to treatment was associated with post-treatment fatigue in patients treated with

radiation therapy, this relationship was not observed in patients treated with chemotherapy. The authors suggest that, as radiation therapy may be less fatigue-inducing than chemotherapy, psychological factors may play a greater role in the patients' experience of CRF. Thus, the role of catastrophising may vary depending on the type of treatment and its potential to cause fatigue.

Catastrophising in response to fatigue at the end of treatment may also play a role in maintaining fatigue post-treatment. Donovan et al. (2007) identified two fatigue trajectories, a low- and a high- fatigue group, using growth mixture modelling in a prospective study of women treated for early stage breast cancer. Results from a multivariate analysis indicated that catastrophising at the end of treatment was a significant predictor of being in the high-fatigue group across the 6-month follow-up, whereby BMI was the only other significant predictor.

As all of the studies on catastrophising and CRF were carried out on breast cancer patients, the generalisability of these findings is somewhat limited. However, the findings reported to date support the idea that catastrophising in response to CRF can have detrimental effects on fatigue at least in some patient groups and that such cognitions can play a role in persistent CRF after cancer treatment. Furthermore, research on illness beliefs and cognitions that could lead cancer patients to catastrophise also supports these findings. For example, Paddison et al. (2009) explored the association between patients' pre-surgical expectations for recovery and fatigue levels after major colorectal surgery. They reported that patients with more realistic expectations regarding the time-line (i.e., those who expected fatigue resolution to take longer) and the controllability (i.e., those who expected to have less control) of the anticipated post-surgical fatigue at base-line (before surgery) had less persistent fatigue after the surgery. These predictors remained significant even after depression was included in the model. The findings thus suggest that cognitions or beliefs regarding fatigue played a role in subsequent adjustment after treatment. It is possible that patients with unrealistic expectations of recovery overexerted themselves after treatment and thereby remained more fatigued at the follow-up assessment. Nevertheless, it is also possible that patients, whose initial expectations were not met after surgery, became more distressed and more likely to catastrophise in response to fatigue, and that such responses contributed to ongoing fatigue. However, further research is necessary to test such potential explanations.

Donovan and Ward (2005) explored the fatigue representations of women undergoing chemotherapy treatment for gynecological cancer using the 'Symptom Representation Questionnaire' (SRQ). Their findings indicated that fatigue is seen as a severe condition, which is uncontrollable, and lasts a long time. Furthermore, having negative beliefs about the consequences of fatigue and higher level of fatigue-related distress was significantly related to self-reported symptom interference with life activities (Donovan & Ward, 2005; Donovan et al., 2008). These findings are also in line with the idea that maladaptive cognitions regarding fatigue and greater distress in response to symptoms can have a negative impact on CRF. However, the mechanisms through which such beliefs and responses can actually exert an influence on CRF are not clear. For example, are there direct links between patients' cognitions and fatigue or is this relationship mediated by coping behaviours or psychological distress? It was not possible to test for such mediational relationships in Donovan et al.'s study. Further research is necessary in order to elucidate the association between such cognitive-behavioural factors and CRF.

Fears regarding cancer recurrence and activity in relation to fatigue. Fear of physical movement and activity, because of a perceived vulnerability to fatigue, has been associated with activity avoidance and more severe fatigue in patients with CFS (Silver et al., 2002). In addition, activity-related fatigue may be misinterpreted as a sign of disease relapse or recurrence if patients believe that physical disease, such as a viral infection, is responsible for fatigue. Thus, activity may be viewed as harmful not only for the symptom experience but also for the perceived underlying cause of the fatigue, leading to increased activity avoidance and subsequently increased fatigue. Similar processes may occur in CRF. Findings from qualitative research suggest that patients are unsure about what symptoms are 'normal' and are fearful that symptoms like fatigue are an indication that their cancer has returned (Thewes et al., 2004). Thus, fears of cancer recurrence and fears of exacerbating the fatigue through activity may result in reduced activity, increased physical deconditioning and psychological distress, and more severe fatigue.

Young and White (2006) investigated the relationship between activity levels, beliefs regarding physical activity, fear of cancer recurrence, and fatigue in a sample of breast cancer survivors. Fear of recurrence and negative beliefs about activity were associated with and predicted fatigue severity. However, the contribution of negative beliefs regarding activity was not mediated by actual self-reported activity levels, which

were not significantly associated with fatigue. Although it is possible that the subjective activity levels reported by the participants did not accurately reflect their actual activity, as previously discussed in section 3.2.2.6 , nonsignificant associations between both subjective and objective activity and CRF are not uncommon in the literature (e.g., Alexander, Minton, Andrews, et al., 2009; Ancoli-Israel et al., 2006; Fernandes et al., 2006; Servaes, Verhagen, et al., 2002b; Young & White, 2006). Thus, Young and White's findings suggest that beliefs about activity can have a direct influence on fatigue severity or that this relationship is mediated by other cognitive or psychological factors.

Support for such mediational relationships was found in Young and White's (2006) study in relation to fear of recurrence, which had an indirect relationship with fatigue severity via beliefs about activity and psychological distress. Thus, the findings support the idea that patients may associate activity-induced fatigue with possible disease recurrence and therefore that increased fear of cancer recurrence could contribute to fatigue by increasing fear of activity. In addition, the findings suggest that chronic fear of symptom worsening or disease recurrence can lead to the development or worsening of mood disorders, which can also impact on CRF. Another potential link between fear of recurrence and CRF could be through alterations in diurnal cortisol rhythm; Bower, Ganz, Dickerson et al. (2005) suggested that persistent fear of recurrence could influence cortisol slope in cancer survivors, as a flattened cortisol rhythm and elevated evening cortisol levels have been found in individuals under chronic stress. Thus, as flattened diurnal cortisol slopes and a blunted cortisol stress response have been reported in breast cancer survivors with prolonged fatigue (Bower, Ganz, & Aziz, 2005; Bower et al., 2002), fear of recurrence could be a contributing factor.

Two large cross-sectional studies support the relationship between fear of recurrence and persistent fatigue. Bower et al. (2006) found that fear of recurrence was significantly higher in breast cancer survivors who were fatigued 5-10 years after diagnosis compared to those who were not, while Skaali et al. (2009) reported a significant correlation between fear of recurrence and fatigue in long-term testicular cancer survivors who were on average 11.4 years after diagnosis. However, fear of recurrence was not a significant predictor in a multivariate analysis in either of these studies.

Although more research is required to replicate and expand on the findings regarding fear or recurrence and fears regarding activity, the findings to date suggest that flawed reasoning strategies, that involve not only maladaptive illness representations but also beliefs about the impact of recommended management strategies (e.g., increased activity) and anxieties about the disease itself, could contribute to increased disability. As beliefs and cognitions are amenable to change, such influences on fatigue would be particularly suitable targets for CBT. However, further longitudinal research is necessary to establish whether such beliefs are predictive of CRF over time and to understand what factors might mediate such relationships.

Perceived control. Self-efficacy beliefs and perceived control have been identified as powerful cognitive predictors of health outcomes and disability in patients with chronic disease (Hagger & Orbell, 2003). Servaes et al. (2002c) measured disease-free breast cancer patients' sense of control over their fatigue and reported that those with severe fatigue had lower control perceptions than those with non-severe fatigue. Interestingly, the groups did not differ with respect to their internal locus of control of health in general, suggesting that their *specific beliefs* regarding their fatigue, and not their general self-efficacy beliefs, impact on their fatigue outcomes. Over a two-year follow-up assessment of these patients, less perceived control with regard to fatigue at baseline continued to correlate significantly with higher persistent CRF after two years (Servaes et al., 2007). Baseline self-efficacy also significantly predicted persistent CRF severity and remained the only additional significant predictor when baseline fatigue severity was taken into account. These findings thus suggest that control perceptions play an important role in perpetuating fatigue in cancer survivors.

The role of control beliefs is also supported by the effectiveness of mind-body interventions for CRF, such as mediation, mindfulness interventions and CBT (Kwekkeboom et al., 2010). Such interventions help patients to become aware of unhelpful automatic responses to their fatigue such as maladaptive thoughts, feelings and behaviours, and equip patients with the skills to cope with these and achieve personal control over their symptoms (Kwekkeboom et al., 2010; van der Lee & Garssen, 2012). Thus, although limited research has directly explored the role of perceived control in relation to CRF, findings to date support the role of such cognitive factors. Nevertheless, further research on the role of control beliefs and the mechanisms through which they might impact on CRF is required.

Causal beliefs. Illness cognitions such as causal attributions are thought to be important for patients' adjustment to chronic illnesses like CFS (Moss-Morris & Chalder, 2003). In CFS the tendency to attribute fatigue to somatic causes rather than psychological or behavioural ones is common and such somatic causal attributions are believed to increase helplessness and discourage active coping (Butler, Chalder, Ron, & Wessely, 1991; Moss-Morris & Chalder, 2003). Existing findings on CRF patients also support the role of unhelpful causal attributions in the development and maintenance of fatigue. For example, breast cancer survivors with severe fatigue were found to have a higher inclination to attribute their fatigue to factors relating to their breast cancer, such as their surgery or adjuvant treatment, in comparison to those who had non-severe fatigue (Servaes, Verhagen, et al., 2002c). As research on the aetiology of CRF does not support a relationship between persistent post-treatment fatigue in cancer survivors and cancer and/or treatment related factors (Hjermstad et al., 2005; Prue et al., 2006; Servaes, Prins, et al., 2002; Young & White, 2006), such somatic attributions are maladaptive and may decrease patients chances of recovery (Gielissen, Verhagen, et al., 2007).

Dysfunctional cognitions, including the belief that cancer and cancer treatment are continuing to cause post-treatment fatigue, were targeted in Gielissen et al.'s (2007) CBT intervention for disease-free cancer survivors. Pretreatment somatic causal attributions continued to predict fatigue severity at the post-intervention follow-up around two years later. Thus, the authors suggest that such unrealistic attributions in patients with somatically unexplained post-treatment CRF may not have received sufficient attention in the intervention, and highlight the need to change such dysfunctional cognitions in order to improve intervention outcomes.

In contrast to CFS where causal attributions focus primarily on physical factors, research suggests that fatigued breast cancer survivors also report more psychological attributions regarding their fatigue, such as ruminating about their symptoms or sleeping difficulties, than those without CRF (Servaes, Verhagen, et al., 2002c). Furthermore, over a two-year follow-up of patients in this study, stronger psychological attributions at baseline continued to correlate significantly with persistent CRF severity; however, having such attributions was no longer a significant predictor of fatigue in a multivariate model (Servaes et al., 2007).

The mechanism through which causal attributions might impact on fatigue has received little attention. It is possible that patients who attribute their fatigue to

psychological factors believe that they lack control over such causes, thereby increasing their psychological distress and subsequently their fatigue. This is in line with the findings on CFS where psychological causal attributions for CFS have been associated with higher levels of anxiety and depression, and greater mood disturbances have been associated with 'catastrophic' illness perceptions (Edwards, Suresh, et al., 2001). In addition, patients' beliefs about the causes of their fatigue may impact on their adherence to treatment guidelines (Luthy et al., 2010). In a survey of 160 cancer patients hospitalized in a supportive care setting, Luthy et al. found that two-thirds of patients attributed their fatigue to cancer-related morbidities, while only 13% believed that their level of physical activity contributed to fatigue and only 25% believed that progressive physical activity could be beneficial for treating fatigue. Given that activity enhancement is one of the recommended interventions in the NCCN (2012a) guidelines for CRF, these findings suggest that there is incongruence between best practice treatments and patients' own views about fatigue. Such discrepancies are important, as they may influence patients' adherence to recommended management strategies and hence, their fatigue. However, further research is necessary to explore the relationship between patients' beliefs and adherence to treatment and to investigate other potential mechanisms through which causal attributions might impact on fatigue in CRF patient populations.

3.3 Conclusion

Cancer-related fatigue (CRF) is an extremely common, debilitating, and potentially long-term side-effect of cancer treatment, whose aetiology is still not adequately understood. In addition to the multiple potential biological, psychological, and behavioural contributing factors to CRF documented in the literature, there is growing evidence that patients' cognitions regarding their fatigue play a key role in exacerbating and maintaining this condition over time. The cognitive-behavioural model of CRF captures much of what has been reported on the aetiology of CRF and provides a psychological framework that helps to structure thinking about this complex multifactorial symptom. The model details how biological and emotional factors might interact and how dysfunctional cognitions and beliefs can impact on psychological and behavioural responses that have been linked to CRF. However, while many of the proposed model pathways have empirical support or make theoretical sense, further research is necessary to examine the robustness of the model and to test the hypothesised mechanisms underlying CRF.

Most of the studies on CRF to date have focused on a select number of psychological, biological or behavioural predictors and their relationship with fatigue. While such approaches are informative, they neglect the complex nature of CRF, which is likely to be attributable to a number of different factors simultaneously. The relationships among contributing factors warrant careful consideration; firstly, because failing to take account of strong (and possibly causal) relationships between predictors can lead to misleading assumptions about their relationships with CRF, and secondly, because interactions between predictors could result in a circular process of influence that could help to perpetuate fatigue over time. Research that examines how potential contributing factors to CRF relate to one another and evaluates the simultaneous effects of a variety of proposed contributing factors is needed. Furthermore, although cognitive factors such as low perceived control over fatigue and catastrophising have been linked to CRF severity, the role of patients' illness beliefs in the aetiology of CRF, and how such beliefs relate to other proposed psychosocial and behavioural contributing factors, has not been adequately explored. The mediational pathways proposed by the cognitive-behavioural model offer a useful framework for testing such relationships.

Our understanding of CRF has also been limited by a lack of longitudinal research. Numerous cross-sectional studies have looked at the prevalence of CRF at various different treatment and post-treatment timepoints and among different patient groups; however, few studies have examined the course of CRF across the cancer trajectory. Such information is important for the clinical management of this side-effect so that screening and interventions can take place at opportune times. In addition, few studies have explored the predictors of CRF over time. Identifying risk factors for the development or persistence of CRF nonetheless has clear implications for clinical practice, where such knowledge could help to prevent or efficiently treat this side-effect before it becomes a chronic condition. Furthermore, the nature of interactions between predictors and how these might contribute to the persistence of CRF post-treatment cannot be explored unless they are assessed at multiple timepoints. Longitudinal studies that track the development of CRF from before treatment and assess a broad spectrum of psychosocial and physiological predictors across the cancer trajectory are therefore necessary to understand the factors that precipitate CRF and the interplay of factors that help to perpetuate CRF after treatment. The cognitive-behavioural model of CRF explicitly acknowledges the role of diverse contributing factors and captures how

the impact of these factors might change over time; therefore, it offers a useful conceptual framework for guiding such research.

Chapter 4: Predictors of Fatigue in Cancer Patients Before and After Chemotherapy

"My fatigue is just there - its [sic] part and parcel of all I'm going through with stress and worry. I know it will probably increase during chemo but hopefully once chemo is finished it will start to improve" – Mary

4.1 Introduction

Fatigue is a common and debilitating side-effect of cancer treatment; however, significant fatigue can also be present before the initiation of treatment (Ancoli-Israel et al., 2006; Berger et al., 2007). Previous research suggests that severe fatigue affects between 14 and 28% of cancer patients pretreatment (Goedendorp et al., 2008; Goldstein et al., 2012), and comparison with healthy control groups supports higher prevalence and severity of fatigue among cancer patients before the start of adjuvant therapy (Goedendorp et al., 2011; Jacobsen, Hann, et al., 1999; Prue, Allen, Gracey, Rankin, & Cramp, 2009). Fatigue before adjuvant treatment is significantly associated with more fatigue-related symptoms during treatment (Jacobsen, Hann, et al., 1999), fatigue severity after treatment (Wielgus, Berger, & Hertzog, 2009), and persistent cancer-related fatigue (CRF) post-treatment (Goldstein et al., 2012). As CRF is associated with negative outcomes for cancer patients, it is important to elucidate the factors that contribute to fatigue pretreatment so that patients can receive appropriate support.

Pretreatment fatigue may be due to a number of factors including the cancer itself, physiological factors (e.g., pain, anaemia, or alterations in immune responses), or factors associated with the experience of receiving a cancer diagnosis (e.g., anxiety, stress, depression, sleeping problems, or decreased physical activity). However, few studies have examined the predictors of fatigue at this point in the cancer trajectory. Those that have been carried out to date have largely been cross-sectional, have focussed on a limited number of possible contributing factors, and have produced conflicting findings. Prue et al. (2009) reported that distress, physical symptom distress, and overall valuation of life predicted fatigue prior to adjuvant therapy in gynaecological cancer patients, while activity levels made no significant contribution. In contrast, Goedendorp et al (2008) reported that physical activity, but not anxiety, predicted severe fatigue before treatment in a large sample of cancer patients with various malignancies; although significant differences in anxiety between fatigued and

non-fatigued participants were noted. Depressive mood, impaired sleep and rest, and retrospective reports of fatigue one year before diagnosis were also found to contribute to severe fatigue in this study.

It is possible that sleep disturbances prior to treatment are secondary to psychological distress experienced by patients. Previous research on breast cancer patients prior to adjuvant treatment reported significant associations between fatigue and self-reported sleep disturbances, but failed to find evidence of a relationship between fatigue and objective measures of sleep assessed through actigraphy (Ancoli-Israel et al., 2006; Berger et al., 2007). Such findings support the importance of psychological factors in fatigue pretreatment and suggest that patients' beliefs or perceptions of their sleep, rather than actual sleep, play a key role. Of note, anxiety was not assessed in either of these studies. Thus, the role of sleep disturbances in fatigue pretreatment, and whether they are secondary to psychological distress, is not yet clear. In addition, the long-term impact of pretreatment sleep disruption on fatigue outcomes was not explored.

Von Ah, Kang and Carpenter (2008) assessed fatigue before, during and after adjuvant treatment in breast cancer patients and examined the contribution of a range of possible pretreatment predictors, including psychosocial predictors, such as stress, mood disturbance and social support, and physiological factors, such as morning cortisol, cytokine and natural killer cell activity. Greater fatigue prior to treatment was significantly associated with more mood disturbance and higher interleukin-1 beta (IL-1β), while fatigue after adjuvant treatment was significantly associated with higher pretreatment mood disturbance and morning cortisol. However, the small sample size on which these findings are based and the relatively large number of predictors limits the conclusions that can be drawn; additional research with larger samples and longer follow-up periods are necessary to replicate and expand on these findings.

Few other studies have prospectively examined whether pretreatment predictors of fatigue are correlated with fatigue severity post-treatment. Although Prue et al.'s (2009) study was longitudinal and measured fatigue before, during and after adjuvant treatment, baseline predictors of fatigue after treatment, other than baseline fatigue, were not explored. Wielgus et al. (2009) reported that less total sleep time and higher fatigue prior to adjuvant treatment predicted fatigue 30 days after completing chemotherapy in a sample of breast cancer patients. However, psychological factors such as anxiety and depression were not considered in this study.

The current study assessed a comprehensive set of potential psychological and behavioural predictors of fatigue before the initiation of chemotherapy treatment and examined their contribution to fatigue both before and after treatment completion. In addition, given the concerns over the reliability of self-report scales to assess sleeping patterns and physical activity (Shephard & Vuillemin, 2003), and the often conflicting findings regarding objective and subjective measures in this area, actigraphy and sleep diary data were collected from a subsample of participants in order to perform a measurement check on the self-report measures used.

4.1.1 Aims. The aims of this study were to:

1. Explore the extent to which fatigue affects patients before chemotherapy and after treatment.
2. Examine the relationships between fatigue, mood disturbance, stress, physical activity and sleep before the initiation of chemotherapy treatment.
3. Assess whether fatigue before chemotherapy is predictive of fatigue after treatment and whether psychological, behavioural and sleep-related factors before treatment can predict fatigue severity after treatment.

4.2 Method

4.2.1 Design. A prospective longitudinal study was conducted with participants recruited from May 2010 until September 2012 through two outpatient oncology review clinics in a large urban teaching hospital in Dublin. Fatigue, quality of life, and a range of hypothesised psychological, behavioural and sleep–related predictors of CRF were assessed before chemotherapy treatment (baseline/T1); fatigue and quality of life were assessed again after cancer treatment (T2) and at a follow-up assessment at least five months after treatment was completed (T3).

4.2.2 Participant recruitment.

4.2.2.1 Ethics. Ethical approval for the study was obtained from the institutional research ethics committees in both the hospital and the university in which the research was carried out (see Appendix 2). All participants provided written informed consent prior to study inclusion (see Appendix 4), and all procedures followed were in accordance with the Helsinki Declaration.

4.2.2.2 Participant eligibility. The medical charts of consecutive new patients in two oncology outpatients' clinics were prescreened by the researcher in order to assess eligibility. Patients were attending the clinic in order to discuss potential adjuvant or neoadjuvant treatment options for recently diagnosed breast,

gastrointestinal, genitourinary or gynaecological cancer. Potentially eligible patients diagnosed with lymphoma who were scheduled to begin chemotherapy were also referred to the researcher by clinical nurse specialists in the oncology ward, and their medical charts were reviewed prior to their next scheduled visit to confirm eligibility. The inclusion criteria were: (a) a first-time diagnosis of cancer, (b) referral for adjuvant or neoadjuvant chemotherapy with curative intent based on the clinical assessment of the patient's consultant, (c) ability to understand written and spoken English, and (d) being at least 18 years of age. Exclusion criteria were: (a) evidence of advanced cancer where treatment was not likely to be curative, (b) previous diagnosis and treatment for cancer with the exception of non-invasive skin cancer, (c) any other known severe health problems or psychiatric comorbidities (e.g., schizophrenia, dementia, or Alzheimer's disease) that would limit participation, and (d) clinical levels of distress based on the clinical recommendations of the patient's consultant and care team. As recruitment had to be carried out at a difficult time for patients (i.e., between referral for chemotherapy and treatment begin) and patient welfare was paramount, patients who presented with clinical levels of distress were not approached regarding participation; doing so may have contributed further to their level of distress and severe distress may have impeded their ability to give informed consent.

4.2.2.3 Recruitment procedure. Consecutive convenience sampling was used; hence every patient who met the inclusion criteria was approached. Research notes were left in the charts of eligible patients to inform their oncologist about their potential eligibility. If a patient was referred for chemotherapy and the oncologist confirmed their suitability for the study, the patient was given a copy of the study information sheet during or after their consultation and informed that a researcher would discuss the study with them. Patients were then approached by the researcher to discuss the study. Patients referred by clinical nurse specialists were approached by the researcher during scheduled hospital visits before the start of their chemotherapy.

4.2.3 Procedure.

4.2.3.1 Assessment procedures. At the first timepoint, participants met with the researcher in the hospital during one of their scheduled hospital appointments. They were given the first set of questionnaires to complete before their first session of chemotherapy. The questionnaires could be completed at home and stamped addressed envelopes were provided for returning them. A subsample of participants (25% of the sample) was also given an actigraph to wear and a sleep diary to complete along with

the first questionnaire. As a limited number of actigraphs were available, allocation of actigraphs was determined on a convenience basis; a participant was given an actigraph if one was available at their first assessment point. All participants who were asked to wear an actigraph agreed to do so.

For subsequent timepoints participants were contacted by telephone at the appropriate follow-up time and, if they were willing to continue with the study, questionnaires were then posted to them at home. Participants were contacted by telephone if they did not return a questionnaire after two weeks. A final reminder call was made if participants still did not return the questionnaire after a further two weeks had passed.

4.2.3.2 Timing of assessments. Participants followed different treatment pathways; although all participants were treated with chemotherapy, some also had surgery either before or after chemotherapy and/or also received radiation therapy. The baseline assessment was completed after diagnosis and prior to chemotherapy. The post-treatment assessment was completed within six weeks of completing all cancer treatments (surgery, chemotherapy and radiation therapy), with the exception of hormonal treatment and treatment with the monoclonal antibody Herceptin for some breast cancer patients. Participants had finished all cancer treatments at least five months previous to completing the final follow-up questionnaire. In line with previous research on the predictors of fatigue in breast cancer survivors (e.g., Alexander, Minton, Andrews, et al., 2009; Bower, 2007; Cavalli Kluthcovsky et al., 2011), ongoing use of hormonal therapy at post-treatment follow-up assessments was permitted. Previous studies found no relationship between ongoing use of hormonal therapy and fatigue (e.g., Donovan et al., 2007; Goedendorp et al., 2011).

4.2.4 Measures.*Demographic and medical information.* An author-constructed questionnaire was used at baseline to collect the following sociodemographic information: age, gender, menopausal status, marital status, number of children and children living at home, employment status, and educational level. In addition, one item was included as a brief measure of pain: "How would you rate your level of pain on a scale of 0 to 10 over the past 7 days?" (0 – "*No pain*", 10 – "*Worst pain you can imagine*"). Medical data, including type of cancer, disease stage, type of treatment (e.g., surgery, radiation therapy, chemotherapy, hormone treatment) and treatment regimen, time since diagnosis and time of treatments, comorbid medical conditions, and height and weight, were collected from hospital medical charts. In

addition, demographic and medical information provided by patients, such as menopausal status, was verified by cross-referencing with medical records.

4.2.4.2 Outcome measures.

Fatigue. Fatigue severity was assessed using the Functional Assessment of Cancer Therapy - Fatigue scale (FACT-F; Yellen et al., 1997). The FACT-F is a brief (13-item) unidimensional scale that measures the physical impact of fatigue (e.g., "I feel weak all over"). Each item has a 5-point response scale (0 - "*Not at all*" to 4 - "*Very much*") and the sum of the responses, with a possible range from 0 – 52, is used as the overall score, whereby lower scores indicate more severe fatigue. A cut-off of below 36 has been proposed to identify patients at higher risk of clinically significant fatigue (Alexander, Minton, & Stone, 2009). The FACT-F is easy to administer, has good psychometric properties and has been widely used in a range of different cancer patient groups (Agasi-Idenburg, Velthuis, & Wittink, 2010; Minton & Stone, 2009). In a systematic review of CRF scales, Minton and Stone (2009) recommend this scale for research, especially for intervention or longitudinal studies, because it has a validated clinically significant score change (minimum clinical important difference = 3 points). In the present sample, Cronbach's alpha was .94 at baseline, .95 post-treatment and .93 at follow-up.

Quality of life. Quality of life (QOL) was assessed using the five single item Linear Analogue Self Assessments (LASAs) outlined by Locke et al. (2007). These items each target a specific aspect of QOL (physical, emotional, spiritual, and intellectual well-being) as well as an item for overall QOL. Each item has an 11-point response scale (0 – "*As bad as can be*" to 10 – "*As good as can be*"), and the average of these items can be used as a composite QOL measure. A higher mean score indicates better perceived QOL. The psychometric properties of these items were investigated in an oncology patient sample (Locke et al., 2007). Although the items are designed to measure different, but related, aspects of QOL, high internal consistency was found between the items (α = .83, .88, and .88 at three different timepoints). In addition, scores on the LASA scales had moderate to strong significant correlations with similar, more detailed and well-validated measures of QOL that have been used in cancer (e.g., the FACT overall QOL, physical- and emotional- well-being scales), thus supporting the concurrent and construct validity of the LASA. In the present sample, Cronbach's alpha was .86 at baseline, .92 post-treatment and .89 at follow-up.

4.2.4.3 Predictor variables. Self-report questionnaires were used to assess all predictor variables. In cases where individual items from standardised scales were missing, the average of the completed items was used to calculate the total score for a scale, provided that more than half of the items were completed. In instances where half or more of the scale items were missing, no total score was calculated for that scale.

Anxiety and Depression. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). The scale contains 7 items for anxiety (e.g., "Worrying thoughts go through my mind") and for depression (e.g., "I look forward with enjoyment to things"), scored on 4-point (0-3) response scales with a maximum score of 21 for each scale. Higher scores indicate more severe anxiety and depression; scores of between 0 and 7 are considered normal, 8-10 are considered suggestive of a mood disorder, and scores of 11 or higher indicate probable 'caseness' of a mood disorder (Snaith, 2003). Analyses in this study primarily used the HADS scores as continuous variables; however, prevalence figures of anxiety and depression cases are presented using the cut-off scores of 8 or above and 11 or above. The HADS was chosen as a measure of depression because it excludes somatic symptoms of depression, such as fatigue, and therefore avoids potential confounding. However, some concern has been expressed over item 8 "I feel as if I am slowed down" because of its similarity with fatigue. Therefore, in line with previous research (e.g., Stone, Hardy, et al., 2000; Stone, Richards, et al., 2000; Stone et al., 2001), this item was excluded from any analysis that investigated the association between depression and fatigue.

Investigations of the factor structure, discriminant validity, and internal consistency of the HADS have shown that the psychometric properties of the HADS are excellent (Bjelland, Dahl, Haug, & Neckelmann, 2002; Mykletun, Stordal, & Dahl, 2001). The HADS has also been used extensively in research with cancer patients, supporting the validity of this measure (Berger et al., 2009; Fossa et al., 2003; Haghighat et al., 2003). In the present sample, Cronbach's alpha was .84 for anxiety and .85 for depression at baseline.

Stress. Psychological stress was assessed using the Perceived Stress Scale (PSS) – short version (Cohen, Kamarck, & Mermelstein, 1983). The scale contains four items (e.g., "In the last week, how often have you felt that you were unable to control the important things in your life?") measured on 5-point response scales (0 –

"*Never*" to 4 – "*Very often*") and a mean of the item responses is used as an overall score. The 4-item PSS has good internal reliability and adequate test-retest reliability, and is suggested for use in cases where very short scales are required (Cohen et al., 1983). In the present sample, Cronbach's alpha was .75 at baseline.

Physical activity. Self-reported activity levels were measured using the Short International Physical Activity Questionnaire (IPAQ; Craig et al., 2003). The IPAQ and the Short IPAQ have been validated in 12 countries (Craig et al., 2003). The short form provides a brief and straightforward self-report measure of physical activity that has measurement properties equivalent to the long form. Based on 6-items, the total time spent walking and doing moderate and vigorous physical activity in the last seven days can be estimated. A total weekly physical activity estimate can be calculated by weighting the reported total time per week spent on each activity category by a metabolic equivalent (MET) energy expenditure value, according to the published protocol (e.g., walking = 3.3, moderate intensity = 4.0, and vigorous intensity = 8.0; IPAQ, 2005); the total weekly physical activity estimate (MET-mins/week) is calculated by multiplying the activity category MET value by the number of minutes of activity/day by the number of days per week and summing these across activity categories. In addition, the final item of the short IPAQ assesses the average number of hours/day spent sitting on a weekday.

Sleep. Sleep disturbance was measured using the three items employed by Anderson et al. (Anderson et al., 2003), which concern waking up during the night, waking up too early in the morning, and difficulty falling asleep (e.g., "During the past week have you had difficulty falling asleep?"). Each item is measured on a 7-point scale (1 – "*Not at all true of me*" to 7 – "*Extremely true of me*"). A composite mean score can be calculated, whereby higher scores indicate greater self-reported sleep disturbance. These items exhibited adequate internal reliability (α = .71) and good construct validity based on factor loadings (between 0.75 and 0.83) in previous research (Anderson et al., 2003). In the present sample, Cronbach's alpha was .84 at baseline.

In addition, participants were asked to report their typical bedtime, the typical getting-up time, the typical length of time spent sleeping during the night (in hours), as well as the typical length of time (in minutes) it took them to get to sleep at night during the past week. Total sleep period (the number of hours spent in bed at night) was calculated from typical bed- and getting-up times. Sleep-efficacy (the percentage of

time in bed at night spent sleeping) was calculated using the total sleep period and the reported time spent sleeping at night.

4.2.4.4 Actigraphy and diary measures of physical activity and sleep.

Objective data on sleep and activity were obtained using actigraphy (Actiwatch 2, Philips Resprionics Inc., Bend, OR) from a subsample of participants. Actigraphy is a non-invasive method of measuring day- and night-time activity levels through motion-sensitive accelerometers worn on the wrist. Information on body movements and white light was recorded in 15 second epochs. The data were scored using Actiware software version 5.59.0015 (Philips Resprionics, 2009). The Actiwatch and the associated algorithms have been validated against polysomnography (Meltzer, Walsh, Traylor, & Westin, 2012; Tonetti, Pasquini, Fabbri, Belluzzi, & Natale, 2008).

Participants were asked to wear the actiwatch continuously on their nondominant wrist for four days (96 hours) beginning at 1pm on the first day of recording. The Actigraph 2 has an event marker, which is a small button on the side of the device that places a marker on the actogram data and can thereby help with scoring; participants were instructed to push the event marker to indicate 'intent to go to sleep' time and 'wake up' time. As the Actiwatch 2 is waterproof, participants were informed that they should continue to wear the device for washing and showering. As the time-frame between participant recruitment and the start of chemotherapy treatment was typically short, it was not feasible to keep the days of the week on which the actiwatch was worn consistent between participants or to restrict measurement to weekdays or weekends.

Participants were asked to complete a sleep diary each morning upon wakening for the duration of actigraph recording. The diary recorded bed time, lights out time, lights on (wake time), time taken to get to sleep, total duration of sleep, number and duration of awakenings during the night, a rating of sleep quality, and nap times during the day. Participants were given instructions on how to complete the sleep diary and a sample entry was included on the diary to illustrate how responses should be given (see Appendix 5).

Validated algorithms embedded within the software programme were used to estimate sleep and wake states. Actiware uses a threshold-based method algorithm to score activity counts, whereby the level of activity is compared to a value generated by the Actiware sleep algorithm for each epoch. The medium sensitivity threshold (40 counts per epoch), which is the default criterion for the Actiware programme, was used

in the present study. Time limits were set for the 96-hour period, and automatic sleep scoring was performed. The file was reviewed and intervals were adjusted individually for each day and night period using the event markers, sleep diary data, cascading movement count, and light sensor data as decision aides to help determine sleep and wake times. All actigraphy data was scored by the same author to promote consistency in scoring. Aggregated mean actigraphy variables were obtained for five sleep parameters and one activity parameter. The definitions for each of these parameters are listed in Table 4.1. Subjective data on corresponding sleep parameters from the sleep diary was also computed and definitions are included in the table.

Table 4.1 *Sleep/wake and activity parameters assessed using actigraphy and the sleep diary*

Variable	Definition
Actigraphy:	
Total sleep period (TSP-A)	Total number of hours spent resting at night between start of rest period and final wake time.
Total sleep time (TST-A)	Total number of hours of sleep at night.
Sleep efficiency (SE-A)	Percentage of night-time rest period spent sleeping (TST-A divided by TSP-A, multiplied by 100).
Sleep onset latency (SOL-A)	Total number of minutes required for the onset of sleep after first attempting to get to sleep.
Time awake after sleep onset (WASO-A)	Percentage of time awake after sleep onset.
Mean daytime activity count	Average activity count per minute between day and night-time rest periods
Diary:	
Total sleep period (TSP-D)	Time in hours between "Lights off" and "Lights on (wake time)".
Total sleep time (TST-D)	Total number of hours of sleep while in bed at night.
Sleep efficiency (SE-D)	Percentage of time in bed spent sleeping (TST-D divided by TSP-D, multiplied by 100).
Sleep onset latency (SOL-D)	The number of minutes required for the onset of sleep after first attempting to get to sleep.
Time awake after sleep onset (WASO-D)	Total time (in minutes) awake after sleep onset at night.
Sleep quality	Rating of sleep quality on a scale of 0 – "*very bad*" to 10 – "*excellent*".

4.2.5 Analysis. Descriptive statistics were used to describe the demographic and medical characteristics of participants. Differences in fatigue severity between participants with different demographic and medical characteristics were assessed using *t* tests and analysis of variance (ANOVA).

To address the first aim of the study, descriptive statistics were used to describe the presence of fatigue at baseline, post-treatment and follow-up. The extent to which

fatigue affects patients before the start of chemotherapy and after treatment was evaluated by examining the relationship between fatigue and quality of life using Pearson product moment correlations. Regression analysis was conducted to evaluate whether fatigue predicted quality of life at baseline and whether changes in fatigue could predict changes in quality of life over time.

To perform a measurement check on the self-report measures of sleep and physical activity, Pearson correlations were calculated between corresponding self-report, diary and actigraphy measures for each of the sleep and activity parameters. Self-report measures that had a correlation of above .3 with both diary and actigraphy measures for that parameter and were significantly correlated with at least one of these measures were considered valid and retained for subsequent analyses. Self-report measures that did not meet these criteria were not included in any further analysis.

To address the second and third aims of the study, descriptive statistics were used to describe participants' sleep and physical activity patterns, depression, anxiety, stress, and sleep disturbances, and Pearson product moment correlations were used to examine the relationships between these hypothesised predictors and fatigue severity at baseline, post-treatment and follow-up. Hierarchical multiple regression was used to investigate whether psychological, behavioural and sleep-related factors could predict fatigue before and after treatment and at follow-up. For each analysis, demographic and medical factors that were significantly associated with fatigue at that timepoint were entered into the model first, followed by hypothesised predictors in step 2. Fatigue at baseline was also included as a predictor in step 1 for the regression analyses of fatigue post-treatment and at follow-up.

4.3 Results

4.3.1 Study response rate. *Figure 4.1* provides an overview of participant accrual and retention. In total, 136 patients were approached and 120 (88.23%) consented to participate in the study. Of the 16 patients who did not consent to participate, four were excluded because they could not be contacted again before their treatment was scheduled to begin and 12 patients declined to participate. Reasons given for not participating were feeling overwhelmed with the diagnosis and the required treatment (n = 5), having too much to think about already (n = 4), participating in a clinical trial already and therefore not wanting to do another research study (n = 2), and having no interest in research (n = 1).

Two participants failed to return baseline questionnaires and eight patients changed their minds about participation before completing the baseline questionnaire. Reasons given for not continuing with the study were feeling too anxious about the treatments ahead (n = 4) and having too much to think about at the time (n = 4). Participants who participated in the study did not significantly differ from those who withdrew on age, education, stage of disease, or type of treatment (p >.05). A further 10 participants were excluded retrospectively because it emerged that their disease was more advanced than originally diagnosed, and/or they showed signs of disease progression after chemotherapy and their subsequent treatment was no longer considered curative. These 20 patients were excluded from the study sample and were not included in the description of participant characteristics described in the next section. Therefore, there were 100 participants in the sample.

Drop-out from the study after baseline was comparable to previous longitudinal studies on similar patient groups (Prue et al., 2009). Two participants declined to continue with the study before the first follow-up assessment and a further four declined to continue before the second follow-up assessment. Reasons for not continuing were time pressure, feeling overwhelmed or not wanting to fill in any more questionnaires. Three participants could not be contacted to arrange follow-up assessments and six failed to return either a T2 or a T3 questionnaire. Participants who did not complete a follow-up questionnaire (n = 11) were compared with those who completed at least one follow-up (n = 89) in order to ensure that those who chose to remain in the study were not biased. No significant differences were found between these groups in fatigue severity at baseline (p > .05); however, those who did not complete follow-up assessments had significantly higher BMI (M = 30.63, SD = 6.57) and anxiety (M = 10.36, SD = 4.65) at baseline than those who completed follow-up(s) (BMI: M = 26.71, SD = 5.02; Anxiety: M = 7.53, SD = 4.02; p < .05). No further differences on any medical or demographic characteristics, or on the remaining study predictors, were detected.

Twelve participants returned questionnaires for the post-treatment assessment after the 6-week cut-off and were therefore excluded for this timepoint. Sixteen participants were excluded from the follow-up assessment because they were still receiving or had only recently (< five months) stopped receiving treatment with Herceptin for breast cancer. Participants with breast cancer who were treated with Herceptin after the completion of all other cancer treatments (n = 10) were significantly

more fatigued (M = 28.50, SD = 11.98) than those who had not received Herceptin (n = 41; M = 37.88, SD = 10.79), $t(48) = 2.41$, $p < .05$, two-tailed. Therefore, the acute effects of this cancer treatment on fatigue could not be ruled out in these participants, and they could not be considered at least five months post-treatment.

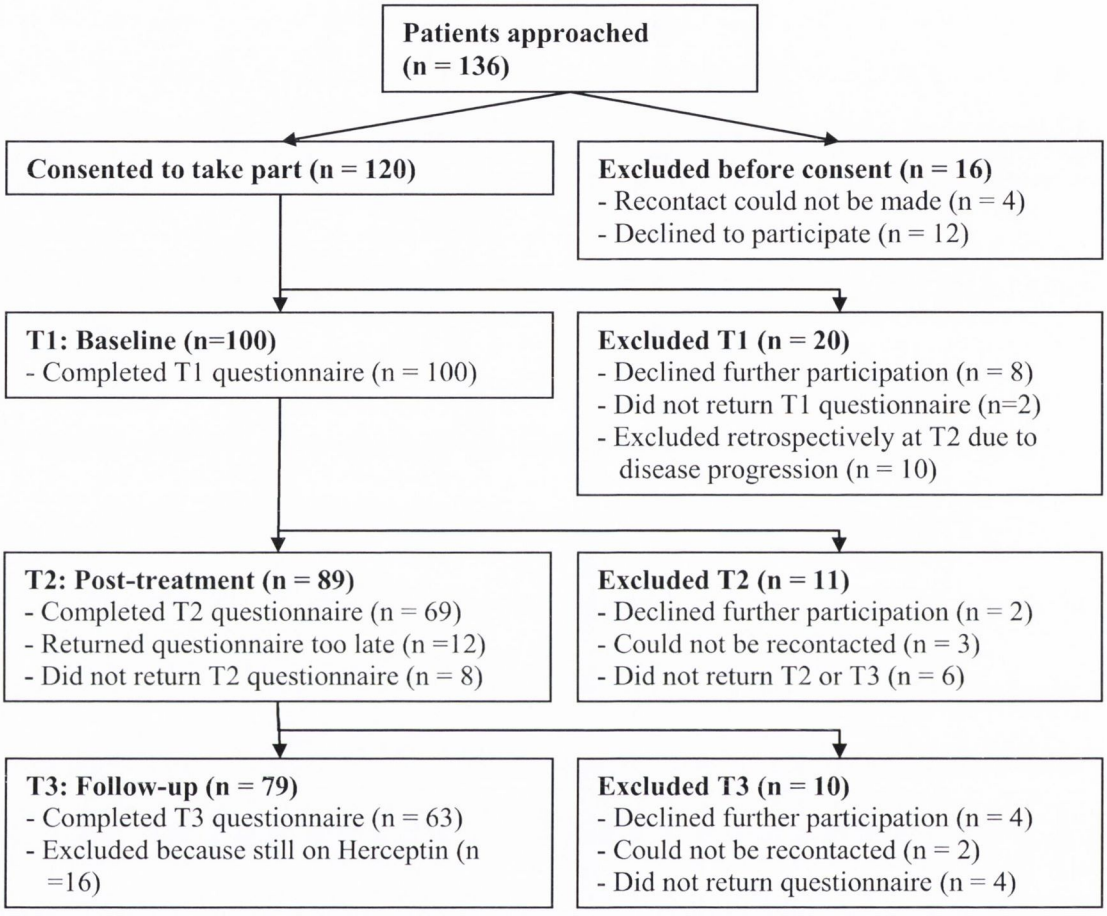

Figure 4.1. Overview of participant accrual and retention.

4.3.2 Participant characteristics.

4.3.2.1 Treatment information. The participants' treatment pathways are illustrated in *Figure 4.2.* Seventy-one participants had surgery prior to the baseline assessment (mean number of days since surgery = 41.83, SD = 19.00). Time since surgery was not associated with fatigue severity at baseline (r = .03, n = 69), and no significant differences in baseline fatigue levels were found between those who had had surgery before T1 (n = 69; M = 36.29, SD = 11.92) and those who had not (n = 28; M = 38.11, SD = 12.62), $t(95) = -.67$, $p > .05$, two-tailed; therefore, data are reported for all participants as one group.

Of those who had adjuvant chemotherapy, 52 (74%) also had radiation therapy before the T2 assessment. Nineteen participants had surgery after the baseline assessment, as well as radiation and chemotherapy. Of those who did not have surgery,

seven received radiation therapy concurrently with chemotherapy, one received radiation after chemotherapy, and two received only chemotherapy. The average time since treatment was 22.12 days (SD = 10.40) at T2 and 231.21 days (SD = 47.58) at T3. There were no significant differences in fatigue severity post-treatment or at follow-up between any of the treatment groups ($p > .05$); therefore, data for all treatment groups were combined for all further analyses.

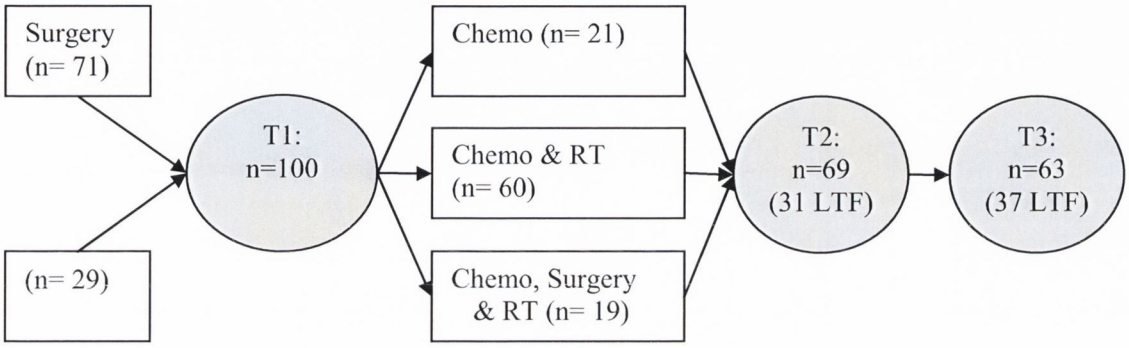

Figure 4.2. Timeline of the three assessment points in relation to participants' treatments.

Note. LTF = Lost to follow-up or excluded from follow-up.

4.3.2.2 Participant characteristics. The demographic and medical characteristics of the participants are displayed in Table 4.2. Participants' ages at diagnosis ranged from 19 to 77 with a mean age of 49.76 years (SD = 10.81). The vast majority of participants were female and either married or living with a long-term partner. All but three participants were white. The majority of participants had children; of these, 81% had children living at home. Most participants were employed full- (n = 51) or part-time (n = 2) and had at least an upper second level of education (≥12 years). More than half of the sample was overweight according to the WHO BMI classification; the mean BMI was 27.14 (SD = 5.32). Less than half of the sample had another health problem at the time of diagnosis; the mean number of comorbidities was 0.86 (SD = 1.10). The most common comorbidities were hypertension, cholesterolemia, thyroid problems, asthma and osteoarthritis. All other comobidities were experienced by five participants or less (see Appendix 6). The vast majority of participants had breast cancer and most participants had lymph nodes positive for cancer at the time of diagnosis (M = 3.31, SD = 4.86). The majority of patients were treated with radiation and surgery as well as chemotherapy. Appendix 6 contains a more detailed breakdown of the surgical treatments and chemotherapy regimens received by participants.

Table 4.2 *Participants' demographic and clinical characteristics (n = 100)*

Demographic characteristics	n	Clinical characteristics	n
Gender		Cancer type	
Male	7	Breast Cancer	77
Female	93	Gynaecological Cancer	12
Menopausal status		Colorectal Cancer	8
Premenopausal	47	Lymphoma	3
Perimenopausal	17	Disease stage	
Postmenopausal	26	I	19
Children		II	44
Has children	73	III	37
Has children living at home	59	Positive lymph nodes present	66
Marital status		Type of treatment	
Married/Partnered	68	Chemotherapy	100
Single	18	Surgery	90
Separated/Divorced	7	Radiation Therapy	79
Widowed	7	Hormonal treatment	69
Employment status		Herceptin	16
Employed	53	Comorbities	
Housewife	22	No comorbidities	51
Retired	11	1 comorbidity	24
Resigned for health	6	2 comorbidity	17
Unemployed	5	≥3 comorbidities	8
Student	2	BMI (kg/m^2) class[a]	
Highest educational level		Underweight (< 18.5)	1
Primary (≤ 8 years)	11	Normal (18.5 – 24.9)	38
9 - 11 years	19	Overweight (25 – 29.9)	38
12 - 14 years	36	Obese (≥30)	23
Third level education	23		
Postgraduate	10		

[a]Based on World Health Organisation BMI classification.

4.3.3 Fatigue and quality of life before chemotherapy and after treatment.

Using a cut-off score of <36 on the FACT-F, 39 participants were significantly fatigued at baseline, 33 (48.5%) were significantly fatigued post-treatment, and 19 (30%) were significantly fatigued at follow-up. Higher fatigue was significantly associated with lower QOL at baseline ($r = .69, p < .01$), post-treatment ($r = .73, p < .01$), and at follow up ($r = .60, p < .01$). Increases in QOL over time were significantly associated with decreases in fatigue severity from baseline to post-treatment ($r = .71, p < .01$) and from post-treatment to follow-up ($r = .57, p < .001$). Changes in fatigue severity ($\beta = .71, p <$

.001) explained 50% of the variance in changes in QOL from baseline to post-treatment, $F(1, 60) = 60.95$, $p < .001$. Changes in fatigue severity ($\beta = .57$, $p < .001$) from post-treatment to follow-up explained 31% of the variance in changes in QOL, $F(1, 45) = 21.69$, $p < .001$.

4.3.4 Subanalysis of objectively and subjectively assessed measures of sleep and activity. The purpose of the subanalysis was to perform a measurement check on the self-report measures of activity and sleep by investigating whether scores on the self-report measures correlated with actigraphy data on activity and sleep and diary data on sleep. Correlations between the three assessment measures are displayed in Table 4.3.

Table 4.3 *Correlations between actigraphy and diary data and self-report measures*

Sleep/Activity Parameter	Type of Measure	Actigraph	Diary
Total sleep period (TSP)	Self-report questionnaire	.36	.58**
	Diary	.78**	-
Total sleep time (TST)	Self-report questionnaire	.24	.37
	Diary	.51*	-
Sleep efficacy (SE)	Self-report questionnaire	.17	-.03
	Diary	.46*	-
Sleep onset latency (SOL)	Self-report questionnaire	.20	.56**
	Diary	.41	-
Sleep disturbance	Self-report questionnaire	.38[1]	.38 / -.65**
	Diary: (1) Time awake after sleep onset (WASO) (2) sleep quality	.51*[1] -.31	-
Activity	Self-report questionnaire: (1) MET-min/week	.31	-
	(2) Time spent sitting per day	-.57**	-

[1]Percentage time awake after sleep onset (WASO-A) was used as the actigraphy indicator of sleep disturbance. *p <.05, **p <.01, ***p <.001.

The self-report measures for total sleep period and sleep disturbance demonstrated the strongest associations with actigraphy and diary measures and met the criteria for inclusion in further analyses. Total sleep time and sleep-efficacy were not significantly correlated with either the diary or the actigraphy data and the observed correlations with these measures were weak. Sleep onset latency was significantly correlated with the corresponding diary measure; however, the correlation with actigraph sleep latency was weak. Although there is evidence that sleep latency is less reliable than other sleep parameters using actigraphy (Berger et al., 2007), this variable was not retained for further analysis.

No diary measures of activity were assessed in the study; however, mean activity count per minute measured by actigraphy had a moderately strong correlation with self-reported total weekly physical activity (MET-mins/week) and a strong significant correlation with self-reported mean time spent sitting per day. These measures of activity were therefore also retained for further analyses. In addition to the empirical grounds for retaining the chosen four measures of sleep and activity, there was also a conceptual rationale for their inclusion; there is minimal conceptual overlap between the measures as they capture diverse aspects of sleep (time spent resting at night and sleep disturbance) and activity (extent of physical activity and time spent inactive during the day).

4.3.5 Demographic and medical factors and fatigue. Greater fatigue before chemotherapy was significantly associated with having a greater number of medical comorbidities (r = -.27, n = 100, $p < .01$) and higher pain severity (r = -.39, n = 99, $p <$ .001). No other significant associations were found between any demographic or clinical factors and fatigue severity at baseline (age, marital status, having children, children living at home, employment status, educational level, BMI, menopausal status, the presence of comorbidities linked with fatigue, disease stage, and lymph node involvement). Differences in fatigue severity and prevalence across different cancer types and gender could not be examined due to the small number of patients with cancers other than breast cancer and the small number of male participants. No significant associations were found between any demographic, clinical or treatment-related factors (time since treatment, treatment types, number of treatment cycles, length of treatments) and fatigue severity post-treatment or at follow-up.

4.3.6 Fatigue severity and correlates of fatigue before and after treatment. Descriptive statistics for fatigue severity at each timepoint and for each of the predictor variables are detailed in Table 4.4. A repeated measures ANOVA determined that there was no significant difference in mean fatigue severity between timepoints, $F(2, 96) = 2.53$, $p > .05$. Forty-eight participants had a HADS anxiety score of 8 or above at baseline, indicating a possible mood disorder, whereby 25 of these had a score of 11 or above, suggesting caseness of a mood disorder. Rates of possible depression were lower; 21 participants had a HADS depression score of 8 or above, whereby eight had a score of 11 or above.

Pearson correlation coefficients between fatigue and the hypothesised predictors are displayed in Table 4.4. Significant, moderately strong, correlations were observed

between fatigue before chemotherapy and fatigue post-treatment, anxiety, depression, stress, and sleep disturbance. Greater fatigue after treatment was significantly associated with greater fatigue at follow-up and higher baseline anxiety and sleep disturbance. Significant associations were also observed between higher fatigue at follow-up and higher levels of depression and stress. Anxiety, depression and stress shared strong positive correlations. Furthermore, the association between anxiety and sleep disturbance was moderately strong and significant.

4.3.7 Predictors of fatigue before chemotherapy. A hierarchical multiple regression was conducted with fatigue before chemotherapy as the dependent variable. Number of comorbidities and pain were entered as independent predictors in step 1 of the analysis, and anxiety, depression, stress, sleep disturbance, total sleep period, and physical activity were entered in step 2.

As the distribution of physical activity was extremely skewed (see mean and median in Table 4.4), the MET-min/week scores were transformed using a $\log_{10}$ transformation. Kolmogorov-Smirnov test of normality on the resulting distribution was not significant ($p > .05$) and skewness and kurtosis values were between ±1. Time spent sitting during the day was not included in the analysis because the large number of missing values for this variable (14%; see Table 4.4) would reduce the total sample size to below the minimum recommended size for regression using listwise deletion (<10 participants per predictor; Meyers, Gamst, & Guarino, 2006). Multivariate outliers were screened by computing Mahalanobis distance for each case on the eight predictor variables. Two extreme cases were detected ($p < .001$) and excluded from the analysis. Two further cases with standardised residuals greater than 3 were eliminated using the SPSS casewise diagnostics routine. Multicollinnearity was not detected and assumptions regarding independent and normally distributed residuals were met.

The final regression model (see Table 4.5) was significant; $F(8, 79) = 14.03$, $p < .001$. Number of comorbidities and pain accounted for 15% of the variation in fatigue before chemotherapy; however, only pain was a statistically significant predictor ($\beta = -.38$, $p < .001$). The addition of the psychological, behavioural and sleep-related predictors in step 2 accounted for 55% of the variance in fatigue. Four of the eight predictors contributed significantly to the prediction of fatigue before chemotherapy ($p < .05$).

Table 4.4 *Descriptive statistics and correlation coefficients between fatigue at baseline, post-treatment and at follow-up and predictor variables at baseline*

	n	Mean (SD)	Median	Min - Max	Possible range	1	2	3	4	5	6	7	8	9	10
1. Fatigue baseline (T1)	100	36.91 (12.00)	40	3 - 52	0 -52	-	.44**	0.24	-.57**	-.65**	-.62**	-.45**	-0.08	0.07	0.08
2. Fatigue post-treatment (T2)	68	34.19(12.45)	36	5 - 52	0 -52		-	.33*	-.33**	-.20	-0.21	-.34**	-0.12	0.14	-0.20
3. Fatigue follow-up (T3)	63	38.95 (9.71)	41	13 - 52	0 -52			-	-0.21	-.35**	-.27*	-0.16	-0.21	-0.09	0.10
4. Anxiety	100	7.84 (4.17)	7	0 - 19	0 - 21				-	.64**	.62**	.40**	-0.05	0.16	-0.17
5. Depression	100	4.45 (3.92)	3	0 - 19	0 - 21					-	.66**	.23*	.23*	-0.01	-0.20
6. Stress	99	1.38 (0.87)	1.5	0 – 3.75	0 - 4						-	.31**	0.14	.21*	-0.07
7. Sleep disturbance	96	4.02 (1.98)	4.17	1 - 7	1 - 7							-	0.01	-0.18	0.09
8. Total sleep period (hrs)	96	9.00 (1.68)	9	3.5 – 15.5	-								-	0.03	-0.05
9. Physical activity (MET-min/wk)	94	4267.74 (4607.38)	2613	0 - 17850	-									-	-.28**
10. Time spent sitting (hrs)	86	5.29 (2.39)	4.25	1 - 11	-										-

Note. The significance associated with the strength of a correlation coefficient varies due to different T1, T2, and T3 sample sizes for the measure of fatigue. *p <.05, **p <.01, ***p <.001.

Table 4.5 *Regression analysis summary for predictors of fatigue before chemotherapy*

Predictor variables	B	SEB	β	R^2	Adjusted R^2	Change in R^2
Step 1						
Comorbidities	-1.48	1.05	-.14			
Pain	-1.8	0.46	-.38***	.17	.15	-
Step 2						
Comorbidities	-0.75	0.79	-.07			
Pain	-0.84	0.37	-.18*			
Anxiety	-0.13	0.29	-.05			
Depression	-1.19	0.42	-.31**			
Stress	-3.80	1.42	-.30**			
Sleep disturbance	-1.10	0.46	-.20*			
Total sleep period	0.04	0.58	.00			
Physical activity	1.37	1.54	.07	.59	.55	.41

Note. Physical activity = Log_{10} MET-min/week. *p <.05, **p <.01, ***p <.001.

4.3.8 Predictors of fatigue after treatment. Fatigue before chemotherapy was entered as a predictor in step 1 of the analysis, and anxiety, depression, stress, sleep disturbance, total sleep period, and physical activity were entered in step 2. No multivariate outliers were detected and assumptions regarding residuals and multicollinnearity were met.

Table 4.6 *Regression analysis summary for predictors of fatigue after chemotherapy*

Predictor variables	B	SEB	β	R^2	Adjusted R^2	Change in R^2
Step 1						
Fatigue at T1	0.46	0.12	0.44***	.19	.18	-
Step 2						
Fatigue at T1	0.48	0.18	.46**			
Anxiety	-0.83	0.57	-.27			
Depression	1.06	0.80	.25			
Stress	2.26	2.60	.17			
Sleep disturbance	-0.79	0.95	-.12			
Total sleep period	-1.05	0.89	-.16			
Physical activity	1.12	3.52	.04	.27	.18	.08

Note. Physical activity = Log_{10} MET-min/week. * p <.05, ** p <.01, *** p <.001.

Fatigue before chemotherapy accounted for 18% of the variation in fatigue after treatment; $F(1, 60) = 14.15$, $p < .001$. The addition of the psychological, behavioural and sleep-related predictors in step 2 did not help to explain any additional variance in the model (see Table 4.6); $F(7, 54) = 2.86$, $p < .05$. Although fatigue before

chemotherapy was still a significant predictor in the final model ($\beta = .46$, $p < .05$), none of the additional predictors made a significant contribution.

4.3.9 Predictors of fatigue at follow-up. Fatigue before chemotherapy were entered as an independent predictor in step 1 of the analysis, and anxiety, depression, stress, sleep disturbance, total sleep period, and physical activity were entered in step 2. Two multivariate outliers were detected ($p < .001$) and excluded. Assumptions regarding residuals and multicollinnearity were met. The regression model was not significant at either step of the analysis, with none of the predictors making a significant contribution to the model ($p > .05$). However, there was a trend towards significance for step 1 of the analysis, with fatigue before chemotherapy ($\beta = .24$, $p = .06$) explaining 4% of the variance in fatigue at follow-up, $F(1, 61) = 3.61$, $p = .06$.

4.4 Discussion

This was the first study to assess the role of a comprehensive set of predictors of CRF before the initiation of chemotherapy treatment and explore their contribution to fatigue before and after treatment, as well as at follow-up. The findings indicate that psychological distress and sleep disturbance play a key role in fatigue before the initiation of treatment. Furthermore, the study provides preliminary evidence that patients who experience fatigue before chemotherapy are at increased risk of experiencing fatigue after cancer treatment has been completed. Based on the current findings there is no evidence that other demographic, clinical, psychological or behavioural indicators at baseline can help to predict fatigue outcomes after treatment.

4.4.1 Severity and impact of fatigue. A substantial number of patients were already fatigued before the initiation of chemotherapy, and the findings suggest that such fatigue adversely affects quality of life; across the three assessments fatigue explained approximately one-third to one-half of the variance in QOL. To our knowledge, this was the first study that examined how changes in QOL related to changes in CRF over the treatment trajectory. The consistent relationship between CRF and QOL, and significant relationships between changes in both variables, highlights the importance of offering support to cancer patients who experience fatigue at all stages of the cancer trajectory.

The presence of fatigue before treatment is in line with previous research (Ancoli-Israel et al., 2006; Berger et al., 2007); however, the percentage of patients with severe fatigue before chemotherapy was higher in the current study than has previously been reported. For example, in contrast to the 39% who scored above the cut-off for

significant CRF in the current study, Goldstein et al. (2012) reported a post-surgery case rate of 24% in breast cancer patients prior to adjuvant treatment, while Goedendorp et al. (2008) also found that 24% of a sample of mixed cancer patients were fatigued before the initiation of treatment. It is possible that differences in the study samples accounted for differences in the prevalence rate. For example, no participants in Goedendorp et al.'s study had undergone surgery at baseline and Goldstein et al.'s study included breast cancer patients only; however, the prevalence of fatigue in the current study was still higher when the analysis was limited to such subgroups. Both Goedendorp et al. and Goldstein et al.'s studies excluded patients with medical co-morbidities that could cause fatigue (e.g., thyroid conditions or arthritis). However, excluding such participants (n = 29) from the current study resulted in only a slight decrease in the prevalence of severe fatigue (37%) and therefore cannot account for these differences. Of note, the generalisability of the prevalence rates reported by Goldstein et al has recently been questioned on account of the number of patients that were excluded from the study (Giacalone, Berretta, Spina, & Tirelli, 2012).

The small sample size, the absence of a comparison group from the general population, and the use of convenience sampling and a self-report measure to assess fatigue in the current study means that the observed prevalence rates of significant fatigue may not accurately reflect the true prevalence of fatigue in cancer patients prior to chemotherapy. The usefulness of the FACT-F in establishing caseness of CRF in clinical practice in lieu of a full diagnostic interview has been questioned due to the low specificity of this measure (Alexander, Minton, & Stone, 2009). However, few studies to date have investigated the prevalence of fatigue before treatment, and those that have, have relied on even briefer and less well established self-report measures of fatigue, such as the six-item SOMA subscale of the Somatic and psychological health report scale (Goldstein et al., 2012) or the eight-item fatigue subscale from the Checklist individual strength (Goedendorp et al., 2008), which have not been included in most comprehensive reviews of scales for assessing CRF (e.g., Agasi-Idenburg et al., 2010; Jean-Pierre et al., 2007; Minton & Stone, 2009). Some authors have suggested a more stringent cut-off of <34 on the FACT-F for the diagnosis of fatigue (Van Belle et al., 2005); the use of these criteria would have somewhat reduced the prevalence of fatigue in the current study (31% at baseline, 44% post-treatment and 24% at follow-up). Additional research with larger and more diverse patient groups, more

comprehensive assessment of CRF, and comparison groups from the general population is required to more accurately quantify the problem of fatigue before treatment.

The number of participants who scored above the threshold for indicating probable caseness of fatigue increased after treatment and decreased again at the final follow-up. However, no significant differences in fatigue severity were detected between the three study timepoints. It is likely that this was due to the small sample size for this analysis, as questionnaires were only available for 50 participants at all of three timepoints. Changes in fatigue between the post-treatment and follow-up assessment points exceeded the minimum clinically significant difference score on the FACT-F (Minton & Stone, 2009), indicating a meaningful decrease in fatigue over the post-treatment follow-up period. Increases in fatigue from pre- to post-treatment, and subsequent decreases a number of months after treatment have been reported in previous studies (Prue et al., 2009).

4.4.2 Predictors of fatigue before chemotherapy. Similar to previous studies (e.g., Prue et al., 2009; Von Ah et al., 2008), demographic and cancer-related factors, with the exception of pain and comorbidities, were not associated with fatigue before the initiation of chemotherapy. Although some participants had undergone prior surgical treatment before the baseline assessment, no significant differences in fatigue were found between these participants and those who had not received any prior surgery. It is somewhat surprising that BMI was not related to fatigue severity in the current study, given the number of studies that have reported an association between BMI and fatigue in cancer patients undergoing treatment (Huang et al., 2010; Wratten et al., 2004) and in cancer survivors (Andrykowski et al., 2010; Gerber et al., 2010). It is possible that BMI plays a greater role in fatigue as patients adjust to the short and long-term side-effects of cancer-treatment. There was no relationship between BMI and post-treatment fatigue in the current study; however, changes in BMI over the course of the study were not monitored.

The finding that increased pain and the number of comorbidities were related to fatigue before treatment indicates the impact that other symptoms and conditions can have on the fatigue experienced by cancer patients, and is in line with the NCCN recommendation that patients with CRF are comprehensively assessed for comorbidities that could contribute to patients' fatigue (National Comprehensive Cancer Network, 2012a). Only two previous studies tested whether medical comorbidities before cancer treatment were associated with fatigue pretreatment

(Fagundes et al., 2012; Goedendorp et al., 2008); in contrast to the current findings, neither study found differences in comorbidities between severely fatigued and non-fatigued participants. Goedendorp and colleagues (2008) also found no relationship between pain and fatigue before treatment. Pain may not have played a role in that study because participants had not received any form of treatment prior to assessment; however, in the current study, prior surgical treatment was not associated with fatigue or pain at baseline (results not shown).

Findings from the current study suggest that psychological factors play a key role in fatigue before treatment; anxiety, depression and stress were all strongly correlated with fatigue prior to chemotherapy. This supports previous findings (Fagundes et al., 2012; Goedendorp et al., 2008; Prue et al., 2009; Von Ah et al., 2008). It is possible that patients' psychological reaction to their cancer diagnosis and apprehension about impending treatments contributed to higher perceived psychological distress and thereby fatigue. The number of participants who scored above the thresholds for indicating possible and probable depression was in line with previous studies of cancer patients (Hinz et al., 2010; Stone et al., 2001) while the mean HADS anxiety score and the number of participants with scores above the cut-off for probable caseness of anxiety (25% with a score of 11 or higher) was even higher in the current study than has previously been reported in both samples of cancer patients (16 - 20%; Haghighat et al., 2003; Hinz et al., 2010; Stone et al., 2001) and the general population (6%; Hinz et al., 2010). However, only depression and stress emerged as significant predicators of fatigue in a multivariate analysis with pain and sleep disturbance. The finding that anxiety was not predictive of fatigue prior to chemotherapy is consistent with the findings of Goedendorp et al (2008).

Sleep disturbance, but not the duration of rest period at night, emerged as a significant independent predictor of fatigue in the current study. This is in line with previous research, which has reported strong relationships between perceived sleep quality and/or impairment and fatigue (Ancoli-Israel et al., 2006; Berger et al., 2007; Fagundes et al., 2012; Goedendorp et al., 2008), but not between direct measures of sleep such as self-reported sleep duration or objectively assessed sleep parameters (Ancoli-Israel et al., 2006; Berger et al., 2007). The results of the current study are strengthened because the validity of self-report measures for sleep and physical activity were investigated by examining the strength of their relationship with actigraph and diary measures; only self-report measures that had a reasonably robust relationship with

corresponding objective and diary parameters were used. This is an important strength of the research design, as previous research has shown a lack of correspondence between subjective and objective measures of sleep and physical activity (Berger et al., 2007; Servaes, Verhagen, et al., 2002b; Shephard & Vuillemin, 2003). As in previous studies, the observed relationships between subjective and objective measures of sleep were not very strong (with significant *r* values ranging between .2 and .4), and the most consistent relationship has emerged between self-reported sleep disturbance and objective measures of sleep disruption (e.g., wake after sleep onset; Ancoli-Israel et al., 2006; Berger et al., 2007). The poor relationship between objective actigraphy data and subjective reports of total sleep time, sleep efficacy, and sleep latency supports the difficulty people have with estimating their actual sleep times.

Although a moderately strong, but not significant, correlation was found between self-reported MET-min/week and the objective mean daytime activity count measured through actigraphy, it is likely that the self-report measure of physical activity was not accurate in the current study. The physical activity data was heavily skewed; the data suggests that many participants substantially overestimated their activity levels while a small number of others may have underestimated their physical activity (i.e., reporting that they did not engage in any activity whatsoever, including walking). A considerable number of participants reported activity levels far in excess of recommended guidelines of physical activity (Haskell et al., 2007) and the mean MET-min/week in the current study was substantially higher than in previous studies on similar patient groups (e.g., Rogers, Markwell, Courneya, McAuley, & Verhulst, 2010), which suggests that the accuracy of responses on this questionnaire was poor. Thus, the absence of a relationship between physical activity and fatigue in the current study should be interpreted with caution.

Few previous studies have explored the association between physical activity and fatigue in newly diagnosed cancer patients, and findings to date are weak. Goedendorp et al. (2008) were the first to report a significant relationship between physical activity and fatigue before treatment; however, physical activity in this study was assessed using a single numeric rating scale, which is not likely to accurately capture actual activity levels as respondents' interpretations of "very physically active" may vary. Prue et al. (2009) also did not find an association between activity and fatigue before treatment; however, their measure of activity (the activity subscale of the Rotterdam symptom checklist) more accurately reflected functional status (e.g., whether

participants were able to perform a of range everyday activities) rather than actual activity levels. Although the physical activity scale used in the current study (the IPAQ) is well-established and brief, breaks activity down into different categories of intensity, and uses examples to help respondents record what types of activity they engage in, the findings suggests that participants still had difficulty with this measure and/or accurately recalling their true activity levels. This is also supported by the large number of participants (14%) who did not complete the last item of this questionnaire on time spent sitting. This variable was not entered into the regression model because doing so would have reduced the sample size substantially. However, it is unlikely that time spent sitting would have played a role as it was not significantly correlated with fatigue or any other predictors associated with fatigue. In line with this, previous research on breast cancer survivors also found no relationship between fatigue and time spent being inactive during the day (George et al., 2012).

4.4.3 Predictors of fatigue post-treatment. The current study provided preliminary data on potential pre-chemotherapy predictors of fatigue after treatment. Few studies to date have explored pretreatment predictors of post-treatment fatigue. In the current study, fatigue prior to chemotherapy explained a considerable percentage of the variance (18%) in fatigue post-treatment. This is in line with previous research that found a significant association between fatigue before treatment and fatigue post-treatment (Prue et al., 2009; Von Ah et al., 2008; Wielgus et al., 2009) and suggests that patients who present for treatment with existing fatigue are at an increased risk of experiencing fatigue after cancer treatment. Although fatigue is a common side-effect of cancer treatment, research suggests that communication about this side-effect in clinical practice is poor (Donovan et al., 2005), and that patients are not always adequately warned about the possibility and extent of treatment-related fatigue (Piredda et al., 2007; Ream et al., 2003). Findings from the current study highlight the importance of screening patients for fatigue even before the initiation of cancer treatment and fully informing patients with existing fatigue about the likelihood of treatment-related fatigue. Although fatigue at follow-up was not significantly associated with pre-chemotherapy fatigue, the trends in the data were in line with previously reported associations between persistent post-treatment fatigue and fatigue prior to adjuvant treatment (Goldstein et al., 2012). It is likely that the current study was limited by the low numbers of participants at follow-up.

No treatment-related factors were associated with fatigue post-treatment or at follow-up. It is possible that the large variation in time since treatment obscured the immediate effects of treatment on fatigue; however, no correlation between time since treatment and fatigue severity was observed and previous studies also failed to find an association between tumour- and treatment- related factors and fatigue post-treatment (Prue et al., 2009; Von Ah et al., 2008). The absence of clinical and demographic predictors of fatigue suggests that psychological factors may play a key role in post-treatment fatigue. Research supports the role of distress in predicting fatigue over the course of the cancer trajectory (Prue et al., 2009; Von Ah et al., 2008), and previous studies suggest that factors such as pretreatment total sleep time (Wielgus et al., 2009), mood disturbance and morning cortisol levels (Von Ah et al., 2008) are associated with fatigue post-treatment. There is some indication from the current findings that distress and sleep disturbances even before cancer treatment are associated with fatigue after treatment. However, no baseline factors, other than fatigue, significantly predicted post-treatment fatigue in the current study. As participants who dropped out of the study had significantly higher anxiety at baseline than those who completed the follow-up assessments, and anxiety at baseline was significantly correlated with fatigue post-treatment, it is possible that the sample was biased and this may have impeded significant relationships from emerging. Nevertheless, it is clear from the current study and previous research (Von Ah et al., 2008; Wielgus et al., 2009) that pretreatment factors only account for a limited proportion of the variance in fatigue post-treatment; other factors such as psychological, cognitive and behavioural reactions during or after treatment are likely to be of central importance in determining fatigue post-treatment.

4.4.4 Limitations. The sample size was small given the number of predictors examined. Furthermore, the sample was predominantly female and included mainly breast-cancer patients; therefore, it does not reflect the incidence and types of cancer in the Irish population. This bias occurred because participants were primarily recruited through oncology clinics for breast, genitourinary and gynaecological cancer, and only those scheduled to receive chemotherapy with curative intent were approached. As chemotherapy is generally only recommended for prostate cancer patients with advanced disease (National Comprehensive Cancer Network, 2012b), no patients with this type of cancer met the inclusion criteria for this study. The relatively small number of colorectal and gynaecological cancer patients recruited may be because these cancers are more likely to present in more advanced stages of disease and to necessitate urgent

treatment, and thus these patients were more difficult to approach regarding the study between the time of their diagnosis and the start of their treatment. The small number of lymphoma patients included may be because new lymphoma patients were not routinely seen in outpatients' clinics and therefore there was no structured system in place for recruiting these patients, as was the case for breast, gynaecological and genitourinary cancer patients. As identification of potentially eligible lymphoma patients was dependent on nursing staff, and the time-frame between diagnosis and treatment was often very brief, recruitment of this patient group was difficult.

Participants with medical comorbidities associated with fatigue, such as thyroid conditions, depression, or arthritis, were not excluded from the current study. This decision was taken in order to reflect the demographic of patients treated for cancer as accurately as possible; however, as a result of this, the fatigue experienced by participants cannot be labelled 'cancer-related fatigue' with any degree of certainty as the exclusion of other medical causes is a criterion for a case definition of CRF (Cella et al., 2001). Chronic fatigue states attributable to other medical conditions and/or their treatment could have contributed to the fatigue participants reported. However, such comorbidities were considered in the analysis. Although a greater number of comorbidities was significantly associated with fatigue prior to treatment, no significant association between comorbidities and fatigue was observed post-treatment or at follow-up. In addition, when comorbidities in which fatigue is a prominent symptom (e.g., thyroid conditions, arthritis, fibromyalgia, and depression) were examined, no significant differences in fatigue severity were observed at any study timepoint between those who had one or more of these conditions and those who did not.

Although the inclusion of actigraph and diary data on sleep and activity was a strength of the study, actigraph data could only be collected from a small subsample. In addition, failure to keep recording times consistent between participants was a limitation, as activity levels and sleeping patterns are likely to vary over weekdays and weekends. Nevertheless, as the data from the self-report questionnaires, actigraphs and sleep diaries were collected at the same time, a high concordance between measures was still expected. Finally, as regression was used to analyse the predictors of fatigue at baseline, and these predictors were assessed at the same time as fatigue, the possibility that causation occurred in the opposite cannot be ruled out. For example, depressive symptoms at this time may have been attributable to fatigue, rather than the

other way around. Further longitudinal research is necessary to understand the nature of the relationships between such factors in patients before treatment.

4.4.5 Implications for practice. Findings from the current study highlight the importance of providing cancer patients with psychological care in tandem with medical care. Although a degree of psychological distress is usual after diagnosis with cancer, the current findings suggest that heightened distress can adversely affect levels of fatigue before treatment. Fatigue both before and during treatment is important because it can impact on the timing and completion of cancer treatment; if patients experience severe fatigue, the dose of treatments such as chemotherapy may be decreased or patients' own willingness to adhere to treatments may be reduced (Hofman et al., 2007). Thus, fatigue can adversely affect patient outcomes. Managing psychological distress before treatment may help reduce subjective experiences of fatigue, and thereby help to increase patients' tolerance for their upcoming treatments.

The high proportion of participants in the current study who reported elevated levels of fatigue before chemotherapy, and the finding that pre-chemotherapy fatigue predicted fatigue post-treatment, highlight the importance of screening for fatigue as part of routine clinical care even before the initiation of treatment. It is important that patients are fully informed about the likelihood of experiencing fatigue during and after treatment and the extent to which this can impact on their lives. When patients are well informed about side-effects, they are better prepared and less distressed when they occur (Ream et al., 2003). For example, a study on a nursing-led intervention that provided patients receiving chemotherapy with information and self-care strategies for managing CRF as well as psychological support, reported that the intervention group had significantly less fatigue, lower associated distress, less anxiety and depression, and demonstrated more adaptive coping than a usual care control group (Ream, Richardson, & Alexander-Dann, 2002, 2006). A Cochrane review also found evidence that specific interventions for fatigue, which are based on educating patients about fatigue and teaching self-care coping techniques and activity management (balancing activities and rest effectively), are effective in reducing fatigue during cancer treatment (Goedendorp, Gielissen, Verhagen, & Bleijenberg, 2009). Such findings support the importance of ensuring that patients are aware of potential side-effects and informing them about ways to manage such effects should they occur. If patients with fatigue before treatment are at an increased risk of post-treatment fatigue, then identifying such patients early on would enable the delivery of targeted interventions to patients most in need.

Chapter 5: Cancer-Related Fatigue and the Common Sense Model: Exploring the Role of Cognitions

"My fatigue is all-encompassing and I have no life outside of it." – Kate

5.1 Introduction

The role of cognitive factors in the aetiology of cancer-related fatigue (CRF) is increasingly supported in the literature (see Chapter 3). For example, higher post-treatment CRF has been associated with greater catastrophising (Donovan et al., 2007), cancer-related causal attributions (Servaes, Verhagen, et al., 2002c), low perceived control over fatigue (Servaes et al., 2007), higher fear of cancer recurrence and negative cognitions regarding activity in relation to fatigue (Young & White, 2006). However, it is not clear how such thinking patterns and beliefs actually impact on fatigue in cancer survivors.

The cognitive-behavioural model of CRF suggests that cognitive factors play a role in symptom perpetuation by influencing a variety of psychological, physiological and behavioural contributing factors to fatigue. For example, dysfunctional beliefs about fatigue could contribute to greater emotional distress and maladaptive coping strategies (see Chapter 3). Cognitive-behavioural therapy (CBT) interventions based on this explanatory model provide a means of evaluating this framework for understanding CRF. However, while the effectiveness of CBT for post-cancer fatigue is supported (Gielissen, Verhagen, et al., 2007; Gielissen et al., 2006), the mediators of intervention-induced changes in CRF have not been adequately examined. Findings to date suggest that the benefits of CBT are not brought about by increases in physical activity (Gielissen et al., 2011; Goedendorp et al., 2010). This is in line with research on the mediators of CBT interventions for chronic fatigue syndrome (CFS; Wiborg et al., 2010), where the key role of cognitive processes, rather than behavioural responses, is increasingly supported (Knoop et al., 2010). Changes in cognitions and whether these lead to changes in fatigue have not been investigated in the context of CRF. However, as CFS and CRF share many of the same proposed contributing factors, insight into the potential mediating role of cognitive processes can be gleaned from studies on CFS.

Research on CFS indicates a number of direct and indirect ways through which cognitive processes might contribute to the perpetuation of symptoms (Knoop et al., 2010). Individuals may be guided by a general negative representation of fatigue, in which they view fatigue as beyond their control, difficult to understand, likely to be

ongoing and to have serious consequences, and thereby difficult to influence. The tendency to attend to fatigue and focus on symptoms could also contribute to the experience of fatigue. In addition, beliefs about activity and fatigue could lead people to underestimate their own performance and abilities and lead to reductions in physical activity. However, changing dysfunctional beliefs about activity could help to decrease fatigue even in the absence of permanent changes to physical activity. Knoop et al. (2010) hypothesise that temporary increases in physical activity during intervention programmes could help to reduce negative perceptions of physical activity and fatigue, decrease focus on fatigue and increase self-efficacy.

While some studies on CRF have included cognitive predictors of fatigue, and a limited number of studies have explored potential mediators of the cognition-fatigue association (e.g., Young & White, 2006), the pathways through which cognitive processes and beliefs are linked to symptom severity are not yet clear. Research that more closely examines the role of specific beliefs or cognitive processes is necessary to understand mechanisms of change in CRF and to improve explanatory models. The aim of the current study was to investigate the illness cognitions of fatigued cancer survivors and explore how different cognitions might impact on symptom severity using the common sense model (CSM; Leventhal et al., 1984) as a theoretical framework.

5.1.1 The common sense model. Like cognitive-behavioural models of illness, the CSM emphasises interactions between cognitive and behavioural responses to a health threat; however, the CSM outlines the specifics of interactions between illness perceptions and coping procedures in greater detail. The model operationalises how individuals conceptualise specific health threats and management strategies and emphasises the *process* of responding to a health threat; the idea that illness perceptions can evolve over time, for example shifting from an acute to a chronic perspective, and that such shifts prompt associated changes in coping strategies, appraisals, and outcome expectancies (Leventhal, Leventhal, & Contrada, 1998). Thus, the CSM provides more detailed information on how an individual responds to a health threat and how different types of cognitions might impact on outcomes. The importance of using content-specific process models, rather than descriptive models, as a guide for examining the mechanisms through which potential contributing factors are connected to health outcomes has been previously noted (Leventhal et al., 2007).

According to the CSM people form cognitive and emotional representations of their condition based on their experience of symptoms, their personal history, and the sociocultural context in which they occur. Representations include beliefs regarding the causes of their illness, its timeline and consequences, and its controllability (Moss-Morris et al., 2002). Each of these cognitions represents a different aspect of the patients' conceptualisation of their illness (see Chapter 2); however, some authors have combined these dimensions under one general negative representation construct (e.g., Knoop et al., 2012). Indeed, some researchers have suggested that because of the strong intercorrelations between the dimensions of the model, the representations should be conceptualised as groups of beliefs rather than single cognitions (Heijmans, 1998).

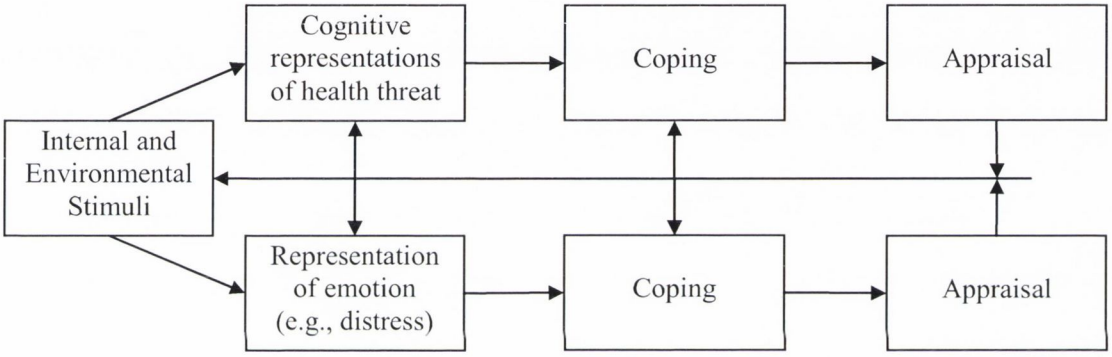

Figure 5.1. The common sense model of health and illness.
Source: Leventhal et al. (1997).

A key tenet of the CSM is that illness representations impact on patients' health and help to perpetuate symptoms by influencing coping (Hagger & Orbell, 2003). The CSM is thus a mediational model in which there are explicit causal links between cognitions and coping behaviours (see *Figure 5.1*). Although research supports the idea that the relationships between cognitions and outcomes are mediated by coping, not all studies have found evidence of such pathways (Hagger & Orbell, 2003). Some researchers have reported that cognitive representations are better predictors of outcomes than coping (Carlisle et al., 2005; Heijmans, 1998; Moss-Morris, Petrie, & Weinman, 1996; Scharloo et al., 1998; Singh & Dixit, 2009) and a meta-analytic review found stronger relationships between illness representations and outcomes than illness representations and coping (Hagger & Orbell, 2003). Such findings suggest that cognitions can impact on outcomes independently of coping behaviours. This is in line with findings from CBT interventions that improvements in fatigue are not mediated by

changes in activity but changes in cognitive processes (Knoop et al., 2010). It is also possible that cognitions impact on outcomes by influencing psychological factors such as mood disturbances; for example, maladaptive cognitions could lead to higher levels of distress, pain and disability (Carlisle et al., 2005), which have also been associated with CRF in cancer survivors (e.g., Cavalli Kluthcovsky et al., 2011; Reinertsen et al., 2010).

5.1.2 The CSM and CRF. Only one study to date has directly applied the CSM to CRF. Donovan and Ward (2005) explored the fatigue representations of gynaecological cancer patients undergoing chemotherapy using the 'Symptom Representation Questionnaire' (SRQ; Donovan & Ward, 2005; Donovan et al., 2008) based around Leventhal's model. Although this questionnaire is a useful tool for understanding patients' perceptions about the different cancer-related symptoms they are experiencing, the dimensional structure of the SRQ was not in line with the CSM and the scale does not fully capture the complexity of CRF. For example, it does not allow exploration of the range of possible causal factors that can play a role in CRF or changes in causal attributions over time. Furthermore, although Donovan and Ward (2005) explored correlations between fatigue representations, coping behaviours, and symptom interference, their findings fail to give much insight into the nature of this relationship due to methodological limitations in how coping was assessed. Three types of fatigue management strategies were included: communicating with a healthcare professional, adherence to recommendations for managing fatigue, and self-directed coping. This method of assessing coping proved problematic for two reasons. First of all, less than half of the sample had actually been given symptom-management recommendations and therefore, adherence was not a good measure of coping. Secondly, the authors were unable to clearly categorize the self-directed coping strategies into active and passive coping based on the participants' open-ended responses. While the majority of participants reported that they used sleep or rest, many did not elaborate on how exactly this coping strategy was used. This was problematic, because although rest is often recommended to patients, there is a qualitative difference between getting sufficient sleep or rest, which could be categorized as active coping, and resting through activity avoidance which can lead to physical deconditioning and thereby contribute further to fatigue. Thus, the link between patients' representations of their fatigue and subsequent symptom outcomes is not yet clear. In order to adequately address this question, more in-depth measures of

coping that assess specific self-management behaviours are required. Furthermore, other possible mediators of the cognition-outcome link, such as psychological distress and mood disturbance, should be explored.

5.1.3 Aims of the study. No research to date has comprehensively tested a theoretical model of how cognitions might impact on CRF. The current study examined the role of cognitions in CRF in three phases. Phase 1 tested the utility of the CSM for CRF by exploring the relationships between cognitive representations of CRF and fatigue severity, and examining whether there was any evidence that these relationships were mediated by coping strategies specific to fatigue. Emotional representation of CRF as a mediator between cognitions and fatigue was also assessed. Phase 2 examined the role of cognitive representations within a wider multivariate model of CRF, which included established psychological, behavioural, and sleep-related predictors of CRF as well as cognitive processes that have been previously linked to fatigue in cancer survivors (i.e., catastrophising in response to fatigue, fear of cancer recurrence, and negative cognitions regarding activity in relation to fatigue). Finally, phase 3 explored whether there is any evidence that changes in cognitions and/or changes in coping are associated with changes in CRF over time.

5.2 Phase 1: The Common Sense Model and Cancer-Related Fatigue

5.2.1 Rationale. According to the CSM, people's cognitive representations of an illness can impact on illness outcomes by influencing coping behaviours. No previous research has comprehensively tested the CSM in the context of post-treatment CRF. The aims of the current study were to describe cancer survivors' cognitive and emotional representations of fatigue and to examine the relationships between cognitive representations, coping and fatigue. The following hypotheses were formed based on the CSM:

1. Cognitive representations of fatigue would be strongly associated with fatigue severity.
2. The relationship between cognitions and fatigue would be mediated by coping strategies.
3. The relationship between cognitions and fatigue would be mediated by emotional representation of CRF.

5.2.2 Method.

5.2.2.1 Participants and procedure. Secondary data analysis was carried out on data collected from three different studies. The first study consisted of a

questionnaire study on CRF (described in Chapter 2); participants were recruited through cancer associations and support groups in Ireland and the United Kingdom or through their oncology care team. Cancer patients and survivors who self-reported fatigue were eligible to participate; however, only those participants (n = 82) who were at least three months post-treatment were included in the current analysis as the focus was on post-treatment fatigue. Potential participants were informed that their participation was entirely voluntary. After giving informed consent, participants completed questionnaires on-line or in hard-copy and returned them using stamped-addressed envelopes.

The second study consisted of a larger longitudinal study (described in Chapter 4), in which a mixed sample of cancer participants was recruited through their oncology care team in a large Dublin hospital and assessed before and after chemotherapy and after a follow-up period post-treatment. Only data from participants (n = 46) who self-reported fatigue at a follow-up assessment that was at least three months post-treatment were included in the current analysis. All participants gave written informed consent, completed questionnaires in hard-copy and returned them using stamped-addressed envelopes.

The third study involved an intervention trial for CRF in which patients with persistent fatigue after cancer treatment were recruited for a manualised CBT intervention (Collier & O'Dwyer, 2011). Ethical approval for the study was obtained from the institutional research ethics committees in both the hospital and the university in which the research was carried out (see Appendix 2). All participants provided written informed consent prior to study inclusion (see Appendix 7) and all procedures followed were in accordance with the Helsinki Declaration. Participants in this study consisted of disease-free cancer survivors who were at least six months post-treatment and met the diagnostic criteria for CRF developed by the fatigue coalition (Cella et al., 2001; Cella et al., 1998). Participants for this study were recruited from the outpatient clinics for medical oncology, urology, surgery, haematology, and gynaecology in a large Dublin hospital. Hospital medical staff were informed of the study and the target participant group by the research team through presentations at grand rounds, team meetings, hospital intranet and e-mails. Potentially eligible patients were identified and informed about the study by their doctor or clinical nurse specialists. Patients who were interested in taking part in the study were then either given an information leaflet about the study or asked for their permission to provide their contact details to the researchers.

Leaflets and posters with information about the study and contact details for the research team were also on display in the waiting areas of the outpatients' clinic and sent to cancer groups and associations for distribution among their members. Patients who expressed an interest in the study were contacted by telephone by a member of the research team in order to provide further information about the study and to screen patients for eligibility (see Appendix 8 for the eligibility criteria and screening protocol). The baseline assessments of the 36 patients who met the eligibility criteria and provided written informed consent to take part in this study were used in the current analysis. Thus, in total, 164 cancer survivors with a variety of cancer diagnoses were included in the current analyses.

5.2.2.2 Measures. Demographic (age, gender, marital and employment status) and medical information (cancer type and treatment, time of diagnosis and treatment, comorbid medical conditions) was obtained through a questionnaire.

Fatigue. The Functional Assessment of Cancer Therapy Fatigue (FACT-F) subscale (Yellen et al., 1997) assessed fatigue severity. This scale was previously described in Chapter 4. In the present sample, Cronbach's alpha was .90.

Cognitive representations of CRF. The Illness Perception Questionnaire (IPQ) for CRF (Pertl, Hevey, Donohoe, & Collier, 2012) was used to assess the CSM cognitive representations and to assess emotional distress using the emotional representation construct of the scale as a proxy measure. This scale was validated in a sample of cancer patients and survivors and exhibited good psychometric properties (Pertl et al., 2012). In the current study the internal consistency of each subscale was .80 or above, with the exception of treatment control which had a Cronbach's alpha value of .64. In line with previous studies (e.g., Knoop et al., 2012), a composite negative representation of fatigue score was also calculated from the 18 cognitive representation items (reflecting timeline, control, consequences, and coherence), with a higher score indicating a more negative perception of CRF (i.e., the belief that fatigue is likely to be ongoing and cyclical, out of one's personal control and not likely to be managed by treatment, will have serious consequences, and is difficult to understand; α = .82). Finally, as the causal attributions items of the IPQ can represent a number of different sub-factors that can vary across different conditions (Moss-Morris et al., 2002), factor analysis was used to determine the underlying attributional dimensions, which were then combined into different subscales (see results section 5.2.3.2).

Coping. The specific coping strategies used by participants to manage their fatigue were assessed using a scale based on the Illness Management Questionnaire (IMQ, Ray, Weir, Stewart, Miller, & Hyde, 1993), which was originally developed to assess cognitive and behavioural coping in CFS. Items were selected from the IMQ and rephrased (e.g., replacing "my illness" with "my fatigue") in order to make them suitable for patients with CRF. Additional items were added to the scale based on clinical observations, the coping strategies reported by patients with CRF in previous research, and the interventions and general management strategies recommended in the NCCN *Clinical Practice Guidelines in Oncology* for CRF (National Comprehensive Cancer Network, 2010).

The coping with CRF scale consisted of 18 items (see Appendix 9) that refer to different strategies for managing fatigue (e.g., "I avoid doing anything that may tire me"); respondents were asked to rate how often (1 = *never*, 6 = *always*) they engage in each strategy. Exploratory factor analysis was conducted to examine the underlying factor structure of the scale. The results are included in the Appendix 9. Six subscales emerged: maintaining activity (attempting to ignore symptoms and carrying on with activities; $\alpha = .74$), activity avoidance (excessive use of rest and avoidance of physical activity; $\alpha = .65$), accommodating to fatigue (organising one's life to avoid overexertion and control stress; $\alpha = .84$), focussing on symptoms (a preoccupation with symptoms; $\alpha = .83$), information seeking (seeking information about the illness and readiness to try remedies; $\alpha = .87$), and seeking emotional support (talking to others about anxieties and concerns; $\alpha = .87$). Mean scores were calculated for each subscale with higher scores reflecting greater use of that strategy.

5.2.2.3 Analysis. Descriptive statistics were used to describe the characteristics of respondents, their cognitive and emotional representations of CRF and the coping strategies they used. The factor structure underlying the IPQ-CRF causal attributions was explored using principal components analysis (PCA) with a Varimax rotation. The number of factors was determined by examining the Eigenvalues and the scree plot; item loadings greater than 0.5 were taken to represent a factor. Interrelationships between cognitive representations, emotional representation, coping strategies, and fatigue were explored using Pearson product moment correlations. A more stringent α-level of .01 was used to reduce the risk of Type I errors because of the large number of correlations undertaken. Multiple regression analysis was used to explore whether the CSM cognitive representations were predictive of fatigue severity and coping strategies

and whether coping strategies were predictive of fatigue severity. Only variables that correlated with a *p*-value of .01 or less were entered into the multiple regression models. No problems with multicollinearity were detected in the data.

In order to examine whether coping strategies and/or emotional representation of CRF mediated the relationship between cognitive representations of fatigue and fatigue severity, the composite cognitive representation subscale was used to capture the maximum variation in cognitions and thereby tease out any mediational effects. Hayes' (2012) PROCESS macro for SPSS was used to test the mediational models. In the first model, the negative representation of fatigue construct was the predictor, fatigue severity was the outcome and coping strategies that were significantly associated with fatigue were entered as the mediators. In the second model the emotional representation component of the IPQ-CRF was entered as the mediator. The analyses were examined to determine (1) the direct effect of negative representations on fatigue severity, (2) whether negative representations were related to coping strategies/emotional representation, (3) whether coping strategies/emotional representation were related to fatigue severity and (4) the indirect effect of negative representations on fatigue severity through coping strategies/emotional representation. The significance of the indirect effects was tested using bias-corrected bootstrap confidence intervals (CIs; Hayes, 2012); the dataset was randomly resampled 5,000 times with replacement. The mean mediation effect was used as the population parameter. When the 95% bootstrap confidence intervals around this parameter contained zero, the mediation hypothesis was rejected. CIs that did not contain zero provided evidence of a significant indirect effect. The index of mediation (the completely standardized indirect effect) was used as a measure of effect size (Preacher & Kelley, 2011). In addition, for the second model in which there was only a single mediator, the Kappa-squared method (K^2) method of assessing effect size was also used. Preacher and Kelly (2011) suggest that K^2 can be interpreted in the same light as squared correlation coefficients following Cohen's (1988) guidelines, whereby .01 is seen as a small effect, .09 as a medium effect and .25 as a large effect.

Table 5.1 *Characteristics of the overall sample and participants split by study sample*

	Study 1 (n = 82)		Study 2 (n = 46)		Study 3 (n = 36)		Overall sample (n = 164)	
	n	%	n	%	n	%	n	%
Gender								
Male	11	13.4%	3	6.5%	8	22.2%	22	13.4%
Female	71	86.6%	43	93.5%	28	77.8%	142	86.6%
Menopausal status								
Premenopausal	7	8.5%	24	52.2%	8	22.2%	39	29%
Perimenopausal	23	28.0%	4	8.7%	8	22.2%	35	26%
Postmenopausal	36	43.9%	13	28.3%	11	30.6%	60	45%
Children								
Has children	34	41.5%	37	80.4%	23	63.9%	94	67%
Children living at home	34	41.5%	32	69.6%	20	55.6%	86	55%
Marital status								
Married/Partnered	62	75.6%	29	63.0%	19	52.8%	110	67.5%
Single	16	19.5%	9	19.6%	7	19.4%	32	19.5%
Separated/Divorced	-	-	5	10.9%	4	11.1%	9	5.5%
Widowed	3	3.7%	3	6.5%	6	16.7%	12	7.5%
Employment status								
Employed	38	46.4%	24	52.2%	18	50%	80	49.5%
Housewife	6	7.3%	12	26.1%	2	5.6%	20	12.5%
Retired	13	15.9%	4	8.7%	6	16.7%	23	14.5%
Resigned for health	16	19.8%	2	4.3%	7	19.6%	25	15.5%
Unemployed	6	7.4%	3	6.5%	1	2.8%	10	6%
Student	2	2.4%	-	-	1	2.8%	3	2%
Cancer type								
Breast cancer	28	34.1%	37	80.4%	16	44.4%	81	50%
Gynaecological cancer	19	23.2%	4	8.7%	3	8.3%	26	16%
Lymphoma	20	24.4%	1	2.2%	5	13.9%	26	16%
Leukaemia	5	6.1%	-	-	4	11.1%	9	5.6%
Gastrointestinal cancers	4	4.8%	4	8.7%	-	-	8	5%
Prostate	3	3.7%	-	-	1	2.8%	4	2.5%
Head and neck	1	1.2%	-	-	4	11.2%	5	3.1%
Lung	2	2.4%	-	-	-	-	2	1.2%
Sarcoma	-	-	-	-	1	2.8%	1	0.6%
Treatment type								
Chemotherapy	76	92.7%	46	100%	28	77.8%	150	92%
Surgery	58	70.7%	41	89.1%	25	69.4%	124	76%
Radiation Therapy	37	45.1%	37	80.4%	28	77.8%	102	63%
Hormonal treatment	20	24.4%	33	71.7%	13	36.1%	66	43%
Bone marrow transplant	-	-	-	-	2	5.6%	2	1.2%
BMI (kg/m^2) class[a]								
Underweight (< 18.5)	2	2.4%	-	-	1	2.8%	3	2%
Normal (18.5 – 24.9)	32	39.0%	21	45.7%	14	38.9%	67	43%
Overweight (25 – 29.9)	19	23.2%	15	32.6%	12	33.3%	46	29%
Obese (≥30)	25	30.5%	10	21.7%	6	16.7%	41	26%
Comorbities								
No comorbidities	47	57.3%	23	50%	15	41.7%	85	53.8%
1 comorbidity	12	14.6%	11	23.9%	13	36.1%	36	22.8%
2 comorbidity	8	9.8%	9	19.6%	4	11.1%	21	13.3%
≥3 comorbidities	10	12.1%	3	6.5%	3	8.3%	16	10.1%

5.2.3 Results.

5.2.3.1 Participant characteristics. Table 5.1 compares the demographic characteristics of the three study groups and describes the overall sample characteristics. The overall mean age was 50 years (*SD* = 11.54 years), which was similar across the three groups (study 1 M = 49.96, *SD* = 10.87; study 2 M = 49.57, *SD* = 10.94; study 3 M = 50.71, *SD* = 13.93). The overall mean time since treatment was 2 years and 1 month (*SD* = 39 months; Median = 10.43 months); participants from study 2 had finished their treatment more recently (M = 0.49 years, *SD* = 2.04 months) than those from study 1 (M = 2.53 years, *SD* = 32 months) and study 3 (M = 2.64 years, *SD* = 48 months). Forty-seven percent of the overall sample (n = 74) suffered from an additional medical condition. The most common types of conditions reported were arthritis (n = 17), high blood pressure (n = 14), thyroid problems (n = 11), asthma (n = 10), depression (n = 9), cholesterol (n = 7), back pain (n = 7) and diabetes (n = 5). All other conditions were reported by less than five participants.

Table *5.2 PCA of attribution items with Varimax rotation and Cronbach's alpha values for causal attribution subscales*

	Component					
	1	2	3	4	5	6
Psychological attributions (α= .84)						
Family problems or worries	**.87**	.08	.08	-.04	-.08	.03
Mental attitude (e.g., thinking about life negatively)	**.79**	.06	.34	.10	.16	.06
Distress (e.g., anxiety or depression)	**.76**	.36	.22	.10	-.06	.00
Stress	**.76**	.30	.30	-.12	-.01	.12
Overwork	**.54**	.36	.03	-.29	.17	.33
Medical/somatic attributions (α= .76)						
Hereditary - it runs in my family	.06	**.75**	.09	-.21	.20	.16
Problems with my immune system	.23	**.72**	.25	.12	-.38	-.15
Other non-cancer related illnesses/conditions	.30	**.71**	.19	.04	.05	-.18
Poor medical care in the past	.18	**.70**	.35	.06	.21	-.03
Pain	.19	**.68**	-.01	.18	.16	.19
Behavioural attributions (α= .82)						
Decreased activity	.20	.09	**.87**	.06	-.17	.13
Decreased physical fitness	.26	.18	**.85**	-.04	-.10	.13
My diet / Nutrition	.24	.18	**.69**	-.11	.39	.02
My personality	.31	.22	**.59**	-.20	.25	-.35
My own behaviour	.04	.49	**.58**	-.18	.26	.25
Cancer treatment-related attributions (α= .69)						
Side-effects from my cancer and/or my treatment	.04	.10	.01	**.90**	.07	-.01
My cancer treatment (e.g., chemotherapy, surgery etc.)	-.06	-.02	-.13	**.87**	.06	-.02
The cancer	-.01	.23	.05	.16	**.82**	.00
Sleep disturbances	.16	.05	.18	-.02	.01	**.88**

Note. Factor loadings in bold font indicate the items that loaded on to each component.

5.2.3.2 Factor analysis of IPQ-CRF causal attributions. The factor analysis of 19 items produced 6 factors with Eignevalues over 1, which accounted for 75% of the variance (see Table 5.2 for item loadings). Six causal attribution subscales emerged; these were labelled psychological, medical/somatic, behavioural, cancer treatment-related, cancer-related and sleep-related attributions and they accounted for 17.5%, 17%, 17%, 10%, 7% and 6.5% of the total rotated variance respectively. The final two factors consisted of single items. The internal reliability of the causal attribution subscales are displayed in Table 5.2. The average of the items in each subscale was calculated for use in further analysis.

5.2.3.3 Fatigue and cognitive representations of fatigue. Participants' ratings of fatigue representations are presented in Table 5.3. In total, 86.6% of the sample (n = 142) scored within the cut-off for significant fatigue (FACT-F score of < 36); the mean severity score was 23.06 (*SD* = 10.07). On average, participants related 10 symptoms included in the illness identity scale to their CRF. The mean number of fatigue-related symptoms experienced by participants was 9.12 (*SD* = 2.93). All 12 symptoms specifically related to CRF were experienced by at least 70% of participants, with the exception of significant distress or impairment in social or occupational functioning which was experienced by 57%. The three most frequently experienced symptoms were diminished energy or increased need to rest (95%), insomnia (86%), and diminished concentration (82%). The six generic symptoms were experienced by less than half the sample (35 – 42%), with the exception of pain (58%) and stiff joints (74%).

The most commonly reported causal attributions (agree or strongly agree with the statement) were cancer-treatment (93%), side-effects of cancer treatment (91%), cancer (62%), sleep disturbances (62%), stress (60%) and decreased physical fitness (53%). All other causes were endorsed by less than half of participants; the least common causal attributions were heredity (5%) and poor medical care in the past (7%). This pattern was reflected in the mean scores for the composite causal attribution subscales presented in Table 5.3. Mean scores on the consequences and emotional representation constructs indicated that the majority of participants felt that their fatigue had a negative effect on their lives and caused them distress. However, mean scores on both treatment- and personal-controllability were above the mid-point, indicating moderately high perceived control. Furthermore, the majority of participants reported moderately high coherence scores. Participants did not believe that their fatigue would

last a long time; however, the majority reported that the timeline of their fatigue was cyclical.

Participants' ratings of the coping strategies they used are presented in Table 5.3. The strategies most often used by participants were accommodating to the fatigue and maintaining activity levels. Mean scores on the seeking emotional support and information seeking coping scales were also above the mid-point. Activity avoidance coping or symptom focussing were not used by the majority of participants.

5.2.3.4 Correlations among CSM cognitive and emotional representations and fatigue. A number of moderately strong significant inter-relationships were observed among the CSM representations (see Table 5.3). Participants who identified more symptoms as part of their CRF (i.e., had a higher identity score) had more chronic timeline perceptions and reported more severe consequences, a more negative emotional representation, more negative representations of CRF, and stronger treatment-related and psychological causal attributions. Significant correlations were observed among longer timeline perceptions, severe consequence perceptions, and lower perceived personal control. Having longer timeline perceptions was also associated with a more negative emotional representation and medical/somatic causal attributions. Higher perceived personal control was correlated with higher behavioural and psychological causal attributions and higher treatment control and coherence perceptions. Participants who perceived more severe consequences had lower coherence perceptions. Finally, a more negative emotional representation was associated with higher perceived consequences, lower coherence, and stronger medical and psychological causal attributions.

Fatigue had a moderately strong significant correlation with nearly all of the CSM representations; only treatment-control and timeline-cyclical were not significantly associated with fatigue. More severe fatigue was associated with a stronger illness identity, believing that fatigue would last a long time, more severe perceived consequences, less personal control, lower coherence, and more negative emotional representations. The strongest correlations emerged between fatigue and identity, consequences, emotional representation and the composite negative cognitive representation score. Of the causal attributions, only stronger medical/somatic attributions were significantly associated with more severe fatigue.

Table 5.3 *Descriptive statistics and correlations between fatigue and CSM cognitive and emotional representations*

	Mean (SD)	Min -Max	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.
1. Fatigue severity	23.06 (10.07)	2 - 50	**-.62****	**-.48****	-.18*	**-.65****	**.30****	-.05	**.37****	**-.56****	**-.60****	-.13	**-.26****	-.03	-.18*	.01	.07
2. Identity	10.14 (4.29)	0 - 18	-	**.32****	.16*	**.47****	-.12	.10	-.11	**.50****	**.35****	**.24****	.20*	.04	**.25****	-.06	.04
3. Timeline chronic	2.74 (1.05)	1 - 5		-	.10	**.55****	**-.25****	-.12	-.12	**.40****	.66**	.13	**.22****	.12	.20*	.09	-.02
4. Timeline cyclic	3.66 (0.91)	1 - 5			-	**.22****	-.07	-.06	**-.24****	.15	.50**	-.05	.06	.17*	**.23****	-.11	.17*
5. Consequences	3.33 (1.00)	1 - 5				-	**-.24****	.02	**-.21****	**.55****	.68**	.10	.14	.09	.16*	-.03	-.12
6. Control personal[1]	3.23 (0.85)	1 - 5					-	**.31****	**.27****	-.14	-.58**	-.10	-.05	**.27****	**.24****	-.04	.14
7. Control treatment[1]	3.09 (0.72)	1.33 - 5						-	.06	.13	-.38**	-.14	.09	.09	.19*	.07	-.03
8. Coherence[1]	3.31 (0.98)	1 - 5							-	**-.26****	-.57**	-.02	-.18*	-.01	-.02	-.07	-.03
9. Emotional rep.	3.18 (1.13)	1 - 5								-	**.44****	.15	**.33****	.17*	**.31****	.09	-.04
10. Negative rep.	3.02 (0.53)	1.17 – 4.17									-	.12	.18*	.03	.08	.01	-.02
Causal attributions:																	
11. Treatment	4.51 (0.66)	2 - 5										-	.13	-.08	-.06	.20*	-.05
12. Medical	2.34 (0.85)	1 – 4.75											-	**.36****	**.38****	**.26****	.16
13. Behavioural	2.64 (0.96)	1 – 4.80												-	**.59****	.15	**.22****
14. Psychological	2.92 (1.03)	1 - 5													-	.12	**.29****
15. Cancer	3.57 (1.32)	1 - 5														-	.03
16. Sleep	3.78 (3.44)	1 - 5															-

Note. [1]higher scores indicate higher perceived control and coherence. rep = representation. *p <.05, ** p < .01, *** p <.001.

5.2.3.5 Correlations between coping and cognitions and fatigue. Symptom focussing had the strongest relationship with fatigue severity (see Table 5.4). More severe fatigue was significantly associated with greater use of symptom focussing, activity avoidance, information seeking and seeking emotional support. The coping strategies that had the strongest correlations with cognitions were symptom focussing and information seeking, which correlated significantly with identity beliefs, timeline-chronic, consequences, emotional representations, and the composite cognitive representation construct. Greater use of symptom focussing as a coping strategy was also significantly associated with lower perceived personal control and lower perceived coherence. Greater use of activity avoidance coping was associated with stronger identity beliefs. Finally, the use of emotional support as a coping strategy was significantly related to stronger identity beliefs, more severe perceived consequences and a more negative emotional representation.

5.2.3.6 Test of the CSM. *Cognitive representations as predictors of fatigue.* Cognitive representations that were significantly correlated with fatigue severity (timeline-chronic, consequences, personal control, coherence and medical attributions) were entered into a multiple regression analysis of fatigue severity. As the identity construct of the IPQ-CRF (which assessed the number of symptoms identified as part of CRF) was conceptually related to the outcome variable fatigue, this representation was not included as a predictor. Assumptions of normally distributed and independent residuals were met; however, four cases with large standardised residuals were removed after diagnostic checks indicated that they could have an undue influence on the regression model. The cognitive representations accounted for 58% of the variance in fatigue severity, $F(5, 145) = 42.21$, $p < .001$. Consequences explained most of the variance in fatigue with more severe consequence perceptions ($\beta = -.54$, $p < .001$), lower coherence ($\beta = .22$, $p < .001$) and stronger medical/somatic attributions ($\beta = -.13$, $p < .05$) significantly predicting greater fatigue.

Table 5.4 *Descriptive statistics for coping strategies and correlations between coping and fatigue and CSM illness representations*

	Activity avoidance	Maintaining activity	Accommodating to CRF	Symptom focussing	Information seeking	Emotional support
1. Fatigue severity	**-.25****	.02	.04	**-.58****	**-.40****	**-.25****
2. Identity	**.28****	-.02	-.01	**.58****	**.41****	**.24****
3. Timeline chronic	.14	-.11	-.02	**.38****	**.24****	.06
4. Timeline cyclic	-.06	-.03	.07	.15	.12	.06
5. Consequences	.17*	-.09	-.05	**.56****	**.37****	**.21****
6. Control personal	-.17*	.09	.02	**-.30****	-.07	-.07
7. Control treatment	-.08	.07	.03	.06	.15	.19*
8. Coherence	-.03	.01	.08	**-.22****	-.06	-.05
9. Emotional representation	.15	-.07	.01	**.57****	**.39****	**.29****
10.Negative representation	.16	-.12	-.03	**.47****	**.23****	.09
11. Treatment attribution	.09	-.18*	-.10	.20*	-.07	-.01
12. Medical attribution	.05	.01	-.03	.10	.02	.02
13. Behavioural attribution	-.07	-.02	-.07	.04	.01	-.08
14. Psychological attribution	-.06	.01	-.15	.12	.03	-.07
15. Cancer attribution	-.09	-.01	-.03	.08	-.01	.07
16. Sleep attribution	-.18*	.10	.08	-.05	-.06	-.05
Mean (SD)	2.72 (1.09)	3.88 (1.28)	4.15 (1.35)	2.54 (1.34)	3.09 (1.58)	3.39 (1.60)
Min-Max	1 - 6	1 - 6	1 - 6	1 - 6	1 - 6	1 - 6

*p <.05, ** p < .01, *** p <.001.

Cognitive representations as predictors of coping. Multiple regression analyses of coping strategies were carried out with the cognitive representations that were significantly correlated with coping as predictors in the model. All of the models were significant at the $p < .01$ level and explained between 4 and 34% of the variance (see Table 5.5). More severe perceived consequences was the only significant predictor in each of the models, predicting significantly greater use of symptom focussing, information seeking and seeking emotional support. Multiple regression analyses of activity avoidance, maintaining activity and accommodating to CRF coping were not carried out as none of the cognitive representations were significantly correlated with these coping strategies.

Table 5.5 *Multiple regression analyses of symptom focussing, information seeking and emotional support seeking with cognitive representations as model predictors*

	Symptom focussing			Information seeking			Emotional support		
	B	SEB	β	B	SEB	β	B	SEB	β
Timeline chronic	0.11	0.10	.09	0.06	0.42	.04	Not entered		
Consequences	0.61	0.10	.46***	0.54	0.13	.35***	0.34	0.13	.21**
Personal control	-0.21	0.11	-.13	Not entered			Not entered		
Coherence	-.10	0.10	-.07	Not entered			Not entered		
	R^2= .34			R^2= .14			R^2= .05		
	Adj. R^2= .32			Adj. R^2= .13			Adj. R^2= .04		
	$F(4, 150) = 19.28$, $p<.001$			$F(2, 152) = 12.12$, $p<.001$			$F(2, 152) = 7.14$, $p<.01$		

*p <.05, ** p < .01, *** p <.001.

Coping strategies as predictors of fatigue. Coping strategies that were significantly correlated with fatigue severity (activity avoidance, focussing on symptoms, information seeking and seeking emotional support) were entered into a multiple regression analysis of fatigue severity. Coping strategies accounted for 37% of the variance in fatigue severity, $F(4, 149) = 23.2$, $p < .001$. Focussing on symptoms explained most of the variance in fatigue with greater use of focussing on symptoms (β = -.48, $p < .001$) and information seeking (β = -.18, $p < .05$) significantly predicting greater fatigue.

Does coping mediate the relationship between cognitive representations and fatigue? Using the PROCESS procedure for SPSS, the model depicted in *Figure 5.2* was estimated to derive the total (path *c)*, direct (path *c'*) and indirect (paths a_1b_1 and a_2b_2) effects of negative representation on fatigue severity through the coping strategies of symptom focussing and seeking information.

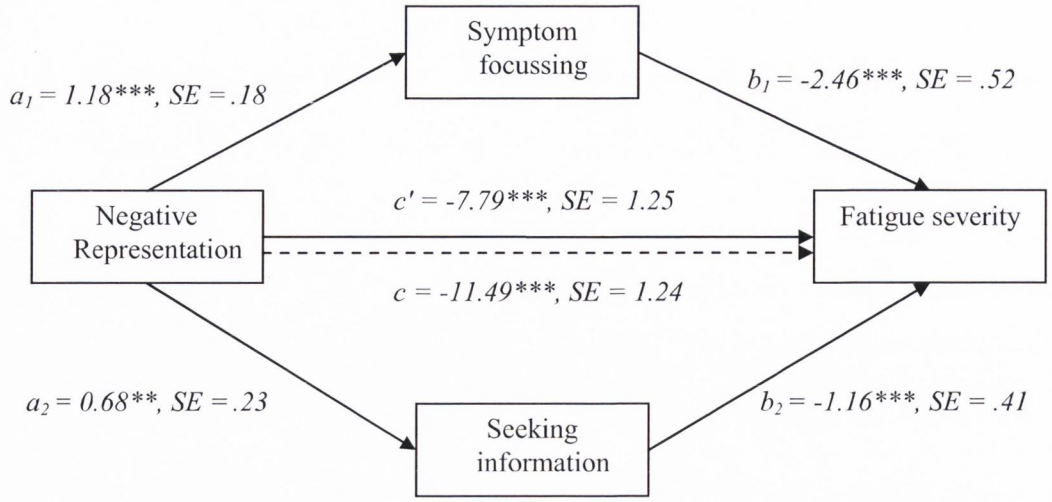

Figure 5.2. Path coefficients for simple multiple mediation analysis of negative representation of fatigue on fatigue severity through symptom focussing and information seeking.

Note. Dashed line denotes the effect of negative representation on fatigue when coping strategies are not included as mediators. a_1, a_2, b_1, b_2, c, and c' are unstandardised regression coefficients. $R_{Y,X}^2$ (proportion of variance in Y [fatigue] explained by X [negative representation]) = .36; $F(1, 153) = 85.96***$. $R_{M1,X}^2$ (proportion of variance in M_1 [symptom focussing] explained by X) = .22; $F(1, 153) = 43.63***$. $R_{M2,X}^2$ (proportion of variance in M_2 [seeking information] explained by X) = .05; $F(1, 153) = 38.99**$. $R_{Y,M1,M2,X}^2$ (proportion of variance in Y explained by X, M_1 and M_2) =.50; $F(3, 151) = 51.06***$. $**p < .01$, $***p < .001$.

The results of the mediational analysis supported each of the hypothesised pathways. The total effect was significantly different from zero; negative representations of fatigue explained 36% of the variance in fatigue severity, whereby participants who had a more negative representation of fatigue had more severe fatigue. Both the direct effect (path c') and the indirect effects (a_1b_1 and a_2b_2) of cognitive representations were significantly different from zero after coping strategies were entered into the model as mediators. There was a significant negative indirect effect of cognitive representation on fatigue through focussing on symptoms (point estimate = -2.91, *SE* = 0.69; 95% bias-corrected CI -4.42 to -2.12). Participants who had negative representations were more likely to use focussing on symptoms as a coping strategy and those who used this coping strategy were more fatigued. The index of mediation (a_1b_{1cs}) for the effect of cognitive representation on fatigue through focussing on symptoms was -.15 with 95% CIs of -.23 to -.09.

A significant negative indirect effect of cognitive representation on fatigue through seeking information was also observed (point estimate = -0.79, *SE* = 0.38), with 95% CIs of -1.80 to -0.22. Participants who had negative representations were more likely to use information seeking as a coping strategy and those who used this coping strategy were more fatigued. The completely standardised indirect effect (a_2b_{2cs}; index of mediation) for the effect of cognitive representation on fatigue through seeking information was -.04 with 95% CIs of -.09 to -.01. The results are thus consistent with the idea that more negative representations of fatigue influences fatigue severity directly and indirectly through coping behaviours. The total indirect effect of the model was -3.70, with CIs of -5.41 to -2.45. The index of mediation for the effect of cognitive representation on fatigue through coping strategies was -.19 with 95% CIs of -.28 to -.13.

Does emotional representation mediate the relationship between cognitive representations and fatigue? Using the PROCESS procedure for SPSS, the model depicted in *Figure 5.2* was estimated to derive the total (path *c)*, direct (path *c'*) and indirect (path *ab*) effect of negative representation on fatigue severity through emotional representation. The results of the mediational analysis supported each of the hypothesised pathways. The total effect was significantly different from zero; negative representations of fatigue explained 36% of the variance in fatigue severity, whereby participants who had a more negative representation of fatigue had more severe fatigue. The direct relationship between negative representations and fatigue remained significant even after emotional representation was entered into the model as a mediator (path *c'*). Analysis revealed a significant negative indirect effect of cognitive representation on fatigue through emotional representation (point estimate = -3.48, *SE* = 0.81; 95% CI of -5.34 to -2.12). Thus, participants who had more negative cognitive representations were more likely to have more negative emotional representations, and those with more negative emotional representations were more fatigued; for each unit increase in negative representations, fatigue worsened by 3.48 units on average as a result of the effect of negative cognitive representations on emotional representation, which in turn impacted on fatigue. The completely standardised indirect effect (ab_{cs}) of cognitive representation on fatigue through emotional representation was -.18 with 95% CIs of -.27 to -.11. A medium to large effect size was observed using Preacher and Kelly's (2011) K^2 method; K^2 was .20 with a 95% CI of .13 to .29. Thus the evidence is consistent with the idea that more negative cognitive representations of fatigue influences fatigue both directly and indirectly through emotional representation.

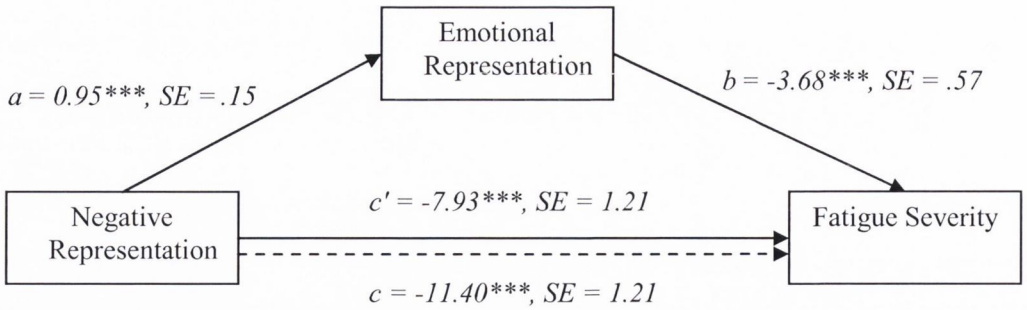

Figure 5.3. Path coefficients for simple mediation analysis of negative cognitive representation of fatigue on fatigue severity through emotional representation.
Note. Dashed line denotes the effect of negative representation on fatigue when emotional representation is not included as a mediator. *a*, *b*, *c*, and *c'* are unstandardised regression coefficients. $R_{Y,X}^2$ (proportion of variance in Y [fatigue] explained by X [negative representation] = .36; $F(1, 159) = 88.42$***. $R_{M,X}^2$ (proportion of variance in M [emotional representation] explained by X) = .20; $F(1, 159) = 38.99$***. $R_{Y,MX}^2$ (proportion of variance in Y explained by X and M) = .49; $F(1, 159) = 76.77$***. ***$p <$ .001.

5.2.4 Discussion. The findings show that cancer survivors form identifiable cognitive representations of their fatigue and that these representations can predict both the coping strategies they use to manage fatigue and fatigue severity. Furthermore, the findings suggest that emotional representation and coping strategies, in line with Leventhal's CSM, can act as partial mediators between cognitive representations and fatigue outcomes.

5.2.4.1 Cancer survivors' cognitive and emotional representations of fatigue. Participants attributed a wide range of symptoms to their CRF. Although the vast majority of participants scored within the cut-off for significant fatigue and experienced a high number of the symptoms associated with CRF, only just over half of the sample reported they experienced the key symptom (significant distress or impairment in social or occupational functioning) required for a diagnosis of CRF using diagnostic criteria (Cella et al., 2001). In line with previous research (e.g., Servaes, Verhagen, et al., 2002c) participants held strong cancer treatment-related causal attributions but many participants also acknowledged the role of stress and sleep disturbances in contributing to their fatigue. Participants indicated that they had a clear understanding of CRF; they perceived their fatigue to be cyclical but not chronic, to have a serious and negative impact on their

lives and to cause them emotional distress. Both treatment- and personal-controllability beliefs were moderately high indicating that participants felt they had some control over their fatigue.

Bivariate analysis demonstrated that cognitive representations were related to one another in theoretically consistent ways; reporting serious consequences from CRF was related to the belief that fatigue would last a long time and would have a cyclical timeline, the belief that one has low personal control over the condition, low perceived understanding of the condition, and stronger psychological causal attributions. Participants who perceived the timeline of their fatigue to be chronic were more likely to report low personal control and more negative emotional representations in response to the fatigue as well as medical and psychological causal attributions.

5.2.4.2 Can cognitive representations predict coping and fatigue in cancer survivors? Cognitions regarding fatigue were related to coping strategies in logical ways. For example, participants who engaged in more symptom focussing and information seeking had a stronger illness identity, more chronic timeline perceptions, more serious perceived consequences, and a more negative emotional representation. Lower control and coherence perceptions were also associated with greater symptom focussing. Cognitive representations of fatigue predicted symptom focussing, seeking information and emotional support, with consequence perceptions playing a central role.

Nearly all cognitive representations were significantly associated with fatigue and together cognitive representations explained a substantial proportion of the variance in fatigue severity. Of the causal attributions, only medical attributions were significantly associated with fatigue severity. Treatment-related control perceptions and cancer treatment-related causal attributions were not significantly associated with fatigue; however, the relatively low reliabilities of these constructs may have impacted on their ability to show significant relationships. Thus, it is not possible to definitively state that they do not play a role in CRF based on these findings. As treatments for cancer are known to cause fatigue and as there is no clearly defined 'treatment' specifically for such fatigue, the treatment-control items may have led to participant confusion about what was meant by the idea of treatment control. Thus, refinement of the treatment-control construct in the context of CRF may be necessary. Furthermore, cancer- and sleep-related causal attributions were both only measured with a single item, which may have limited the variability of the data on these subscales. Additional development of the measures used to assess these constructs may reveal a role for such causal attributions.

5.2.4.3 Do coping strategies mediate the relationship between cognitions and fatigue? The results provide evidence of direct links between cognitive representations and fatigue outcomes; however, consistent with Leventhal's model, there was also evidence that this relationship was partly mediated by coping strategies, specifically through focussing on symptoms and information seeking. As the current study is based on cross-sectional data, causal relationships between cognitions, coping and fatigue could not be established. However, the findings are in line with the idea that having more negative representations of fatigue can lead to greater use of such coping strategies, and thereby to greater fatigue. The finding that focussing on symptoms was a mediator supports previous research that suggests that this coping strategy is maladaptive in chronic conditions (e.g., Knoop et al., 2010; Ray, Jefferies, & Weir, 1997). Focussing on symptoms was associated with more negative emotional representations of fatigue, more chronic timeline perceptions and lower perceived personal control, which is in line with the idea that this coping strategy could lead to increased emotional distress and disengagement from daily activities (Gray & Rutter, 2007). Use of information seeking as a coping strategy also predicted higher fatigue. Although information seeking is thought to be a positive strategy, it may have been negatively associated with fatigue in the current study through similar processes as focussing on symptoms. Greater preoccupation with symptoms may have led participants to search for more information on CRF, and this may have contributed further to their symptom focussing. Similar results have been reported in the context of CFS (Gray & Rutter, 2007), whereby individual who engaged in greater information seeking were more likely to have more severe fatigue . Furthermore, as having longer timeline perceptions, more severe consequence beliefs, and a more negative emotional representation of fatigue were associated with greater use of information seeking in the current study, such individuals may have been more motivated to inform themselves about their condition. In addition, it is possible that having more severe fatigue led to greater use of information seeking.

There was no evidence in the current study that active coping strategies played a role in fatigue; both maintaining activity and accommodating to fatigue were not associated with fatigue severity. Although patients with CRF are encouraged to stay active and to exercise, overdoing activities and pushing through fatigue are thought to be harmful (Collier & O'Dwyer, 2011; Gielissen, Bleijenberg, et al., 2007). Thus, it is surprising that greater use of 'maintaining activity' was not linked to greater fatigue. Similarly, accommodating to the fatigue by using strategies such as pacing activities and

scheduling activities at peak times of energy was not associated with lower fatigue, although the NCCN guidelines for CRF (2012a) recommend the use of this approach. These findings cannot be explained by low internal reliability of the subscales or low variability in the data. It is possible that the participants had low activity levels even before their illness and therefore maintaining their usual pace of activity after treatment did not impact on fatigue. Prospective longitudinal research and more rigorous ways of assessing activity levels are necessary to explore these relationships further. Nevertheless, there is some limited evidence in the current study that activity levels do play a role; greater avoidance of activity was significantly associated with greater fatigue. However, this relationship was no longer significant in a multivariate model when symptom focussing, information seeking and seeking emotional support were included as predictors. Although seeking information and emotional support are active coping strategies, the findings suggest that CRF is predicted more strongly by engaging in passive or limiting coping; focussing on symptoms, unhelpful cognitions, negative emotional representations of CRF and activity avoidance were associated with greater fatigue, while active behavioural strategies, such as pushing through fatigue or accommodating to it, did not seem to play a role. Such patterns are not specific to CRF; similar findings have been noted in patients with chronic illnesses including CFS, where limiting coping strategies such as cognitive-avoidant coping and behavioural disengagement coping have been consistently linked to disability while associations between active coping and adaptive physical functioning are often weak (Ax et al., 2001; Heijmans, 1998). Furthermore, intervention studies on CFS suggest that cognitive processes rather than behavioural responses are central to the perpetuation of symptoms (Knoop et al., 2010).

5.2.4.4 Is the relationship between cognitions and fatigue mediated by emotional representations? Findings from the current study are consistent with the idea that the influence of cognitions on fatigue is partially mediated by negative emotional representations; a medium to large indirect effect of cognitive representation on fatigue through emotional representations was observed. This supports the emerging literature on the role of psychological distress in chronic illnesses (Gray & Rutter, 2007). However, emotional distress was measured using the emotional representation component of the IPQ-CRF, which assesses distress in response to fatigue rather than distress in general. Thus, the outcome measure (fatigue) is implicated in producing the emotional distress that was assessed. The CSM supports a dynamic system of influences

where patients' cognitive and emotional representations can influence illness outcomes through coping but outcomes and coping strategies can also lead patients to redefine their cognitions and emotional representations (Leventhal et al., 1998). Thus, emotional distress in response to an illness can impact on outcomes and outcomes can in turn impact on emotional distress in an ongoing cycle. Consequently, using a measure of distress in response to fatigue (i.e., the IPQ emotional representation subscale) is in line with the CSM. However, the approach used to assess mediational relationships in the current study is not ideal given that the data was cross-sectional and the model under investigation is dynamic with reciprocal relationships between predictors, mediators and outcomes. Mediational analysis assumes a clear one directional processes of causation, whereby the predictor and mediators impact on the outcome and not vice versa. Clearly, a more rigorous way of testing the dynamic relationships between cognitions, distress and fatigue is needed, preferably with longitudinal data. However, the aim of the current study was to see if there is any evidence for such mediational relationships when this process is artificially dissected at one point in time. The findings provide tentative evidence for such relationships, supporting the idea that more negative cognitive representations of fatigue can lead to greater emotional distress and thereby impact on fatigue outcomes.

5.2.4.5 Limitations General limitations relevant to the three phases of this study are discussed at the end of the chapter; however, some limitations specific to this phase of the analyses are considered here. The data used for this analysis came partly from cancer groups, which may provide members with emotional support and information about how to manage cancer-related side-effects such as fatigue. Furthermore, such groups may promote acceptance of side-effects. Such factors may have influenced participants' cognitions, psychological distress in response to fatigue, and their coping strategies as well as the relationships between such factors. In addition, some participants were recruited for an intervention study for CRF and may thus have been more likely to engage in problem focussed coping strategies for their fatigue. Furthermore, as they were motivated to take part in an intervention trial, they may have suffered from more severe fatigue or their fatigue may have caused them greater distress or impairment. In order to ensure that there were similar relationships between study variables in the three subgroups, the pattern of correlations between beliefs, coping and fatigue within each group was examined (see Appendix 10). The same patterns emerged regardless of study group, with two exceptions. The first was the relationship between fatigue and

information seeking coping; this was negative and statistically significant in the questionnaire and intervention study subsamples, while no relationship was evident in the longitudinal study sample. This may have restricted the predictive power of this coping strategy in the composite sample and could indicate that the observed relationship with fatigue severity is not applicable to all patients.

The second exception was the relationships between some of the attributional beliefs and fatigue, which varied in magnitude and sometimes direction between the subgroups. As attributional beliefs were not included in the mediational analyses these differences would not have impacted on the results. However, it may explain the lack of relationships found between causal attributions and other variables, such as fatigue and coping, and suggests that the reported relationships with attributional beliefs should be interpreted with caution. Different patterns of correlations regarding attributional beliefs may be due to differences in the study recruitment procedures. Participants recruited for the intervention study underwent more vigorous screening to ensure that they suffered from *CRF* and not fatigue related to other medical conditions; thus, different factors may have contributed to the fatigue experienced by the other two subsamples, and it is possible that the nature of the relationship between beliefs, coping and fatigue varies due to the perceived origin of the fatigue. Future studies should be mindful of this limitation and consider how different comorbidities might impact on patients' perceptions of fatigue. Nevertheless, it should be noted that all participants included in this analysis indicated that they suffered from fatigue that was due to their cancer and/or cancer treatments.

Another limitation concerned the use of regression analysis to predict outcomes of interest (e.g., fatigue and coping) from variables (i.e., beliefs) measured at the same timepoints as these outcomes. The possibility that causation occurred in the opposite direction cannot be ruled out. The hypotheses and the analyses presented were based on strong theoretical models and predictions; nevertheless, longitudinal research is necessary to establish whether beliefs at one timepoint can predict coping and fatigue severity at a future time. Furthermore, intervention studies that actually test whether changing beliefs impacts on such proposed outcomes could shed light on the nature of causation between these factors.

5.2.4.6 Practical implications. A number of important findings that can inform clinical practice emerged from the current study. No adaptive coping strategies for fatigue were identified based on the results; however, the findings suggest that engaging

in passive coping in response to fatigue is harmful. Specifically, focussing on symptoms was associated with poorer outcomes; such a relationship is in line with CBT approaches to treating CRF, which try to move patients' focus away from symptoms and reduce emotional responses to the condition, while encouraging patients to take on a more active role in their recovery (Collier & O'Dwyer, 2011; Gielissen, Bleijenberg, et al., 2007).

Although there was evidence that coping strategies partly mediated the relationship between cognitions and fatigue, the direct association between cognitive representations and fatigue severity was stronger than the indirect pathways through coping or emotional representation. This finding is important and supports emerging evidence from the CFS literature that cognitions rather than behaviours play a central role in the maintenance of fatigue. The study thus highlights the importance of understanding patients' own conceptualisations of their conditions in order to provide adequate care and treatment. Intervention studies that examine the role of cognitions in reducing fatigue are necessary to explore these relationships further.

5.2.4.7 Recommendations for further study. This was the first study to systematically test the CSM in the context of fatigue in cancer survivors. Prospective longitudinal studies are needed to determine the direction of causality and to properly test the dynamic structure of the CSM. The idea that patients' cognitive representations of CRF can impact on coping, emotional representation and fatigue in an ongoing reciprocal cycle that maintains CRF over time is conceptually sound and in line with correlational research carried out to date. However, more rigorous tests of such processes are needed.

5.3 Phase 2: Multifactorial Predictors of Fatigue in Cancer Survivors

5.3.1 Rationale. Many different biological, psychological, behavioural and cognitive variables have been proposed as contributing factors to ongoing fatigue in cancer survivors (Oh & Seo, 2011; Payne, 2004). However, previous studies on CRF have focussed on select subsets of such predictors; few studies have tested multifactorial or mediational models. The current study explored the contribution of a wide range of predictors to fatigue in cancer survivors using a cognitive-behavioural model of perpetuation (see Chapter 3) as a theoretical framework.

Similar to Winningham's Psychotropic Entropy Model (1994), the cognitive-behavioural approach maintains that fatigue can develop as a secondary symptom from patients' psychological and behavioural responses to cancer and other experienced symptoms including psychological factors and somatic side-effects or sensations. Thus,

according to both models, a combination of psychological, physiological and behavioural factors can help to maintain fatigue after cancer treatment has been completed. However, the cognitive-behavioural model also questions the factors that help to sustain the contributing factors to persistent CRF by focussing on patients' beliefs and thinking patterns and proposing dynamic relationships between predictors and outcomes. Therefore, the relationships between potential predictors are as important as their relationships with fatigue.

Although cognitive processes, such as catastrophising and beliefs such as kinesiophobia and fear of recurrence (FOR), have been included as predictors in some previous studies (e.g., Donovan et al., 2007; Servaes et al., 2007; Servaes, Verhagen, et al., 2002c; Young & White, 2006), the role of cognitions in the context of other established psychological and behavioural contributing factors has not been comprehensively tested and few studies have explored mediational models of fatigue. Thus, the mechanisms through which cognitions might impact on fatigue are not clear. For example, while fear of activity would intuitively be expected to impact on fatigue through activity avoidance and lower physical activity levels, only one study has investigated mediational pathways between negative beliefs about activity and CRF and no evidence of an indirect pathway through activity level was found (Young & White, 2006). It is also possible that maladaptive beliefs may influence fatigue through other behavioural factors, such as the coping strategies used, as proposed in the CSM model (Leventhal et al., 1984). Alternatively, negative thinking patterns could be a symptom of, or indeed a contributing factor, to depressed mood or distress and thereby contribute to persistent fatigue. In line with this idea, Young and White's (2006) findings indicated that the relationship between FOR and post-treatment CRF was indirectly mediated by psychological distress and beliefs about activity. Thus, unhelpful cognitions may contribute to fatigue by impacting on psychological factors and/or cognitive responses such as catastrophising, which in turn could also feed into other contributing factors like sleep disturbances. There are therefore many potential mechanisms through which cognitive processes and beliefs could play a role in post-treatment fatigue. However, although mediational pathways have been integrated into some theories of CRF (e.g., Winningham's Psychotropic Entropy Model, 1994), they have received little attention in the empirical literature.

The aims of the current study were to test the contribution of psychological (anxiety, depression, and stress), social (social support), behavioural (activity levels and

coping strategies), sleep-related (sleep disturbances), and cognitive (catastrophising, negative representations of fatigue, causal attributions, negative beliefs about activity and fear of cancer recurrence) factors in a multivariate model of fatigue severity in cancer survivors and to examine the interrelationships between these proposed predictors. In addition, in keeping with the cognitive-behavioural framework, specific mediational pathways between cognitive factors and fatigue were also explored. As cognitions may be linked to fatigue through many possible mechanisms, three specific mediational pathways were selected a priori based on the cognitive-behavioural model and previous findings. The following predictions were made:

1. Psychological, behavioural, social, sleep-related, and cognitive factors would all significantly predict fatigue in a multivariate model.
2. There would be strong interrelationships between the predictors of fatigue severity.
3. The relationship between negative beliefs about activity and fatigue would be mediated by psychological distress, activity avoidance coping and lower physical activity levels.
4. The relationship between negative representations of fatigue and fatigue would be mediated by psychological distress, catastrophising and symptom focussing.
5. The relationship between fear of cancer recurrence and fatigue would be mediated by psychological distress, catastrophising, symptom focussing and lower activity levels.

5.3.2 Method.

5.3.2.1 Participants and procedure. The data used in this section came from the same dataset described in phase 1; however, only data from the second and third studies were included as participants in the first study did not complete questionnaires on all of the factors incorporated in the current secondary analysis. Thus, there were 82 participants in total, all of whom were at least three months post-treatment and self-identified as having CRF.

5.3.2.2 Measures. The questionnaires used to assess demographic (age, gender, marital, educational level and employment status) and medical information (cancer type and treatment, time of diagnosis and treatment, and comorbid medical conditions), fatigue (FACT-F; Yellen et al., 1997), anxiety and depression (HADS; Zigmond & Snaith, 1983), stress (PSS short form; Cohen et al., 1983), sleep disturbance (items developed by Anderson et al., 2003), and physical activity (IPAQ; Craig et al., 2003)

have been previously described in Chapter 4. Negative cognitive representations of fatigue and coping strategies were assessed using the IPQ-CRF (Pertl et al., 2012) and the CRF coping strategies questionnaire described in phase 1 of this chapter (see section 5.2.2.2). Given the number of predictors included in the current study, the IPQ composite negative representation subscale was used. With the exception of the activity avoidance coping subscale (which had an alpha value of .59 that could not be improved by removing items), the internal reliability of the scales used to measure fatigue and each of the predictors was good (Cronbach's alpha > .75); mean scores were therefore calculated for each measure.

Questionnaires were also included to assess social support and other cognitive factors that have been related to CRF (catastrophising, fear of cancer recurrence and negative beliefs about activity in relation to fatigue). These are described below.

Social support. A brief author-constructed scale was included in order to assess patients' perceived social support regarding their fatigue. Patients were asked whether they believed those closest to them gave them adequate support, understood their fatigue experience, and understood how their fatigue affects them. These three items were scored on a 7-point response scale, which ranged from '*no, definitely not*' to '*yes, definitely*'. The internal reliability of the social support scale was .94. A composite social support score was calculated such that higher scores indicated higher perceived social support.

Catastrophising. The Fatigue Catastrophising Scale (FCS) developed by Jacobsen and colleagues (Jacobsen, Azzarello, & Hann, 1999) was used. This scale was based on the catastrophising subscale of the Cognitive Coping Strategies Inventory (Butler, Damarin, Beaulieu, Schwebel, & Thorn, 1989) and contains 10 items (e.g., "I find myself expecting the worst when I'm fatigued") rated on 5-point Likert scales ranging from 1 - *'never true'* to 5 -*'all of the time true'*. A total score can be calculated by obtaining the mean of the 10 ratings, whereby higher scores indicate greater catastrophising. The FCS was found to have good internal reliability in previous research (Jacobsen et al., 2004); in the current study the internal reliability was .91.

Fear of recurrence (FOR) of cancer. The Fear of Recurrence Scale developed by Kornblith (Greenberg et al., 1997) was used to assess FOR. The scale consists of 5-items assessing concerns regarding cancer relapse (e.g., "Because cancer is unpredictable, I feel I cannot plan for the future"). Each item is rated on a five-point scale which measures the degree to which a participant agrees with each statement. A higher total score indicates

lower FOR. The scale was found to have satisfactory reliability (α = .69 and .75) in two studies of adult leukaemia survivors (Greenberg et al., 1997; Hill et al., 1998) and it has also been used in a previous study examining the moderators of CRF in a sample of adult breast cancer survivors (Young & White, 2006). In the current study the internal reliability of the FOR scale was .84.

Beliefs about activity in relation to fatigue. The Tampa Scale of Kinesiophobia-Fatigue (TSK-F) beliefs about activity subscale (Silver et al., 2002) was used to assess this construct. The subscale consists of six items (e.g., "I am afraid that I might make my symptoms worse if I exercise.") with four-point Likert response scales ranging from 1 - *'strongly disagree'* to 4 - *'strongly agree'*. The scale was found to have satisfactory levels of internal consistency in previous research (Silver et al., 2002). A total score can be calculated, whereby a higher score indicates a stronger belief that physical movement and activity is harmful for fatigue. In the current study, Cronbach's alpha for this scale was low (α = .56); therefore, three items (items 2, 5 and 6) were excluded in order to improve the internal reliability of the measure to .69.

5.3.2.3 Analysis. Descriptive statistics were used to describe the demographic and medical characteristics of participants. Pearson product moment correlations and *t* tests were used to explore whether any demographic and medical characteristics were significantly associated with fatigue severity. Interrelationships between psychological, behavioural, social, sleep-related, and cognitive factors and fatigue were explored using Pearson correlations. A more stringent α-level of .01 was used to reduce the risk of Type I errors because of the large number of correlations undertaken. Hierarchical multiple regression analysis was used to investigate the predictors of fatigue severity. Only variables that correlated with fatigue at a *p*-value of .01 or less were entered into the multiple regression model. Demographic and medical variables were entered into the model first to control for their potential confounding effects. The psychosocial predictors were then entered into the model in a predetermined order to test the study hypothesis. No problems with multicollinearity were detected in the data. To test the specific mediational pathways hypothesised, Hayes' (2012) PROCESS macro for SPSS (previously described in section 5.2.2.3 of phase 1 in this chapter) was used. The significance of the indirect effects were tested using 95% bias-corrected bootstrap confidence intervals (CIs) from 5,000 samples (Hayes, 2012). CIs that did not contain zero provided evidence of a significant indirect effect.

Table 5.6 *Demographic characteristics of participants (n = 82)*

Demographic characteristics	n	%	Clinical characteristics	n	%
Gender			Cancer type		
Male	11	13.4%	Breast Cancer	53	66.3%
Female	71	86.6%	Gynaecological Cancer	7	8.8%
Menopausal status			Lymphoma	6	7.5%
Premenopausal	32	47.1%	Colorectal Cancer	4	5%
Perimenopausal	12	17.6%	Leukaemia	4	5%
Postmenopausal	24	35.3%	Head and neck	4	5%
Children			Prostate	1	1.3%
Has children	60	75.9%	Sarcoma	1	1.3%
Has children living at home	52	65.8%	Type of treatment		
Marital status			Chemotherapy	74	91.4%
Married/Partnered	48	58.5%	Surgery	66	81.5%
Single	16	19.5%	Radiation Therapy	65	80.2%
Separated/Divorced	9	11%	Hormonal treatment	46	56.1%
Widowed	9	11%	Combination of treatments		
Employment status			Surgery, chemo & RT	50	61.8%
Employed	42	52.4%	Surgery & chemo	10	12.3%
Housewife	14	17.5%	Chemo & RT	10	12.3%
Retired	10	12.5%	Surgery & RT	4	5%
Resigned for health	9	11.3%	Surgery, chemo or RT	7	8.6%
Unemployed	4	5%	Comorbities		
Student	1	1.3%	No comorbidities	38	47%
Highest educational level			1 comorbidity	24	29.6%
Primary (≤ 8 years)	7	8.6%	2 comorbidity	13	16%
9 - 11 years	10	12.3%	≥3 comorbidities	6	7.4%
12 - 14 years	25	30.9%	BMI (kg/m^2) class[a]		
Third level education	23	28.4%	Underweight (< 18.5)	1	1.3%
Postgraduate	16	19.8%	Normal (18.5 – 24.9)	35	44.3%
			Overweight (25 –29.9)	27	34.2%
			Obese (≥30)	16	20.3%

5.3.3 Results.

5.3.3.1 Participant characteristics. Table 5.6 describes the participants' demographic and medical characteristics (see Table 5.1 for a breakdown of characteristics for each study group). The mean age was 50 years (*SD* = 12.25 years); the mean time since treatment was one year and 5.16 months (*SD* = 24.71 months; Median = 7.4 months). The vast majority of participants were female and either married or living with a long-term partner. The majority of participants had children (mean number of children = 2.00, *SD* = 1.68), mostly still living at home. Most participants were employed full- (n = 41) or part-time (n = 1) and had at least an upper second level of education (≥12 years). More than half of the sample was overweight according to the

WHO BMI classification; the mean BMI was 26.72 (*SD* = 5.29). Just over half of the sample (n = 43) suffered from an additional medical condition; the mean number of comorbidities was 0.86 (*SD* = 1.03). The most common types of conditions reported were arthritis (n = 11), high blood pressure (n = 9), thyroid problems (n = 7), asthma (n = 7), depression (n = 5), high cholesterol (n = 5), and back pain (n = 5). All other conditions were reported by less than five participants. The majority of participants had breast cancer and nearly all participants were treated with chemotherapy. Nearly two-thirds of the sample had received a combination of surgery, chemotherapy and radiation therapy.

5.3.3.2 Relationships between demographic and medical factors and fatigue.

Greater fatigue was significantly associated with longer time since treatment (r = -.42, p < .001). No other significant associations were found between any demographic or clinical factors and fatigue severity (gender, having children, children living at home, relationship status, employment status, educational level, BMI, or menopausal status). Differences in fatigue severity across different cancer types could not be examined due to the small number of patients with cancers other than breast cancer. No significant differences were found between participants who had and those who had not received surgery, chemotherapy, radiation therapy or hormonal treatments. Furthermore, no differences in fatigue were found between those who received the treatment combination of surgery, chemotherapy and radiation therapy and those who did not.

5.3.3.3 Relationships and interrelationships between fatigue and the hypothesised psychological, behavioural, social, sleep-related and cognitive predictors.

Significant correlations were observed between fatigue and ten of hypothesised predictors at the p < .01 level (significant correlations displayed in Table 5.7). Greater fatigue severity was associated with higher levels of anxiety, depression and stress, lower levels of physical activity, lower perceived social support, greater catastrophising, a more negative cognitive representation of fatigue and greater use of symptom focussing, information seeking and emotional support seeking coping strategies. Fatigue was not significantly (p > .05) associated with sleep disturbance (r = -.21), time spent sitting (r = -.03), FOR (r = .16), fear of activity (r = -.18), any causal attributions (r = -.01 to -.24), or the coping strategies activity avoidance (r = -.19), maintaining activity (r = -.05) and accommodating to fatigue (r = .09).

Table 5.7 *Significant correlations between the predictors and fatigue severity and intercorrelations among the significant predictors*

	2	3	4	5	6	7	8	9	10	11
1. Fatigue[1]	-.44**	-.61**	-.65**	.40**	.33**	-.55**	-.62**	-.70**	-.38**	-.33**
2. Anxiety	-	.63**	.49**	-.09	-.25*	.69**	.39**	.44**	.06	.28*
3. Depression[2]		-	.61**	-.17	-.25*	.57**	.39**	.47**	.16	.03
4. Stress			-	-.18	-.32**	.45**	.41**	.43**	.10	.04
5. Physical activity				-	.07	-.20	-.33**	-.34**	-.17	-.14
6. Social Support					-	-.36**	-.37**	-.23*	-.14	-.05
7. Catastrophising						-	.49**	.68**	.24*	.10
8. Neg. cognitive representation							-	.53**	.29*	.17
9. Symptom focussing								-	.40**	.29*
10. Information seeking									-	.49**
11. Emotional support										-

Note. [1]higher fatigue scores indicate greater fatigue. [2]HADS depression excluding item 8 ("I feel as if I am slowed down"). Neg. cognitive representation = negative cognitive representation. *$p < .05$, **$p < .01$, ***$p < .001$.

Interrelationships between the hypothesised predictors of fatigue are also displayed in Table 5.7. All of the factors that were significantly related to fatigue were also significantly related to one another, with the exception of physical activity, and the information seeking and emotional support coping strategies. Nevertheless, physical activity was significantly associated with negative cognitive representations and symptom focussing; information seeking was significantly associated with a negative cognitive representation and catastrophising, as well as symptom focussing and information seeking; and a significant relationship was observed between information seeking and depression. Thus, each of the predictors of fatigue was significantly interrelated with at least some of the other factors linked to fatigue. The cognitive dimensions and anxiety had the largest number of, as well as the strongest, interrelationships with other predictors. For example, having a more negative cognitive representation of fatigue was significantly associated with eight of the nine other factors related to fatigue; a more negative representation was associated with greater anxiety, depression and stress, lower physical activity, lower social support, and greater use of symptom focussing and information seeking.

5.3.3.4 Multiple regression analyses of fatigue severity. The parameters of the regression model are presented in Table 5.8. Assumptions of normally distributed and independent residuals were met; however, four cases with large standardised residuals

and/or Mahalanobis distance values were removed after diagnostic checks indicated that they could have an undue influence on the regression model. In addition, as the distribution of physical activity was heavily skewed, the MET-min/week scores were transformed using a $\log_{10}$ transformation; a Kolmogorov-Smirnov test of normality on the resulting distribution was not significant ($p > .05$). The final regression model was significant; $F(11, 43) = 20.58$, $p < .001$. Time since treatment was entered into the model in step 1 and accounted for 21% of the variation. Social support and negative cognitive representations of fatigue were entered in step 2 in order to first asses their independent contribution to the model; this produced a significant change in R^2 and increased the proportion of variance explained to 43%. Finally, the addition of anxiety, depression, stress, physical activity level, catastrophising and the coping strategies focussing on symptoms, information seeking and seeking emotional support in step 3 produced a further significant change in R^2, increasing the proportion of variance explained to 80%. Both social support and negative cognitive representations of fatigue continued to be significant predictors. In total, seven of the 10 hypothesised predictors that were entered into the model as well as time since treatment made significant contributions to the final model.

Table 5.8 *Summary of hierarchical multiple regression analyses on fatigue severity*

Predictor variables	B	SEB	β	R^2	Adjusted R^2	Change in R^2
Step 1						
Time since treatment	-0.01	0.01	-.47***	.22	.21	-
Step 2						
Time since treatment	-0.01	0.01	-.31**			-
Social support	1.23	0.59	.23*			
Negative cognitive representation	-8.23	2.54	-.39**	.46	.43	.24
Step 3						
Time since treatment	0.01	0.01	-.16*			
Social support	0.75	0.37	.14*			
Negative cognitive representation	-4.91	1.79	-.23**			
Anxiety	0.92	0.26	.37**			
Depression	-0.93	0.30	-.31**			
Stress	-4.60	1.21	-.37***			
Catastrophising	1.24	1.42	.09			
Physical activity[1]	2.40	1.68	.09			
Focussing on symptoms	-3.26	0.75	-.43***			
Information seeking	0.88	0.50	.15			
Seeking emotional support	-2.07	0.50	-.35***	.84	.80	.38

[1]The $\log_{10}$ transformation of MET min/week was used as a measure of physical activity.

*p <.05, ** p < .01, *** p <.001.

5.3.3.5 Mediation analyses.

Is the relationship between beliefs about activity and fatigue mediated by psychological distress, activity avoidance coping or lower physical activity levels? Although negative beliefs about activity were not significantly associated with fatigue in this study, it was still possible that they were related indirectly through behavioural or psychological factors. However, no significant associations were found between negative beliefs about activity and the hypothesised psychological mediators or physical activity. Although negative beliefs about activity were related to the hypothesised coping mediator (activity avoidance), this coping strategy was not related to fatigue severity. Therefore, there was no evidence for these mediational pathways in the data and this model was not tested.

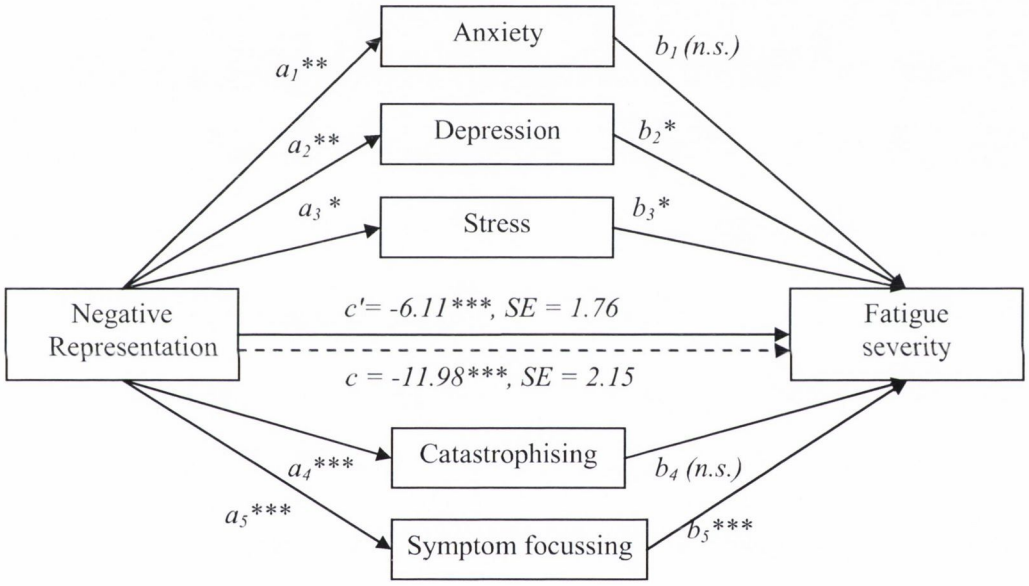

Figure 5.4 Path coefficients for the multiple mediation analysis of negative representation on fatigue severity through psychological distress, catastrophising and symptom focussing.

Note. Dashed line denotes the total effect of negative representation on fatigue when the mediators are not included. c and *c*' are unstandardised regression coefficients. Regression coefficients of indirect pathway are detailed in Table 5.9. (n.s.) = pathway not significant, *p <.05, ** p < .01, *** p <.001.

Is the relationship between negative representations of fatigue and fatigue mediated by psychological distress, catastrophising or symptom focussing? Negative representation of fatigue was significantly associated with both fatigue and each of the

hypothesised mediators. Using the PROCESS procedure for SPSS, the model depicted in *Figure 5.4* was estimated. Time since treatment was entered as a covariate in the model.

The total effect was significantly different from zero; negative representations of fatigue and the covariate time since treatment explained 41% of the variance in fatigue severity, whereby participants who had a more negative representation of fatigue (path *c*, see *Figure 5.4*) had more severe fatigue, $F(2, 75) = 26.07$, $p < .001$. The covariate time since treatment did not make a significant contribution to the model ($\beta = -0.01$, SE = .01, $p > .05$).

Table 5.9 *Regression coefficients and indirect effects of negative representation of fatigue on fatigue severity derived from Hayes's mediation macro*

	Direct effect of negative rep. on proposed mediators: ($a_1 - a_5$): β (SE)	Direct effect of proposed mediators on fatigue: ($b_1 - b_5$): β (SE)	Indirect effect ($a_1b_1 - a_5b_5$)	
			Point estimate	95% bias-corrected bootstrap CI
1. Anxiety	3.39** (1.00)	0.33 (0.27)	1.13 (1.03)	-0.44 to 3.80
2. Depression	2.43** (0.87)	-0.70* (0.32)	-1.70 (0.93)	-4.35 to -0.37
3. Stress	0.54* (0.20)	-3.19* (1.36)	-1.72 (1.11)	-4.80 to -0.14
4. Catastrophising	0.81*** (0.17)	0.97 (1.55)	0.79 (1.49)	-1.57 to 4.16
5. Symptom focussing	1.28*** (0.31)	-3.42*** (0.80)	-4.36 (1.35)	-7.54 to -2.22

Note. a_1-$_5$ and b_1-$_5$ are unstandardised regression coefficients. $R_{M1,C,X}^2$ (proportion of variance in M_1 [anxiety] explained by X [negative representation] and C [the covariate time since treatment])= .19; $F(2, 61) = 7.25$**. $R_{M2,C,X}^2$ (proportion of variance in M_2 [depression] explained by X and C) = .16; $F(2, 61) = 5.92$*. $R_{M3,C,X}^2$ (proportion of variance in M_3 [stress] explained by X and C) = .14; $F(2, 61) = 4.95$*. $R_{M4,C,X}^2$ (proportion of variance in M_4 [catastrophising] explained by X and C) = .29; $F(2, 61) = 12.37$***. $R_{M5,C,X}^2$ (proportion of variance in M_5 [focussing on symptoms] explained by X and C) = .27; $F(2, 61) = 11.22$***. $R_{Y,C,M1\text{-}5,X}^2$ (proportion of variance in Y [fatigue] explained by X, M_1-$_5$ and C) =.76; $F(7, 56) = 25.49$***. *p <.05, ** $p < .01$, *** p <.001.

The results of the mediational analysis supported a significant direct pathway between negative representation of fatigue and fatigue severity (path *c*') and significant indirect pathways mediated by depression (a_2b_2), stress (a_3b_3) and symptom focussing (a_5b_5; see Table 5.9). The results did not support significant indirect pathways between negative cognitive representations and fatigue through anxiety or catastrophising. The total indirect effect of the model was -5.87 with 95% CIs of -9.55 to -2.67. The covariate time since treatment did not make a significant contribution to the indirect model ($\beta = -0.01$, SE = .01, $p > .05$).

Is the relationship between fear of cancer recurrence and fatigue mediated by psychological distress, catastrophising, symptom focussing or lower activity levels? FOR was not significantly correlated with fatigue in this study; however, FOR could have an indirect effect on fatigue through behavioural or psychological mediators. No significant associations were found between FOR and the hypothesised behavioural predictors physical activity and symptom focussing; therefore, these mediators were not included in the model. However, FOR was related to the hypothesised mediators psychological distress and catastrophising. Using the PROCESS procedure for SPSS, the model depicted in *Figure 5.5* was estimated. Time since treatment was entered as a covariate in the model.

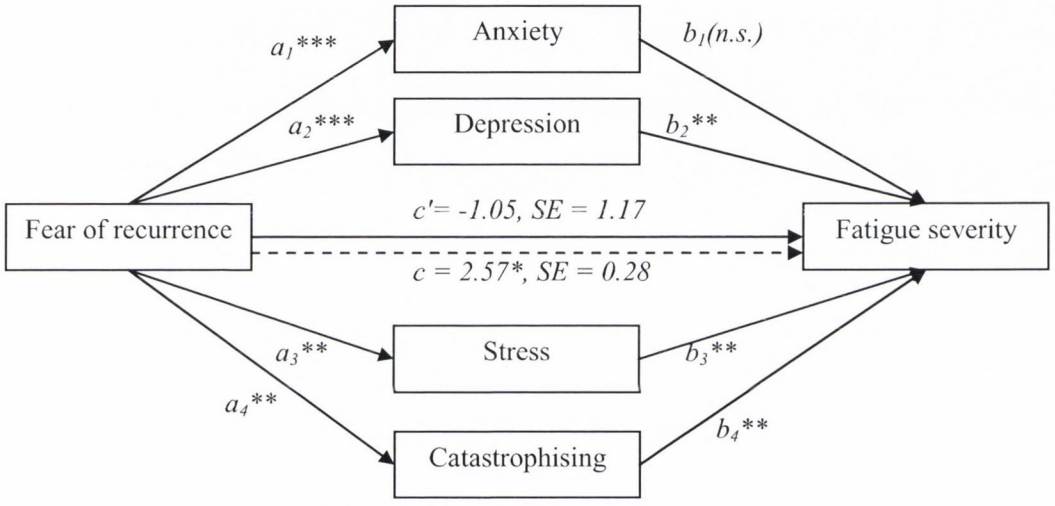

Figure 5.5 Path coefficients for simple multiple mediation analysis of FOR on fatigue severity through psychological distress and catastrophising.

Note. Dashed line denotes the total effect of FOR on fatigue when the mediators are not included. *c* and *c'* are unstandardised regression coefficients. Regression coefficients of indirect pathway are detailed in Table 5.10. (n.s.) = pathway not significant, *p <.05, ** p < .01, *** p <.001.

The total effect was significantly different from zero; FOR and time since treatment explained 21% of the variance in fatigue severity, whereby participants who had greater FOR (path *c*, $p < .05$) and were longer post-treatment ($\beta = -0.01$, SE = .01, $p < .001$) had higher levels of fatigue, $F(2, 64) = 8.38$, $p < .001$. The results of the mediational analysis did not support a significant direct pathway between FOR and fatigue severity (path *c'*) or a significant indirect pathway between FOR and fatigue through anxiety. However, significant indirect pathways mediated by depression (a_1b_1),

stress (a_2b_2), and catastrophising (a_4b_4) were supported (see Table 5.10). The total indirect effect of the model was 3.62 with a 95% CI of 1.31 to -6.53. The covariate time since treatment also made a significant contribution to the indirect model (β = -0.01, SE = .01, $p < .05$).

Table 5.10 *Regression coefficients and indirect effects of FOR on fatigue severity derived from Hayes's mediation macro*

	Direct effect of FOR on proposed mediators ($a_1 - a_4$): β (SE)	Direct effect of proposed mediators on fatigue: ($b_1 - b_4$): β (SE)	Indirect effect ($a_1b_1 - a_5b_4$)	
			Point estimate	95% bias-corrected bootstrap CI
Anxiety	-2.49*** (0.48)	0.40 (0.33)	-0.99 (0.79)	-2.68 to 0.51
Depression	-1.92*** (0.41)	-0.74** (0.41)	1.42 (0.74)	0.31 to 3.38
Stress	-0.29** (0.10)	-4.88** (1.63)	1.41 (0.84)	0.28 to 3.83
Catastrophising	-0.40** (0.09)	-4.45** (1.53)	1.78 (0.86)	0.58 to 4.18

Note. a_1-$_4$ *and* b_1-$_4$ are unstandardised regression coefficients. $R_{M1,C,X}^2$ (proportion of variance in M_1 [anxiety] explained by X [FOR] and C [the covariate time since treatment])= .32; $F(2, 64) = 14.84$***. $R_{M2,C,X}^2$ (proportion of variance in M_2 [depression] explained by X and C) = .30; $F(2, 64) = 13.55$***. $R_{M3,C,X}^2$ (proportion of variance in M_3 [stress] explained by X and C) = .15; $F(2, 64) = 5.62$*. $R_{M4,C,X}^2$ (proportion of variance in M_4 [catastrophising] explained by X and C) = .25; $F(2, 64) = 10.56$***. $R_{Y,C,M1\text{-}4,X}^2$ (proportion of variance in Y [fatigue] explained by X, M_1-$_4$ and C) =.60; $F(6, 60) = 15.08$***. *p <.05, ** $p < .01$, *** p <.001.

5.3.4 Discussion. The results support a cognitive-behavioural model of fatigue, in which patients' beliefs, psychological well-being and behavioural responses to cancer and fatigue, as well as interrelationships between these, impact on post-treatment fatigue in cancer survivors. Fatigue was related to a wide-range of different psychosocial predictors, which were also strongly interrelated with one another. In a multivariate model of fatigue, numerous psychological, cognitive, and behavioural factors independently predicted fatigue severity, explaining a large proportion of the variance. Furthermore, the findings supported indirect associations between negative beliefs about fatigue and FOR and fatigue severity through cognitive responses and psychological mediators.

5.3.4.1 Correlates among fatigue and psychological, behavioural and cognitive factors. The strongest associations with fatigue severity were observed with anxiety and depression, catastrophising, negative cognitive representations, and focussing on

symptoms. Negative cognitive representations regarding fatigue was significantly correlated with nearly all of the other psychosocial variables linked to fatigue, with the coping strategy seeking emotional support as the only exception. This finding is in line with a cognitive-behavioural model of CRF that stresses the central importance of patients' beliefs in maintaining both symptoms and contributing factors to fatigue over time. In the current study, for example, participants who had more negative cognitive representations of fatigue engaged in more symptom focussing and had lower levels of activity; such findings support the idea that interrelationships between cognitions and behaviours can help to sustain contributing factors to CRF. The perpetuating role of psychological factors, such as anxiety, stress and depression, through their relationship with other social, cognitive and behavioural factors was also supported.

Surprisingly, fatigue was not significantly correlated with sleep disturbances or FOR in the current study. This contrasts with previous research where sleep disturbances especially have emerged as strong predictors of fatigue (Banthia et al., 2009; Cavalli Kluthcovsky et al., 2011; Schultz et al., 2010; Skaali et al., 2009; Young & White, 2006). However, nonsignificant trends in the expected directions were observed. It is possible that significant relationships did not emerge because of the relatively small sample size; nevertheless, the strong correlations observed between fatigue and other hypothesised predictors suggest that this was not prohibitive. Furthermore, the size of the correlation coefficient between fatigue and sleep disturbance in this study was smaller than has been previously reported (e.g., Banthia et al., 2009).

Greater self-reported physical activity levels were significantly related to fatigue severity, indicating that participants who did less physical activity were more likely to be fatigued. However, physical activity was not associated with negative beliefs about activity or activity avoidance coping; suggesting that fear of aggravating fatigue by engaging in exercise did not account for lower levels of activity. Kinesiophobia and activity avoidance were also not significantly related to fatigue severity. Thus, the role of maladaptive coping strategies and beliefs relating specifically to exercise were not supported by the findings. These results were thus more in line with Winningham's Psychotropic entropy model of fatigue (1994), which proposes that reduced physical activity levels after cancer treatment can lead to physical deconditioning and thereby contribute to fatigue, than the cognitive-behavioural model, which emphasises the interplay between cognitions, psychological factors and behaviours in contributing to outcomes. It is possible that significant relationships did not emerge in the current study

because of the low internal reliability of both of the activity avoidance and fear of activity subscales. However, psychological factors were also not associated with physical activity. These findings suggest that the association between activity and fatigue is relatively independent of other factors and may be due more to patient's physical abilities after treatment or their activity levels in general rather than their psychological responses to cancer and fatigue or their beliefs. Nevertheless, activity level was not a significant predictor of fatigue in the multivariate model, although this variable was significantly correlated with fatigue. Furthermore, significant associations were observed between physical activity and other significant predictors (e.g., negative cognitive representations of fatigue and focussing on symptoms); thus, there was some tentative support for interrelationships between such factors. Additional research with more robust measures of beliefs relating to activity and objective measures of activity levels is needed in order to explore these relationships further.

In contrast to Young and White's (2006) findings, FOR was not significantly associated with fatigue in the current study, although the trends in the data were in the expected direction. Neither was there any support for the hypothesis that participants who had greater FOR were more likely to avoid activity or have lower activity levels in general. It is possible that participants did not perceive activity to be a contributing factor to their fatigue. In line with this, FOR was not associated with focussing on symptoms of fatigue while those who had higher FOR were more likely to have stronger cancer-related causal attributions and have a stronger tendency to catastrophise in response to fatigue. Thus, rather than contributing to fatigue through behavioural mechanisms, the findings indicate that FOR could play a role in fatigue through its association with psychological factors and cognitive response patterns. This was supported by the mediational analysis, which indicated that the association between FOR and fatigue was indirect, and was mediated by depression, stress and catastrophising. Young and White's findings also supported an indirect relationship between FOR and fatigue via psychological distress.

No significant associations were found between fatigue and any causal attributions. This contrasts with previous research that reported that patients with higher fatigue are more likely to attribute their fatigue to cancer treatment-related and psychological factors (Servaes et al., 2007; Servaes, Verhagen, et al., 2002c). Furthermore, this finding does not provide support for the cognitive-behavioural theory that unhelpful causal attributions can be harmful and contribute to the persistence of symptoms (Gielissen et al., 2006). However, no mediational models of causal

attributions were tested in the current study, thus it is possible that such cognitions play an indirect role through maladaptive coping strategies or psychological factors.

The finding that activity-related coping strategies such as maintaining activity, activity avoidance and accommodating to the fatigue were not associated with fatigue severity also does not support the cognitive-behavioural perspective. Using coping strategies that involve pushing through the fatigue and overdoing things by trying to maintain pre-cancer levels of activity are thought to be harmful for patients, while being mindful of fatigue by pacing activities but not resting excessively are thought to be beneficial for fatigue (Gielissen, Bleijenberg, et al., 2007; Winningham, 2001). It is possible that the reliance on self-report measures for such behavioural coping strategies accounted for the lack of significant associations. Furthermore, the low internal reliability of the activity avoidance subscale may have prevented such relationships from emerging. Thus, the hypothesis relating to association between activity avoidance and fatigue could not be rejected with confidence. Further research using diary methods or third party evaluations of coping behaviours would be beneficial for exploring these relationships further.

5.3.4.2 Predictors of fatigue severity in cancer survivors. In contrast to previous studies on cancer survivors (e.g., Andrykowski et al., 1998; Fagundes et al., 2011; Servaes et al., 2007; Servaes et al., 2001) time since treatment was a significant predictor of fatigue severity in the current study. This finding should not be interpreted as suggesting that fatigue progressively worsens after cancer treatment. It is likely that this association was a function of the sample used, which consisted of two heterogeneous subgroups. A substantial proportion of the sample was made up of patients who had volunteered to take part in an intervention for persistent CRF; these patients were thus longer post-treatment and had to meet more stringent eligibility criteria (the diagnostic criteria for CRF) than those who were included from the longitudinal study (who self-reported significant fatigue). Time since treatment was controlled in the multivariate analysis of fatigue severity; however, the use of two diverse subgroups was a significant limitation of this study.

Findings from the multivariate model of fatigue indicated that numerous psychological, social and cognitive factors can contribute to cancer survivors' fatigue and that such factors explain much of the variance in fatigue severity. Both social support and negative cognitive representations of fatigue continued to be significant independent predictors in the final model even after the remaining psychological and behavioural

contributing factors were entered. These findings highlight the diversity of factors that can contribute to CRF and support a multidimensional approach to assessment and treatment.

Seeking emotional support was one of the strongest predictors of fatigue in the multivariate model, whereby those who sought more support experienced higher fatigue. It is likely that a worse symptom experience and higher emotional distress in response to symptoms led to greater use of this coping strategy. However, it is also possible that seeking emotional support for fatigue is related to symptom focussing, whereby excessive attention to negative symptoms can result in even greater symptom burden. While patients should be encouraged to seek emotional support for distressing symptoms like fatigue, it is important that such support does not add force to negative emotional representations of fatigue. Rather emotional support and treatments should give patients the opportunity to express their concerns and prevent worries and fears from dictating a patient's life by identifying and challenging unhelpful thinking patterns and fears regarding fatigue. The importance of feeling supported by others is evidenced in the current findings by the strong association between social support and fatigue, and the significant independent contribution of social support in a multivariate model of fatigue that contained many other psychosocial predictors.

Although both catastrophising and physical activity had strong associations with fatigue, neither was significant in the multivariate model. However, the significant indirect pathway between FOR and fatigue via catastrophising in the mediation analysis supports a role for catastrophising. The strong association with anxiety especially may have limited the impact of catastrophising in the multivariate analysis. Interestingly though, although significant mediation effects were observed through stress, depression and catastrophising, there was no evidence that FOR was mediated by anxiety; thus the independence of these predictors is supported. It is possible that a sequential process of indirect pathways that encompasses both catastrophising and anxiety links FOR to fatigue.

The results of the mediation analysis of negative representations on fatigue were consistent with the idea that more negative representations of fatigue influence fatigue indirectly through psychological distress and coping. Such pathways support the cognitive-behavioural approach as well as the CSM (Leventhal et al., 1998). In line with the hypothesis, participants who had more negative representations of fatigue were more likely to have higher depression and stress and engage in greater symptom focussing, and

those who reported higher depression, stress and symptom focussing were more fatigued. However, a significant direct effect of negative representations was also observed. Such findings suggest that while cognitions may impact on psychological and behavioural predictors of fatigue and thereby contribute to the maintenance of symptoms, cognitions may also play a more direct role. This is in line with findings from CSM research that support a relationship between cognitions and outcomes that is independent of coping (Hagger & Orbell, 2003).

5.3.4.3 Limitations. Although these findings largely support existing theories of CRF and contribute to the empirical literature on the mechanisms of fatigue in cancer survivors, several limitations must be noted. First, the sample size was small for the number of predictor variables included and this may have led to inflated R^2 estimates. Previous studies that have tested multivariate models of CRF have also reported large effect sizes (e.g., Okuyama et al., 2000; Von Ah et al., 2008; Young & White, 2006); nevertheless, as the recommended number of participants required for regression models of this magnitude were not met, the results should be interpreted with caution. It is also possible that the large proportion of variance explained was due to a common method bias. Future studies could use structural equation modelling and a latent variable to factor out common method variance; however, even if a latent variable is used, it may not fully capture common method variance in the data. A better approach would be to measure variables in multiple ways; for example, using diary methods, objective data on physical activity and sleep, and third-party data for assessing factors such as the coping strategies used.

Alternative strategies of assessment could also improve the reliability of measurements, especially regarding activity-based factors. In the current study, the distribution of physical activity was heavily skewed, with some participants reporting that they did no physical activity whatsoever and a considerable number of others reporting activity levels far in excess of recommended guidelines of physical activity (Haskell et al., 2007), which suggests that the accuracy of responses on this questionnaire was poor. Although a transformation was used to correct the distribution of the physical activity data, the measurement of this variable in the current study may have restricted relationships with physical activity from emerging and actual physical activity levels may not have been accurately captured. Measurement problems were also encountered with the activity avoidance coping subscale, which had poor internal reliability. Activity

diaries and actigraph methods of assessing these variables may thus be necessary to obtain accurate and reliable data.

As previously stated in section 5.3.4.2 , the heterogeneous nature of the sample, formed from two separate studies on CRF, was problematic. As the aim of this study was to test whether there was any evidence for the relationships proposed by the cognitive-behavioural model of CRF, and there were no theoretical grounds for expecting different relationships across the study subsamples, the decision was taken to maximise participant numbers. However, in order to ensure that the nature of the relationships between fatigue and the study predictors were broadly consistent across the two subsamples, the correlations reported in the results section (Table 5.7) were also computed separately for each subgroup (see Appendix 11). The results suggested that there were no clear indications that the two subgroups should not be combined. The only differences in the observed correlation patterns were that physical activity was significantly related to fatigue in the longitudinal study subsample but not in the intervention subsample and information seeking was significantly related to fatigue in the intervention subsample but not the longitudinal subsample. Thus, combining the subsample may have reduced the observed correlations with these variables. Otherwise, the same patterns of associations were observed. Nevertheless, further research is needed to support the current findings in larger, more representative samples of cancer survivors.

Finally, although hypotheses were tested that made specific predictions about the direction of effects, the cognitive-behavioural model supports a dynamic process of influence between predictors and outcomes; such relationships can only be tested fully using longitudinal data. For example, forming negative cognitive representations could lead patients to catastrophise and contribute to fatigue indirectly through heightened anxiety. Alternatively, anxiety after treatment could cause patients to engage in greater catastrophising, which could lead them to develop negative cognitive representations of fatigue and thereby impact on fatigue either directly or through other behavioural mediators. Thus, the direction of effects is not clear; the relationships tested in the current study using cross-sectional data are a simplistic version of a much more complex and dynamic model. Further limitations that are relevant to all three phases of this study are considered at the end of the chapter.

5.3.4.4 Study implications. The results contribute to the empirical literature on the mechanisms of fatigue in cancer survivors in two ways. First, the results highlight the range of different social, cognitive, psychological and behavioural factors that can

independently contribute to fatigue severity, supporting the multifactorial nature of CRF. Second, in line with the cognitive-behavioural approach, the results support multiple mediation pathways in the aetiology of CRF, whereby cognitions and beliefs regarding fatigue may contribute to ongoing symptoms through a variety of different mechanisms, helping to maintain fatigue but also helping to maintain other contributing factors. The utility of the CSM in this context is also supported and the findings indicate that other cognitions, such as FOR, could be subsumed in the model in theoretically consistent ways. Together, these findings suggest that treatment for fatigue in cancer patients should adopt a multidimensional approach that considers not only the physiological, psychological and physical factors that may be impacting on fatigue, but also cognitive factors that may help to perpetuate such contributing factors.

5.4 Phase 3: Can Changes in Cognitive Representations Predict Changes in Cancer-Related Fatigue?

5.4.1 Rationale. CBT interventions have been effective in reducing fatigue in both patients on active treatment and in cancer survivors (National Comprehensive Cancer Network, 2012a) and there is increasing evidence from cross-sectional and correlational studies (e.g., Servaes et al., 2007; Servaes, Verhagen, et al., 2002c; Young & White, 2006) that cognitive factors can predict CRF. Furthermore, catastrophising after treatment was found to predict the course of post-treatment fatigue in a prospective longitudinal study of breast cancer patients (Donovan et al., 2007). However, no intervention studies have assessed whether changes in fatigue are actually mediated by changes in beliefs and no longitudinal studies have investigated whether cognitions are related to fatigue over time.

The aim of current study was to explore whether there is any evidence that changes in the way people think about fatigue are actually associated with changes in fatigue severity. In line with the CSM model, changes in coping strategies over time were also assessed. In addition, more established psychological and behavioural predictors of fatigue were included to test whether changes in these were related to changes in fatigue. It was hypothesised that increases in fatigue over time would be significantly associated with increases in psychological factors (e.g., anxiety, depression and stress), sleep disturbances, unhelpful cognitions regarding fatigue (e.g., severe consequences perceptions), fear of recurrence (FOR), catastrophising and maladaptive coping strategies (e.g., focussing on symptoms), and decreases in social support, physical

activity and adaptive coping strategies (e.g., accommodating to fatigue and activity avoidance).

5.4.2 Method.

5.4.2.1 Participants and procedure. The participants in this study consisted of a subsample of participants from a larger longitudinal study on CRF (study two in phase 1 of the current study; entire study also described in Chapter 4). In the longitudinal study, a mixed sample of cancer participants was recruited through their oncology care team in a large Dublin hospital and assessed before (T1) and after the completion of treatment (T2) and at a post-treatment follow-up at least three months later (T3). Participants who self-reported that they experienced fatigue at a given timepoint were asked to complete measures on cognitive representations of fatigue and coping with fatigue, in addition to the psychological, behavioural and sleep-related measures previously described in Chapter 4. The subsample on whom the current findings are based (n = 38) consist of those participants who reported fatigue on both post-treatment timepoints (i.e., T2 and T3), thereby enabling examination of changes in post-treatment fatigue, cognitive representations of fatigue and coping. In addition, 20 of these participants had also reported fatigue before treatment; changes in pre- to post-treatment (T1 – T2) fatigue, cognitions and coping could therefore also be examined in this subgroup.

5.4.2.2 Measures. The questionnaires used to obtain demographic (age, gender, marital, educational and employment status) and medical information (cancer type and treatment, time of diagnosis and treatment, comorbid medical conditions) and assess fatigue, psychological factors (anxiety, depression, stress), physical activity, social support, sleep disturbance, cognitive factors (catastrophising, FOR, fear of activity in relation to fatigue [Kinesiophobia], CRF cognitive and emotional representations) and coping strategies have been previously described (see Chapter 4 and section 5.3.2.2 in phase 2 of the current chapter). The internal reliability of a number of subscales was poor. Subscales with alpha values below .60 at a given timepoint, which could not be improved by removing items, were not retained for analysis. Thus, the variables treatment-related causal attributions and activity avoidance coping were excluded. Furthermore, focussing on symptoms coping was excluded for the analyses between T1 and T2 and perceived treatment control was excluded for the analyses between T2 and T3. The internal reliability of all of the other subscales at each of the three timepoints was good ($\alpha > .70$); with the exception of stress ($\alpha = .62$) at T1 and Kinesiophobia ($\alpha = .63$) at T2. Total/mean scores were calculated for these subscales.

5.4.2.3 Analysis. Descriptive statistics were used to describe the demographic and medical characteristics of participants. Change scores on fatigue and on each of the psychological, behavioural and cognitive measures were calculated by subtracting subscale total scores at T2 from scores at T1 and subtracting scores at T3 from scores at T2. Descriptive statistics were used to describe the changes on each subscale over time. As lower scores on the FACT-F indicate higher fatigue, *negative* mean change scores indicate an overall *decrease* in fatigue severity over time, while *positive* mean change scores indicate an overall *increase* in fatigue severity. The same is true for the FOR scale, where higher scores indicate lower FOR. Higher scores on all other scales indicate greater severity (e.g., anxiety or sleep disturbance), greater use (e.g., of coping strategies or physical activity) or stronger beliefs (e.g., in a chronic timeline or causal attributions). Therefore, *negative* mean change scores on all other scales indicate an *increase* in these constructs over time (e.g., improvements anxiety, greater use of a coping strategy or increases in strength of causal attributions), while *positive* scores indicate *decreases* in these constructs over time (e.g., worsening of anxiety, less use of a coping strategy or decreases in the strength of causal attributions). Friedman's ANOVA was used to compare changes in fatigue scores over the three timepoints and Wilcoxon tests were used for *post-hoc* analyses. Pearson product moment correlation coefficients were calculated between change scores of fatigue severity and change scores of psychological factors, activity levels, sleep disturbance, cognitions and coping over time.

5.4.3 Results.

5.4.3.1 Participant characteristics. Table 5.11 describes the participants' demographic and medical characteristics. The mean age was 48.58 years (*SD* = 10.76 years). All but two of the sample were female and the vast majority were either married or living with a long-term partner. Most of the participants had children who were still living at home. Just over half of the sample were employed fulltime and most had at least an upper second level of education (≥12 years). The mean BMI was 26.91 (*SD* = 5.40), with just over half of participants classed as overweight according to the WHO BMI classifications. Half of the sample (n = 19) suffered from an additional medical condition; the mean number of comorbidities was 0.89 (*SD* = 1.16). The most common types of conditions reported were asthma (n = 5), thyroid problems (n = 5), high blood pressure (n = 4), and high cholesterol (n = 4). All other conditions were reported by two participants or less. All but six participants had breast cancer and the majority of the sample was treated with a combination of surgery, chemotherapy and radiation therapy.

Table 5.11 *Demographic characteristics of participants (n = 38)*

Demographic characteristics	n	%	Clinical characteristics	n	%
Gender			Cancer type		
Male	2	5.3%	Breast Cancer	32	84.2%
Female	36	94.7%	Cervical Cancer	3	7.9%
Menopausal status			Colorectal Cancer	3	7.9%
Premenopausal	22	61.1 %	Type of treatment		
Perimenopausal	3	8.3 %	Chemotherapy	100	91.4%
Postmenopausal	11	30.6%	Surgery	35	92.1%
Children			Radiation Therapy	31	81.6%
Has children	31	81.1%	Hormonal treatment	28	87.5%
Has children living at home	28	77.8%	Combination of treatments		
Marital status			Surgery, chemo & RT	28	73.7%
Married/Partnered	25	65.8%	Surgery & chemo	7	18.4%
Single	6	15.8%	Chemo & RT	3	7.9%
Separated/Divorced	5	13.2%	Comorbities		
Widowed	2	5.2%	No comorbidities	19	50%
Employment status			1 comorbidity	9	23.7%
Employed	19	51.4%	2 comorbidity	7	18.4%
Housewife	11	29.7%	≥3 comorbidities	3	7.9%
Retired	2	5.4%	BMI (kg/m^2) class[a]		
Unemployed	3	8.1%	Underweight (< 18.5)	0	0%
Resigned for health	2	5.4%	Normal (18.5 – 24.9)	18	47.4%
Highest educational level			Overweight (25 – 29.9)	12	31.5%
Primary (≤ 8 years)	5	13.5%	Obese (≥30)	8	21.1%
9 - 11 years	8	21.6%			
12 - 14 years	16	43.2%			
Third level education	8	21.6%			

5.4.3.2 Are changes in psychological, behavioural and cognitive factors associated with changes in fatigue? On average participants' fatigue increased between T1 and T2 (*M* change = 5.85, *SD* = 12.42; Min – Max change: -15 to 25) and decreased between T2 and T3 (*M* change = -7.70, *SD* = 12.20; Min – Max change: -35 to 25). The change in fatigue scores was significant ($\chi^2(2) = 7.15$, $p < .05$). *Post-hoc* analyses indicated that fatigue did not change significantly between T1 (Median = 27.00) and T2 (Median = 21.50), $z = -1.72$, $p > .05$, $r = -.27$; however, fatigue was significantly higher at T2 compared to T3 (Median = 33.50), $z = -3.64$, $p < .001$, $r = -.43$.

Increases in fatigue between T1 and T2 were significantly associated with increases in depression ($r = -.63$, n = 20, $p < .01$), stress ($r = -.68$, n = 20, $p < .01$), and sleep disturbances ($r = -.64$, n = 18, $p < .01$). Furthermore, moderately strong nonsignificant correlations ($p > .05$) were observed between increases in fatigue and

changes in several other factors: increases in anxiety (r = -.37, n = 20), catastrophising (r = -.29, n = 20), severe consequence perceptions (r = -.47, n = 16), and sleep-related causal attributions (r = -.31, n = 17) and decreases in coherence perceptions (r = .34, n = 16) and use of the coping strategy maintaining activity (r = .32, n = 15).

Increases in fatigue between T2 and T3 were significantly associated with increases in depression (r = -.34, n = 38, p < .05) and stress (r = -.45, n = 38, p < .01) and decreases in social support (r = .37, n = 38, p < .05) and physical activity (r = .38, n = 33, p < .05). Moderately strong nonsignificant correlations (p > .05) were also observed between increases in fatigue and changes in several other variables: increases in anxiety (r = -.27, n = 38), the coping strategy accommodating to fatigue (r = -.31, n = 31), and psychological- (r = -.30, n = 34), behavioural- (r = -.31, n = 29), and medical/somatic- (r = -.33, n = 38) causal attributions, and decreases in the use of emotional support coping (r = .43, n = 38).

The mean change scores of the remaining variables and their correlations with changes in fatigue can be found in Appendix 12. However, of note, the direction of the correlation with fatigue change scores was different across the two time periods for four variables; increases in fatigue were associated with increases in social support (r = -.23, n = 14), sleep disturbance (r = -.64, n = 18, p <.01), and emotional support coping (r = -.29, n = 9) and decreases in accommodating to fatigue (r = .16, n = 15) between T1 and T2; however, increases in fatigue were associated with decreases in social support (r = .37, n = 31, p < .05), sleep disturbance (r = .18, n = 38), and emotional support coping (r = .43, n = 13) and increases in accommodating to fatigue (r = -.31, n = 31) between T2 and T3.

5.4.4 Discussion. The aim of this study was to carry out a preliminary investigation of whether changes in fatigue over time were associated with changes in the predictors of fatigue, with particular emphasis on changes in cognitive predictors. The findings indicated that changes in depression and stress had the strongest relationships with changes in fatigue. In line with expectations, participants whose depressive symptoms and stress increased were more likely to also experience increases in fatigue severity over both time periods. The relationship between change scores in anxiety and catastrophising and change scores in fatigue demonstrated the same pattern; however, these associations were not significant. These findings support previous research on CRF that has reported consistent relationships between psychological factors and fatigue (Brown & Kroenke, 2009). However, as parallel changes were examined, it was not possible to determine the direction of causation in this study.

There was no evidence from the current results that changes in fatigue were related to changes in fear of activity, FOR, timeline perceptions, or cancer-related causal attributions. However, some cognitive dimensions had moderately large nonsignificant correlations with changes in fatigue. Increases in fatigue over the treatment period (T1 to T2) were associated with increases in severe consequence perceptions and sleep-related causal attributions and decreases in coherence perceptions, while increases in fatigue over the post-treatment period (T2 to T3) were associated with increases in psychological, medical and behavioural attributions. A weaker, nonsignificant association was also observed between changes in fatigue and changes in personal control perceptions over the post-treatment period. Further research with larger samples is necessary in order to investigate these factors further; the findings presented offer some preliminary indications that some cognitive factors may play a role. However, it was clear from the results that changes in psychological factors had much stronger links with changes in fatigue.

In addition to psychological variables, significant correlations were also observed with sleep and physical activity, whose role varied over the two time periods. Physical activity was not correlated with changes in fatigue across the treatment time period; however, increases in physical activity across the post-treatment time period were significantly associated with decreases in fatigue. Interestingly, the opposite pattern was observed with the coping strategy maintaining activity levels. Although changes in this variable were not significantly associated with changes in fatigue, a moderately strong correlation was observed between increases in maintaining activity and decreases in fatigue over the treatment period, while there was no observed link in the post-treatment period. These findings are in line with the idea that increasing physical activity after cancer treatment has a positive effect on fatigue and also suggest that maintaining usual activities, despite fatigue, can be adaptive during the treatment period; thus, the type of activity that is beneficial may vary over the cancer trajectory.

Similarly, while increases in sleep disturbance across the treatment period were significantly correlated with increases in fatigue across the treatment period, no significant associations were observed in the post-treatment time-frame. Such findings suggest that the factors that contribute to CRF may change over time. Furthermore, the specific role of some contributing factors may be qualitatively different at different timepoints. For example, although the correlation was not significant, the direction of the association between fatigue and sleep in the post-treatment period contrasted the direction

of this relationship across the treatment period. Such a shift in the direction of the association was also observed with social support and the coping strategies accommodating to fatigue and seeking emotional support. Specifically, increases in fatigue across the treatment period were associated with increases in perceived social support and seeking emotional support and decreases in accommodating to fatigue. Conversely, increases in fatigue across the post-treatment period were associated with decreases in perceived social support and seeking emotional support and increases in accommodating to fatigue. Such findings, though not statistically significant, suggest that accommodating to fatigue by pacing activities and trying not to overdo things may an effective strategy during treatment; however, increasing use of this strategy after treatment may be harmful. Similarly, patients who reported increases in social support and seeking emotional support actually experienced worsening fatigue over the treatment period, while increases in social support and seeking emotional support after treatment were associated with improvements in fatigue. While this result is in line with previous findings on the importance of social support for patients who experience continued fatigue after treatment (Servaes, Verhagen, et al., 2002c), it is likely that the observed reversed relationship during treatment was not causal but reflected a greater need for support among those with more severe levels of fatigue. Nevertheless, such shifts in the direction of association across different time periods within the cancer trajectory are interesting, and highlight the complexity of the relationships between fatigue and the proposed contributing factors.

5.4.4.1 Limitations. Certain limitations of the current study should be noted. The analysis was based on a very small sample of patients, most of whom were women and had been treated for breast cancer. Thus it is not clear whether the findings can be generalised to a more diverse population of cancer survivors with fatigue. In addition, because change scores across time were calculated for this analysis and bivariate correlations between change scores were calculated, missing data on a subscale at any one timepoint had a substantial impact on the number of observations that were included in each analysis. This meant that, in addition to the small sample size at the outset, the number of participants on which a correlation was based was often even lower, calling the reliability of the results into question. Nevertheless, despite the small number of participants, moderately strong and theoretically sound relationships still emerged.

Although scales with good psychometric properties were used to assess each of the variables, the internal reliability of some scales was poor at one or more timepoints.

Subscales that were not reliable were not retained for analysis as the measurement problems would have made it impossible to accurately interpret the findings. No scale had low internal reliability across all measurement occasions, suggesting that some measures may have been inappropriate or confusing for participants at certain timepoints. For example, although the focussing on symptoms scale had very high Cronbach's alpha values at T2 and T3 ($\alpha \geq .78$), the alpha value for T1 was poor ($\alpha = .40$). The concept of focussing on symptoms (i.e., spending a lot of time thinking about fatigue, believing that fatigue is the most significant thing in one's life, and believing that one's life is ruled by fatigue) may not have been relevant or conceptually sound directly before patients were due to start chemotherapy for cancer. Similar reasoning could explain the somewhat low observed alpha value of the stress scale at T1 and underscores the importance of using scales that have been validated for use in the population of interest. The PSS is a scale of global stress and, although the 10-item version has been used in previous studies on cancer patients undergoing treatment (Golden-Kreutz & Andersen, 2004; Golden-Kreutz et al., 2005) and the shorter 4-item version (used in the current study) has been used with cancer survivors (Alfano et al., 2011), the short form may not be appropriate for assessing stress in cancer patients prior to treatment. In the current study, stress was retained for the analyses because the alpha value was not far below .70; however, the findings relating to this subscale should be interpreted with caution.

The use of difference scores is also not without controversy; methodological problems with difference scores have been widely discussed and have focussed on their frequently demonstrated poor reliability (Gupta, Srivastava, & Sharma, 1988; Lord, 1956). However, many authors have argued in favour of the use of difference scores (Rogosa & Willett, 1983; Zimmerman & Williams, 1982). For example, Rogosa and Willtett (1983) note that difference scores estimate true change and when individual differences in true changes are appreciable, differences scores will show good reliability; however, difference scores cannot detect individual differences in change scores that do not exist. Thus low reliability does not necessarily indicate poor measurement, and difference scores can be accurate and useful measures of change even when reliability is low (Rogosa, Brandt, & Zimowski, 1982). The current study undertook an initial exploratory analysis in order to investigate whether there was any evidence that changes in beliefs were associated with changes in fatigue; however, further research with more sophisticated analytic methods (e.g., growth curve modelling) is warranted. Future studies should also investigate temporal dimensions of these relationships; for example,

whether changes in a predictor over one time period can predict subsequent changes in fatigue. In the current study, the association between change scores in fatigue and the hypothesised contributing factors were assessed over the same timeframes; therefore, the direction of effects could not be determined.

5.5 General Chapter Discussion

The aims of this study were to (1) evaluate whether there is any evidence that fatigued cancer survivors' cognitive representations of their fatigue contribute to their symptom outcomes and (2) examine through what mechanisms cognitive representations might play a role in fatigue. The first research question was addressed in each of the three phases of this chapter. The strong associations between fatigue and many cognitive representations of fatigue in phase 1 and the relatively large contribution of the composite negative representation construct to a multivariate model of fatigue in phase 2, support the idea that patients' beliefs can contribute to the fatigue experienced by patients after cancer treatment. The findings from phase 3 were less compelling; nevertheless, there was some indication that changes in beliefs are linked to changes in fatigue in theoretically-consistent ways, although changes in psychological factors had much stronger (and significant) associations with changes in fatigue. While the findings presented in this chapter are based on correlational data, and therefore causation cannot be inferred, they are in line with established models that posit that patients' thinking patterns and beliefs can impact on their symptom outcomes. The findings suggest that the CSM provides a reasoned approach to more closely examine the types of beliefs that individuals form regarding CRF and to identify specific cognitions that may be particularly significant. The results indicated that severe consequence perceptions and low coherence perceptions had the strongest relationships with fatigue severity. Integrating these specific cognitions into the cognitive-behavioural framework of CRF may therefore add to this explanatory model.

An alternative explanation for the link between cognitions and outcomes is that patients with more severe fatigue form more negative representations of their condition. However, this is not supported by findings from previous studies, which reported that objective clinical measures of disease severity and illness are poorly associated with illness outcomes and illness representations (Carlisle et al., 2005). Such findings thus suggest that representations do not merely reflect an individual's current medical condition and support the idea that maladaptive perceptions can contribute to greater disability.

The second research question was addressed in both phase 1 and phase 2 of this chapter and explored the mechanisms through which cognitions might influence post-treatment fatigue in cancer survivors. Beliefs about fatigue were related to many of the psychological and behavioural factors that have been linked to fatigue, such as symptom focussing, catastrophising, emotional distress in relation to fatigue, general perceived stress, anxiety, depression, and self-reported physical activity, supporting dynamic interrelationships between contributing factors and the idea that patients' beliefs can help to sustain the factors related to post-treatment fatigue. Specific mediational pathways between cognitions and fatigue, through coping and psychological factors, were also supported. In particular, there was evidence that psychological factors (emotional distress and depression) and cognitive processes (focussing on symptoms and catastrophising) partially mediated the relationship between participants' beliefs and fatigue severity. These findings are in line with the CSM and suggest that interrelationships between peoples' beliefs, thinking patterns and psychological responses play a role in persistent CRF. However, there was no indication that active coping strategies (other than perhaps seeking information) or behaviours mediated relationships between cognitions and symptom severity, or indeed that such behaviours were predictive of fatigue.

Although the CSM provided a useful approach to dissecting the various illness beliefs that may drive outcomes, use of this conceptual approach did not substantially add to the more general cognitive-behavioural explanatory model of CRF. Overall the results supported the central role of negative thinking patterns in the perpetuation of chronic illness; however, a pattern of negative symptom perceptions and unhelpful cognitive processes already forms an integral part of cognitive-behavioural models. More detailed examination of the role of severe consequence beliefs and low coherence perceptions specifically may provide further insight into the cognitive factors that contribute to negative cognitive processes such as focussing on symptoms and catastrophising. However, the mechanisms through which specific illness representations might impact on fatigue were not explored in the current study.

5.5.1 Limitations. The results presented in this chapter are based on three heterogeneous subsamples that are unlikely to be representative of cancer survivors with CRF. The specific limitations associated with these samples have been previously outlined; however, it is important to note again that, because of these sampling issues, the results should be interpreted with caution.

All participants included in this chapter self-reported that they experienced "cancer-related fatigue". However, participants with medical conditions that may have contributed to their fatigue were not excluded from the first and second study subsamples; thus, it is possible that the fatigue these participants experienced was not related to their cancer and/or their cancer treatment. Although the diagnostic criteria for CRF necessitate the exclusion of other comorbid psychiatric or somatic conditions associated with fatigue, the assumption that fatigue is secondary to psychopathology has been previously questioned, as the direction of causality between such factors and fatigue in cancer patients is not clear (Young & White, 2006). Although somatic conditions like heart disease and thyroid conditions may contribute to fatigue in cancer survivors, it is unreasonable to assume that the presence of such comorbidities means that the fatigue experienced is not cancer-related. As it was not possible to definitively establish whether the participants' fatigue was as a consequence of cancer/cancer therapy, participants with fatigue-related comorbid conditions were not excluded. While this was a limitation of the study, such difficulties are encountered in clinical practise, even when it is possible to obtain detailed medical and psychiatric histories from patients. The strength and robustness of the association between fatigue and the psychological and cognitive variables included in this research suggests that regardless of whether or not patients have other comorbidities contributing to their post-cancer fatigue, targeting such factors could still be of benefit to patients.

A final limitation that cuts across all phases of this study was that a considerable number of different associations among fatigue and predictor variables were investigated. Although a more stringent *p*-value of .01 was used, the number of correlations carried out was still large; therefore, there was a greater chance of committing a Type I error. Nevertheless, a hypothesis-led approach to correlational analysis was taken; all of the relationships investigated were based on the previous literature and established models that specified plausible associations between the variables of interest. Although the small sample size and the number of analyses carried out must be acknowledged as a limitation of the study, the findings make sense in light of the study's theoretical underpinnings.

5.5.2 Strengths and implications. A number of different approaches were used in this study to evaluate the role of cognitions in the fatigue experienced by cancer survivors. The associations between different types of cognitions and fatigue were explored, the role of cognitive representations in the context of more established predictors was evaluated, and evidence that changes in cognitions are actually linked to

changes in fatigue was assessed. In addition, potential mechanisms of influence were tested based on sound theoretical principles, using sophisticated analytic techniques that went beyond Baron and Kenny's causal steps regression approach (Hayes, 2009). Furthermore, self-management coping strategies specific to CRF were assessed to explore the mechanisms through which cognitions might influence fatigue. Previous research on the CSM has often relied on general measures of coping style rather than assessment of actual coping behaviours that are specific to the condition in question (Hagger & Orbell, 2003). Weak associations with coping have been attributed to the use of such generic measures; thus, the assessment of coping strategies specific to CRF was a strength of the current study.

The findings have both theoretical and clinical implications. The association between fatigue, cognitions and cognitive processes, such catastrophising and focussing on symptoms, support the application of a cognitive-behavioural model to understand the fatigue experienced by cancer survivors. Furthermore, although the findings from phase 3 of this chapter should be interpreted with caution, there was some indication that different contributing factors can play qualitatively different roles at various points in the cancer trajectory. This is in line with the cognitive-behavioural approach that makes a distinction between factors that precipitate the initial experience of fatigue and those help to sustain fatigue over time (Andrykowski et al., 2010). For example, accommodating to fatigue in the short term may be adaptive while undergoing cancer treatment; however, excessive restructuring of one's lifestyle and activities around fatigue after treatment may have a detrimental effect. Further longitudinal research is necessary to investigate the dynamic relationships among contributing factors over time.

The strength of the relationships between beliefs and fatigue supports the cognitive-behavioural approach to understanding this symptom and suggests that assessing and monitoring patients' own representations of their fatigue could be of clinical value. Furthermore, the observed interrelationships between many of the factors associated with fatigue suggest that persistent fatigue may be linked to a specific pattern of responses to this symptom. The findings indicated that problem-focussed behaviours and actions, such as physical activity, maintaining activity and accommodating to fatigue, were inconsistently associated with fatigue severity; thus, the actions that participants performed were not key predictors of fatigue. Instead, the strongest associations were between what participants thought about their fatigue, the extent to which they thought about their fatigue, and their psychological responses. This is in line with the idea that

unhelpful cognitions about fatigue and excessive rumination help to maintain fatigue, and suggests that some patients may define themselves in terms of their fatigue and adopt a sick role that is in line this. Thus, a particular type of illness identity may be associated with persistent fatigue. Further research is necessary to explore whether early interventions that are explicitly built around patients' conceptualisation of CRF are effective in preventing the formation of maladaptive beliefs and decreasing the severity and duration of fatigue post-treatment.

Chapter 6: A Longitudinal Study of Fatigue in Patients Treated with Chemotherapy: Explaining Inter- and Intraindividual Differences in Fatigue Over Time.

"Even before I found I had cancer I was tired. It was always home and work and life. But now I realise that cancer tiredness is much different, so all I can do is take one day at a time - and enjoy life as much as I can!" – Jackie

6.1 Introduction

Fatigue is a common side-effect of chemotherapy that can continue to negatively impact on patients' quality of life post-treatment (Hofman et al., 2007). However, fatigue affects patients to varying degrees and it is not clear why some patients experience more severe or persistent fatigue in response to cancer and/or cancer treatment than others. Although many studies have explored the contributing factors to fatigue in cancer patients at different stages of the treatment trajectory (for systematic reviews see Oh & Seo, 2011; Prue et al., 2006), insufficient longitudinal research has been carried out. The aim of this study was to investigate changes in fatigue over time in patients treated with chemotherapy and to assess intra- and interindividual contributing factors to variations in fatigue from before treatment to follow-up several months post-treatment. Based on the previous literature and the findings presented in the preceding chapters of this thesis, the role of three potential types of contributing factors was investigated: psychological wellbeing, sleep-disturbance and physical activity.

Psychological, sleep- and activity-related factors are key components of many theoretical models of CRF (e.g., the Edmonton fatigue framework, Olson et al., 2008; the integrated fatigue model, Piper et al., 1987; the psychobiological-entropy model, Winningham et al., 1994) and interventions aimed at these factors are the main nonpharmacological interventions recommended by the NCCN (2012a) for CRF in patients both on active treatment and post-treatment. Although a plethora of research supports the role of such factors in CRF over the impact of demographic or medical predictors, inconsistent findings have been reported and most of the research to date has been cross-sectional, limiting the conclusions that can be drawn (Prue et al., 2006). For example, although depression has arguably received the greatest attention and support in the empirical literature, it is still not clear whether depression is a cause or a consequence of fatigue, whether depression and fatigue share a common cause, or whether the strong association between depression and fatigue is merely due to an overlap in symptoms

(Brown & Kroenke, 2009; Oh & Seo, 2011). While studies on symptom clusters in cancer patients support the independence of depression and fatigue (Donovan & Jacobsen, 2007), findings from the few longitudinal studies carried out to date have been inconsistent. Some studies have found that changes in fatigue are significantly related to changes in depression (Stone et al., 2001; Tchekmedyian et al., 2003) while others have reported that depression and fatigue do not follow the same patterns over time (Geinitz et al., 2001; Schumacher et al., 2002; Visser & Smets, 1998). However, causal associations cannot be established by examining changes over only two points in time and, although opposing trajectories do not support a causal relationship, observing different patterns in depression and fatigue over time does not rule out the existence of such a relationship. Longitudinal designs and statistical techniques that are capable of exploring whether depression can account for differences in fatigue between individuals and differences in fatigue within individuals over time are necessary to better understand the nature of this relationship.

Only one study to date has examined bidirectional causal relationships between depression and CRF; Brown et al. (2012) used structural equation modelling to investigate whether initial levels of depression would predict longitudinal changes in fatigue. Although depression and fatigue were strongly correlated, the study found no evidence of a directional relationship. However, the findings were based on data from only two timepoints, 3 months apart, and included patients at various stages of the cancer trajectory (e.g., newly-diagnosed, disease-free and recurrent disease) all of whom experienced at least moderate levels of pain and/or depression. Thus, the findings are not generalisable to patients who do not suffer from clinically significant levels of these symptoms. Furthermore, as some patients were newly diagnosed and others had a cancer recurrence, it is likely that they were undergoing cancer treatment between the assessment timepoints; however, the effects of cancer treatments on fatigue and the relationship between fatigue and depression were not investigated. It is possible that the role of depression qualitatively or quantitatively changes over the course treatment trajectory. For example, cancer and cancer-treatments may trigger fatigue and cause initial increases in fatigue, while depression may play a greater role after the immediate effects of treatment have passed. This is in line with a cognitive-behavioural approach to CRF and research that supports a distinction between precipitating and perpetuating factors in the aetiology of persistent fatigue after cancer (Gielissen, Verhagen, et al., 2007; Gielissen et al., 2006; Goedendorp, Gielissen, Verhagen, & Bleijenberg, 2012).

Additional longitudinal research is thus necessary to understand the nature of the relationship between fatigue and depression.

The same principles as those discussed in relation to depression can be applied to the relationships between fatigue and other psychological factors, such as anxiety and stress as well as sleep-disturbance and physical activity, which have received much less attention than depression in the literature. Anxiety has often been investigated alongside depression and the same mixed findings have emerged (Geinitz et al., 2001; Stone, Hardy, et al., 2000; Tchekmedyian et al., 2003); however, as the role of anxiety was not supported in the results presented in the previous chapters of this thesis, it was not included as a predictor in the current study. Nevertheless, the roles of stress, sleep-disruption and physical activity were investigated. Longitudinal research on the relationship between these variables and fatigue almost exclusively consists of intervention studies; research has evaluated the effectiveness of interventions aimed at distress (Goedendorp et al., 2009), sleep (Dirksen & Epstein, 2008; Savard, Simard, Ivers, & Morin, 2005) and physical activity (Cramp & Daniel, 2008) for fatigue in cancer patients. Longitudinal research that explores the natural covariation between these factors and fatigue can thus add to existing knowledge about the aetiology of CRF.

The current study investigated how ratings of fatigue changed from before chemotherapy to approximately nine months after the completion of cancer treatment, and examined whether proposed psychological, sleep and behavioural contributing factors could predict initial levels of fatigue and the characteristics of the trajectories of fatigue over time. In addition, changes in quality of life (QOL) and how these related to changes in fatigue were also explored. Individual growth curve modelling was used for this purpose.

6.1.1 Research questions and hypotheses. The current study sought to address the following research questions and hypotheses:

1. Is there individual variation in fatigue?
    - Fatigue was expected to vary both between and within participants.
2. Does the level of fatigue change over the occasions of measurement and, if so, what is the shape of the change in fatigue over time?
    - Based on the previous literature fatigue was expected to increase after chemotherapy but then gradually decline after treatment, thus a nonlinear fatigue trajectory was predicted. Differences in the rate of change across individuals were expected.

3. Can medical and demographic differences between individuals explain (a) interdifferences in fatigue and (b) differences in the rate of change in fatigue over time?
    - Based on the findings in Chapter 4, differences between participants in levels of pain and number of comorbidities were expected to contribute to interdifferences in fatigue.
    - Differences in treatment-related factors were expected to influence the rate of change in fatigue after treatment; specifically, receiving radiation therapy (RT) in addition to chemotherapy and receiving ongoing treatment with Herceptin after the completion of chemotherapy were expected to slow or delay the rate of recovery in fatigue after treatment.
4. Can differences in levels of depression, stress, sleep disturbance, and physical activity explain inter- and intra-individual differences in fatigue and differences in the rate of change in fatigue across time?
    - Differences in the levels of these predictors were expected to contribute to between-individual variation in fatigue, and differences in these predictors over the measurement occasions were expected to help explain within-individual variation in fatigue over time.
5. Does QOL change over the measurement occasions and can differences in fatigue explain differences in QOL between individuals and within individuals over time?
    - Fatigue was expected to be a significant predictor of between-individual differences in QOL and changes in QOL within-individuals over the treatment trajectory.

6.2 Method

6.2.1 Design. A prospective longitudinal study was conducted with participants recruited from May 2010 until September 2012 through two outpatient oncology review clinics in a large urban teaching hospital in Dublin. Fatigue, QOL and the hypothesised, psychological, sleep- and physical activity-related predictors were examined in cancer patients through repeated assessments, once before chemotherapy and four times after treatment with approximately three months between each follow-up assessment.

6.2.2 Participants.

6.2.2.1 Ethics. Ethical approval for the study was obtained from the institutional research ethics committees in both the hospital and the university (see Appendix 2) in which the research was carried out. All participants provided written informed consent prior to study inclusion, and all procedures followed were in accordance with the Helsinki Declaration.

6.2.2.2 Participant eligibility and recruitment. The eligibility criteria for this study and the recruitment procedure have been previously described in Chapter 4. Briefly, patients attending oncology clinics to discuss potential adjuvant or neoadjuvant treatment options for recently diagnosed breast, gastrointestinal, genitourinary or gynaecological cancer or lymphoma were approached. Consecutive convenience sampling was used. Eligible patients had a first-time diagnosis of cancer and were referred for chemotherapy with curative intent.

6.2.3 Procedure.

6.2.3.1 Assessment procedures. At the first assessment timepoint, participants met with the researcher in the hospital during one of their scheduled hospital appointments. They were given the first set of questionnaires to complete before their first session of chemotherapy. The questionnaires could be completed at home and stamped addressed envelopes were provided for returning them. For subsequent assessments, participants were contacted by telephone at the appropriate follow-up time and, if they were willing to continue with the study, questionnaires were then posted to them at home. Participants were contacted by telephone if they did not return a questionnaire after two weeks. Another reminder call was made if participants still did not return the questionnaire after a further two weeks had passed.

Table 6.1 *Descriptive statistics for the number of days post-treatment at which questionnaires were completed for each assessment point*

Timepoint:	T1	T2	T2b	T3	T4	T5
Timeframe:	After surgery/ before chemo	0-6 wks 0-42 days	0-6 wks 0-42 days	3-5 months 90-150 days	6-8 months 180 - 240 days	9 months + 270 days +
M (*SD*)	41.83 (19.0)	16.20 (9.3)	25.28 (10.2)	115.30 (17.1)	205.24 (16.2)	294.04 (21.5)

6.2.3.2 Timing of assessments. Each participant was assessed five times, once before treatment (T1) and four times after treatment (T2-T5). The analysis in this chapter focuses on the time since treatment pathways, and thus each assessment point is defined

in terms of where it falls on the participants' treatment trajectory. However, as participants followed different treatment pathways, the timing of these assessments and how they were spaced varied to some extent. Although each participant completed at the most five assessments, there were actually six assessment timepoints (see Table 6.1). This was the case because, although all participants completed an assessment before (T1) and after chemotherapy (T2), some subsequently also had RT, or surgery and RT, after chemotherapy and these participants completed their third assessment after they had finished these additional treatments (T2b). Thus, the timepoint T2b was only relevant for a subsample of participants who had two post-treatment assessment points (the first post-chemotherapy and the second post-RT). All participants were again included in T3 and T4; however, as participants completed at the most five assessments, T5 was only completed by those who had not already completed five questionnaires previously; Thus, one subgroup completed the five assessments at T1, T2, T3, T4 and T5 and the other at T1, T2, T2b, T3 and T4. In line with previous research on the predictors of fatigue in breast cancer survivors (e.g., Alexander, Minton, Andrews, et al., 2009; Bower, 2007; Cavalli Kluthcovsky et al., 2011), ongoing use of hormonal therapy at the follow-up times was permitted. Previous studies found no relationship between ongoing use of hormonal therapy and fatigue (e.g., Donovan et al., 2007; Goedendorp et al., 2011). A more detailed description of the participants' treatment trajectories and how the five study timepoints fitted into these trajectories is included in Appendix 13.

6.2.4 Measures. An author-constructed questionnaire was used at T1 to collect the following sociodemographic information: age, gender, menopausal status, marital status, number of children and number of children living at home, employment status, and educational level. In addition, one item was included as a brief measure of pain: "How would you rate your level of pain on a scale of 0 to 10 over the past 7 days?" (0 – "*No pain*", 10 – "*Worst pain you can imagine*"). Medical data including type of cancer, disease stage, type of treatment (e.g., surgery, radiation therapy, chemotherapy, hormone treatment) and treatment regimen, time since diagnosis and time of treatments, comorbid medical conditions, and height and weight were collected from hospital medical charts.

Participants completed the questionnaires listed in Table 6.2 at each of the study assessment points. In cases where individual items from standardised scales were missing, the average of the completed items was used to calculate the total score for a scale, provided more than half of the items were completed. All of these measures have been previously described in Chapter 4. The internal reliability of each subscale was

good (α = .72 to .94). As the distribution of physical activity, measured using MET-mins/week, was heavily skewed, the Log_{10} of MET-mins/week was used for all analyses reported.

Table 6.2 *Overview of the questionnaires used at each study timepoint*

Dimension	Questionnaire	No. of Items	Min-Max (score calculation)
Fatigue	Functional Assessment of Cancer Therapy - Fatigue scale (FACT-F; Yellen et al., 1997)	13	0-52 (sum of 13)
Quality of Life (QOL)	Linear Analogue Self Assessments (LASAs) on QOL (Locke et al., 2007)	5	0-5 (mean of 5)
Pain	NCCN (2009) pain screening item	1	0-10 (one item)
Depression	Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983)	6[1]	0-18 (sum of 6)
Stress	Perceived Stress Scale (PSS; Cohen et al., 1983)	4	0-16 (sum of 4)
Physical activity	Short International Physical Activity Questionnaire (IPAQ short form; Craig et al., 2003)	7	n/a (MET-mins/wk)
Sleep disturbance	3 author-constructed sleep disturbance questions and 4 items on typical bedtime, wake time, sleep latency & sleep duration	7 4	1-7 (mean of 3) & 4 items (mins/hours)

[1]Item 8 of the HADS scale ("I feel as if I am slowed down") was excluded from the composite depression score in all of the analyses presented in this chapter because of the similarity between this item and fatigue.

6.2.5 Analysis. Descriptive statistics and frequency distributions were generated to describe the participants' demographic and medical characteristics and the mean levels of fatigue, QOL, depression, stress, sleep disturbance and physical activity at the different measurement occasions. Multilevel modelling (MLM; growth curve modelling) was used to investigate changes in fatigue over time. This method addresses both within-person (intraindividual) and between-person (interindividual) variability simultaneously by analysing change on two levels; the level 1 model describes how each person changes over time, while the level 2 model captures whether the rate of change varies across individuals in a systematic way (Singer & Willett, 2003). Level 2 outcomes can be modelled as a function of characteristics that differ between individuals (e.g., treatments received). Combining Level 1 with Level 2 results in a mixed model with fixed and random effects and reflects how interindividual differences influence the final outcome of interest, while also taking intraindividual contributions to change into account (Shek & Ma, 2011).

MLM was chosen for the longitudinal analyses of the data because it does not require a balanced design; thus, the number and the spacing of assessments could vary across respondents and missing data for assessment points were permissible (Shek & Ma, 2011). Although an effort was made to assess each participant at corresponding timepoints, the actual number and timing of assessments were not the same across respondents: the treatment pathways and the length of individual treatments varied between participants, scheduled treatments were often deferred on medical grounds or because of scheduling conflicts, and participants did not always return questionnaires or complete and return questionnaires promptly. The second advantage of MLM is that it allows the study of both intra- and interindividual differences in growth parameters, thereby enabling examination of the patterns of change and the effects at both individual and group levels. Furthermore, the effects of predictors at higher levels (e.g., treatment type) and predictors of individual growth can be flexibly added to the model to examine relationships between predictors and changes in the outcome variable over time. Such predictors can be discrete or continuous as well as time variant (e.g., depressive symptoms) or time-invariant (e.g., gender).

The data were analysed through PASW 18 statistical software using the mixed model procedure. The maximum likelihood (ML) estimation method was used, as both fixed and random effects were explored (Singer & Willett, 2003). The repeated measures of the dependent variable (i.e., fatigue) were conceptualised as being nested within individuals. This method modelled individual change over time, determined the shape of growth curves, explored systematic differences in change related to hypothesised explanatory variables, and examined the effects of covariates on differences in the initial status and the rate of growth. An unstructured covariance matrix was specified at Level 2, which places no constraint on how each level of the random effect would relate to another one and estimates all possible variances and covariances (Singer & Willett, 2003). To determine the best model, -2 log likelihood (-2LL; i.e., likelihood ratio test/deviance statistic), Akaike Information Criterion (AIC), and Bayesian Information Criterion (BIC) were used; smaller values on these goodness of fit indices indicate better model fit for the data (Shek & Ma, 2011).

The analysis proceeded as follows. To address the first research question, the unconditional model with no predictor variables was examined (no change model) to assess the amount of variation that existed in intra- and inter-individual levels. The outcome variable (fatigue) was centered around the grand mean. Next, the

intraindividual variability in fatigue over time was examined using unconditional growth models (i.e., without the inclusion of predictors). In this study, time refers to the occasion of assessment (T1 – T5) that describes where a participant is in terms of their treatment trajectory, rather than an absolute time since diagnosis or treatment. The pretreatment assessment point (T1) was set at 0 and T2/T2a, T2b, T3, T4 and T5 were set at 1, 2, 3, 4 and 5 respectively. Three models, that represented different trajectories of fatigue over time were examined: linear time effect, which explored whether participants' fatigue levels changed at a constant rate; a quadratic effect, which explored whether there was curvature in the trajectory of fatigue (i.e., acceleration or deceleration over time with one stationary point); and a cubic effect, which explored whether fatigue changed at a nonlinear growth rate with two stationary points. These analyses addressed the second research question by identifying the change parameters that best described individual changes in fatigue over time. The proportion of intra-individual variability in fatigue accounted for by time was also examined.

To address the third research question, interindividual differences in initial fatigue levels and rates of change in fatigue were examined by adding potential demographic medical and treatment-related predictors as fixed effects and examining their interactions with time. To address the fourth research question, interindividual differences in initial fatigue and intraindividual differences in fatigue across time were examined by adding the time-variant hypothesised psychosocial predictors (i.e., depression, stress, sleep disturbance and physical activity) to the model at Level 1. The model was adjusted for the presence of covariates that might affect individuals' fatigue by including the significant ($p < .05$) demographic and medical predictors from the previous step. Finally, to address the fifth research question the same steps outlined above were used to examine inter- and intraindividual variability in QOL over the measurement occasions. The proportion of variability in QOL between and within participants that could be explained by fatigue was assessed.

6.3 Results

6.3.1 Study response rate. A breakdown of the drop-out rate and flow of participants through each study timepoint is included in *Figure 6.1*. In total, 136 patients were approached and 120 (88.23%) consented to participate in the study. Of the 16 patients who did not consent, four were excluded because they could not be contacted again before their treatment was scheduled to begin and 12 patients declined to participate. Reasons given for not participating were feeling overwhelmed with the

diagnosis and the required treatment (n = 5), having too much to think about already (n = 4), participating in a clinical trial already and therefore not wanting to do another research study (n = 2), and having no interest in research (n = 1).

Eight participants, who had consented to take part in the study, changed their minds about participation before T1. Reasons given for not continuing with the study were feeling too anxious about the treatments (n = 4) and having too much to think about at the time (n = 4). A further 10 participants were excluded because it emerged that their disease was more advanced than originally diagnosed and/or they showed signs of disease progression after chemotherapy and their subsequent treatment was no longer considered curative. These 18 patients were excluded and are not represented in the description of participant characteristics in the next section. Therefore, there were 102 participants in the final sample.

Drop out from the study after T1 was low (n = 9; 8.82%); however, not all participants returned questionnaires for every timepoint. In addition, as occasion of measurement (e.g., T2 = after chemotherapy) was used to define time in the current study, questionnaires that were completed outside the specified timeframe for a given assessment point were excluded to minimise the amount of variation in time since treatment in this subsample, so that reasonable comparisons could be made across participants at each timepoint. Five participants dropped out at T2; three of these could not be contacted to arrange follow-up assessments and two declined to continue with the study. Reasons for not continuing were feeling overwhelmed or not wanting to fill in any more questionnaires. Of the 74 participants who received further treatment after chemotherapy, T2b questionnaires were only available for 46 participants; five questionnaires were not returned and 17 were completed outside the specified timeframe, one of which was completed within the T3 timeframe and was therefore included at this later timepoint instead (T3 for this participant was used for T4 and T4 was used as T5). A further two participants dropped out at T2b; one could not be contacted to arrange further follow-up assessments and the other declined to continue with the study due to time pressure. At T3, 79 questionnaires were completed and returned within the specified timeframe; 10 questionnaires were excluded, five participants did not return questionnaires, and one participant dropped out of the study due to time pressure.

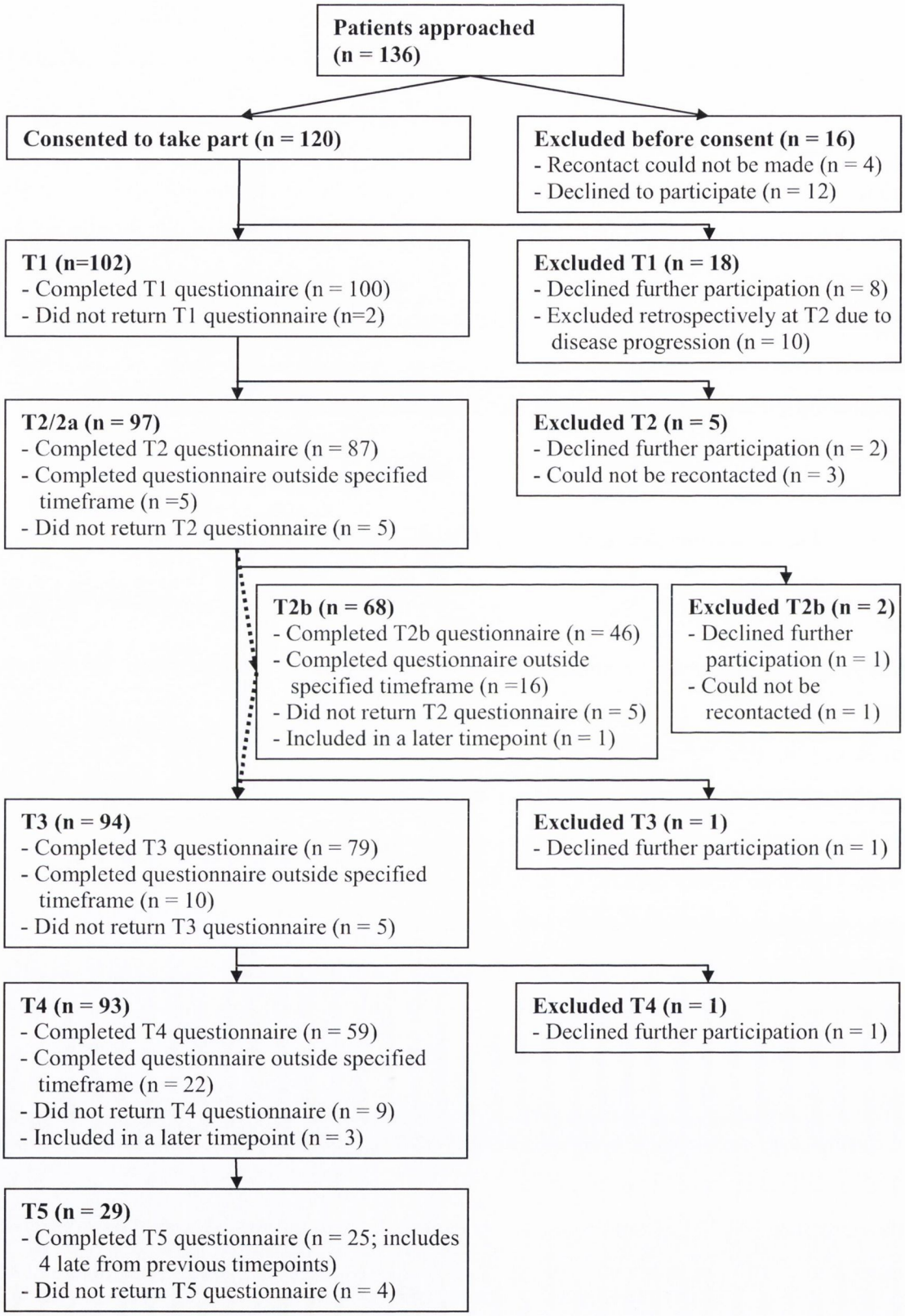

Figure 6.1. Overview of drop-out rate and flow of participants through each study timepoint.

At T4, nine participants did not return questionnaires and one participant dropped out because she was feeling overwhelmed; 25 participants returned questionnaires outside the specified timeframe and were therefore excluded for this timepoint, three of these questionnaires were completed within the T5 timeframe were therefore included at this timepoint instead. Finally, 21 of the 28 participants who did not have additional treatments after chemotherapy completed and returned T5 questionnaires; in addition, four T4 questionnaires that had been completed late and fell into the T5 timeframe were also included. Four participants did not return questionnaires for this final timepoint.

Of the final sample of 102 participants, complete data sets (questionnaires from five study timepoints) were available for 73 participants; 14 participants completed questionnaires at four timepoints, three at three timepoints, seven at two timepoints and five at one timepoint only. Thus a total of 449 questionnaires were collected; however, 53 of these questionnaires were excluded because they were returned outside the specified timeframe for an assessment point. Therefore, data from 396 questionnaires (out of a potential 510 for 102 participants across five timepoints) were analysed, giving an overall questionnaire response rate of 77.64%.

6.3.2 Participant characteristics. The demographic and medical characteristics of the participants are displayed in Table 6.3. Participants' ages at diagnosis ranged from 19 to 77 with a mean age of 49.45 years (*SD* = 10.92). The vast majority of participants were female and either married or living with a long term partner. All but three participants were white. The majority of participants had children; of these, 81% had children living at home. Most participants were employed full- (n = 51) or part-time (n = 2) and had at least an upper second level of education (≥12 years). More than half of the sample was overweight according to the WHO BMI classification; the mean BMI was 27.19 (*SD* = 5.37). Less than half of the sample had another health problem at the time of diagnosis; the mean number of comorbidities was 0.85 (*SD* = 1.10). The most common comorbidities were hypertension (n = 15), cholesterolemia (n = 12), thyroid problems (n = 12), asthma (n = 8), osteoarthritis (n = 6) and depression (n = 6). The vast majority of participants had breast cancer and most participants had lymph nodes positive for cancer at the time of diagnosis (*M* = 3.26, *SD* = 4.82). The majority of patients were treated with radiation and surgery as well as chemotherapy. Appendix 14 contains a more detailed breakdown of participants' treatments regimens and their comorbidities.

Table 6.3 *Participants' demographic and clinical characteristics (n = 102)*

Demographic characteristics	n	%	Clinical characteristics	n	%
Gender			Cancer type		
Male	7	6.86%	Breast Cancer	79	77.45%
Female	95	93.14%	Gynaecological Cancer	12	11.76%
Menopausal status			Colorectal Cancer	8	7.84%
Premenopausal	49	53.30%	Lymphoma	3	2.94%
Perimenopausal	17	18.40%	Disease stage		
Postmenopausal	26	28.30%	I	19	18.63%
Children			II	46	45.10%
Has children	74	72.55%	III	37	36.27%
Has children living at home	60	58.82%	Positive lymph nodes present	66	64.71%
Marital status			Type of treatment		
Married/Partnered	69	67.65%	Chemotherapy	102	100%
Single	19	18.63%	Surgery	92	90.20%
Separated/Divorced	7	6.86%	Radiation Therapy	81	79.41%
Widowed	7	6.86%	Hormonal treatment	70	68.63%
Employment status			Herceptin	16	15.69%
Employed	54	52.94%	Comorbities		
Housewife	24	23.53%	No comorbidities	52	50.98%
Retired	11	10.78%	1 comorbidity	25	24.51%
Resigned for health	6	5.88%	2 comorbidity	17	16.67%
Unemployed	5	4.90%	≥3 comorbidities	8	7.84%
Student	2	1.96%	BMI (kg/m^2) class[a]		
Highest educational level			Underweight (< 18.5)	1	0.98%
Primary (≤ 8 years)	11	10.89%	Normal (18.5 – 24.9)	39	38.24%
9 - 11 years	20	19.80%	Overweight (25 – 29.9)	38	37.25%
12 - 14 years	37	36.63%	Obese (≥30)	24	23.53%
Third level education	23	22.77%			
Postgraduate	10	9.90%			

[a]Based on World Health Organisation BMI classification.

6.3.3 Descriptive statistics for fatigue, the hypothesised psychosocial predictors, and quality of life. The mean level of fatigue increased by 7.45 points from T1 to T2 and subsequently decreased between T2 and T4 by a total of 8.66 points; although there was less change in the latter part of the trend compared to the initial change between T2 and T2b (see Table 6.4). Between T4 and T5 a slight increase in fatigue was observed. The pattern of changes suggests a nonlinear growth trajectory with accelerations and decelerations in fatigue severity over time. This was supported by visual inspection of the data; *Figure 6.2* illustrates individual cubic growth trajectories of fatigue across the measurement occasions.

Table 6.4 *Descriptive statistics for the variation in fatigue, predictors and QOL over time*

		Fatigue	Depression	Stress	Sleep disturbance	Physical activity	QOL
T1: 0	*M* (*SD*)	36.81 (12.09)	3.13 (3.36)	1.38 (0.87)	4.08 (1.99)	3.41 (0.50)	6.92 (1.91)
(n=71)	Min-Max	03 - 52	0 - 16	0 – 3.75	1 - 7	2 – 4.25	1.80 - 10
T2: 1	*M* (*SD*)	29.36 (12.69)	4.44 (4.21)	1.39 (0.94)	3.81 (1.87)	3.18 (0.51)	6.05 (2.29)
(n=87)	Min-Max	03 - 52	0 - 18	0 - 4	1 - 7	1.78 – 3.98	0 -10
T2b:2	*M* (*SD*)	34.93 (11.27)	2.46 (2.39)	1.07 (0.77)	3.95 (1.71)	3.37 (0.47)	7.11 (2.13)
(n=46)	Min-Max	14 - 52	0 - 8	0 – 2.50	1 - 7	2.47 – 4.52	1.40 - 10
T3 (3)	*M* (*SD*)	36.89 (10.15)	2.82 (3.16)	1.20 (0.94)	3.49 (1.78)	3.58 (0.40)	6.98 (2.09)
(n=79)	Min-Max	05 - 52	0 - 16	0 - 4	1 - 7	2.69 – 4.67	0 -10
T4: 4	*M* (*SD*)	38.02 (10.64)	2.29 (3.01)	1.25 (0.87)	3.70 (1.79)	3.45 (0.60)	6.92 (2.18)
(n=58)	Min-Max	09 - 52	0 - 13	0 – 3.75	1 - 7	1.52 – 4.51	2 - 10
T5: 5	*M* (*SD*)	37.72 (11.57)	2.24 (2.88)	1.06 (0.77)	3.51 (1.82)	3.49 (0.35)	7.13 (2.00)
(n=23)	Min-Max	10 - 52	0 - 09	0 – 2.25	1 - 7	2.91 – 4.25	2.80 - 10

Note. Lower scores indicate higher fatigue on the FACT-F. Depression scores exclude item 8 of the HADS. The Log_{10} of MET-mins/week is reported for physical activity.

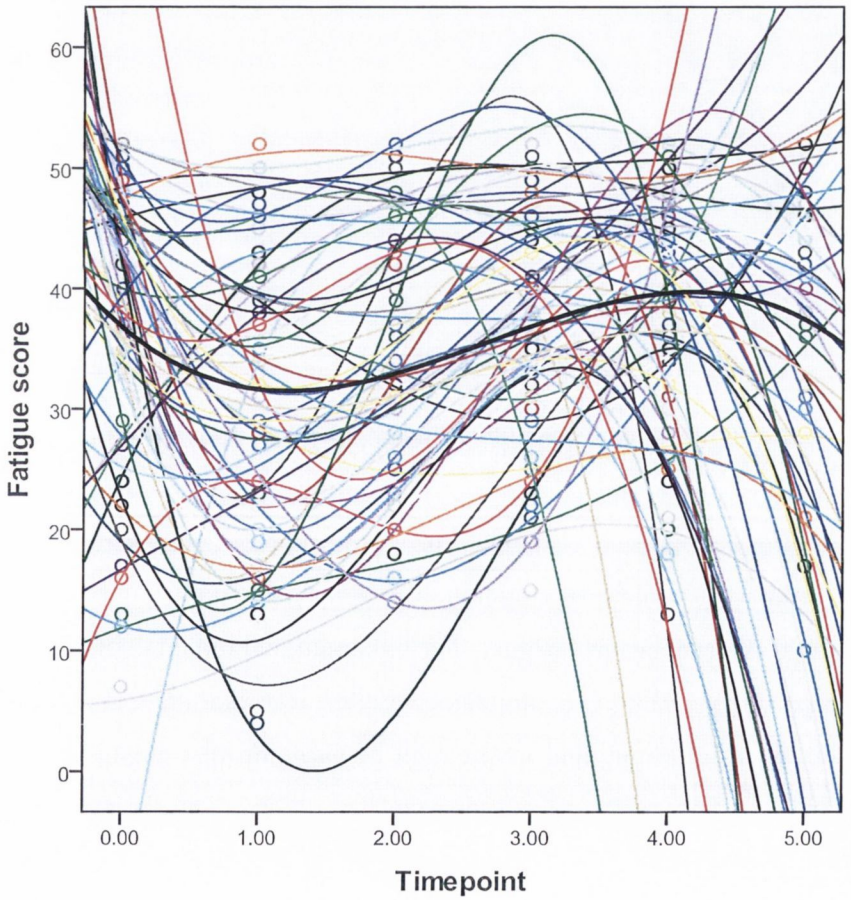

Figure 6.2. Individual cubic growth trajectories in fatigue.

Note. Bold line indicates overall cubic fit line. As a minimum of four timepoints are necessary to fit a cubic growth pattern, only participants for whom scores were available on at least four timepoints (n = 67) were included in this figure to aid interpretation.

Depression, physical activity and QOL showed patterns similar to fatigue over time, whereby there was a decrease in QOL and physical activity and an increase in depression between T1 and T2 and subsequent increases in QOL and physical activity and a decrease in depression after T2 (see *Figure 6.3*). Stress and sleep exhibited different patterns over time; both were highest at T1, stress decreased at time T2b, increased somewhat at T3 and T4 and subsequently decreased to its lowest point at T5, while sleep disturbances decreased at T2, and subsequently followed a pattern of slight increases followed by slight decreases over the remaining measurement occasions.

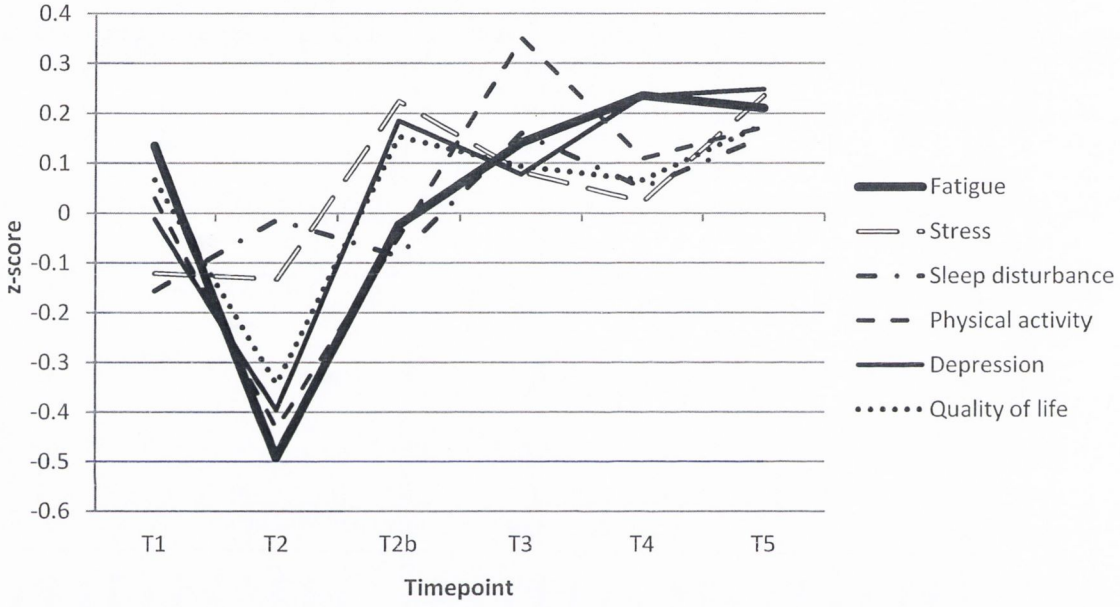

Figure 6.3. Trajectory of fatigue, stress, sleep disturbance, physical activity, depression and QOL over time.

Note. Scores on each variable represent z-scores. The signs of the z-scores were reversed for depression, stress and sleep to aid interpretation of patterns over time.

6.3.4 Individual differences in fatigue. The unconditional model (Model A; see Table 6.5) with no predictor variables (i.e., no change model) was examined to assess the mean of the outcome variable fatigue and the amount of variation that existed in intra- and interindividual levels. The estimated grand mean was -0.36. The variation at the intercept (β = 53.86, p <.001) and the residual variation (β = 88.28, p <.001) were significant, indicating that there were significant differences both between participants and within participants; thus, the results suggested that fatigue varied from occasion to occasion, and participants varied from one another. The intraclass correlation coefficient (ICC), which describes the amount of variation that is related to interindividual

differences (Shek & Ma, 2011), was 37.89, indicating that approximately 38% of the total variation in fatigue was due to differences between participants.

6.3.5 Individual and mean changes in fatigue over time. Unconditional growth models that represented different trajectories of time (Model B: linear, Model C: quadratic and Model D: cubic growth; see Appendix 15) were used to determined the shape of growth curves in the data, assess whether the addition of time could account for intraindividual variability in fatigue, establish whether there were differences in the participants' initial fatigue scores, and examine whether there were differences in participants' rate of growth over time. The simple default Level 1 covariance matrix was used for the analyses presented below. However, in line with recommendations (Heck, Thomas, & Tabata, 2010; Singer & Willett, 2003), other covariance structures for Level 1 were considered so that the fit of covariance structures that do not assume constant variances for all occasions and/or uncorrelated residual covariances across repeated measurements could be tested. Nevertheless, the original covariance matrix structures were retained; the rationale for this is briefly discussed below.

Table 6.5 *No change and cubic change models for the fatigue data (n = 102) compared with a cubic model that incorporates the predictors pain and number of comorbidities*

		Model A No change	Model D Cubic change	Model E Pain and no. of comorbidities
Fixed effects				
Composite model	Intercept (T1)	-0.36	1.09	6.05***
	Time (linear)	-	-11.15***	-7.83***
	$Time^2$ (quadratic)	-	6.11***	3.98***
	$Time^3$ (cubic)	-	-0.79***	-0.48**
	Pain	-	-	-1.42***
	Number of comorbidities	-	-	-1.87
	Time*Comorbidities	-	-	-3.52*
	$Time^2$*Comorbidities	-	-	2.34**
	$Time^3$*Comorbidities	-	--	-0.35**
Variance components				
Level 1	Within person (residual)	88.28***	67.75***	60.45***
Level 2	In T1 (intercept)	53.86***	86.54***	60.51***
	In linear term (slope)	-	3.08	3.21*
	Covariance between linear term & intercept	-	-10.55*	-9.72*
No of parameters		3	8	13
Goodness of fit	-2LL (deviance statistic)	2973.42	2927.49	2823.06
	AIC	2979.42	2943.49	2849.06
	BIC	2991.32	2975.21	2900.45

*$p < .05$, **$p < .01$, ***$p < .001$.

Model fit. Goodness of fit tests of the deviance between the linear and the quadratic models ($p < .01$) and between the quadratic and cubic models ($p < .001$) indicated that a cubic model (Model D) fit the data significantly better (Shek & Ma, 2011). In addition, both the AIC and the BIC goodness of fit indices declined (by 28 points and 24 points respectively from the quadratic to the cubic model). More detailed output on each of the unconditional growth models can be found in Appendix 15; however, as the cubic model provided the best fit and the cubic parameters were retained for subsequent models, only the output relating to this model is discussed. This output is presented in Table 6.5.

Intraindividual variability in fatigue. There was a decline of 20.53 in the within-individual residual variation between unconditional model and the cubic growth model (see Table 6.5), which suggests that about 23% of the residual variation within individuals was accounted for by a cubic growth pattern (Singer & Willett, 2003). The within-individual variation that remained was significant, supporting further exploration of the effects of time variant predictors.

Initial levels of fatigue. The intercept for the cubic growth model was 1.09, which represents the estimated average centered fatigue score at T1 when no covariates were included in this model. As this value was not significant, it suggests that the average fatigue score at baseline was not different from the overall grand mean fatigue score across the different measurement points. However, the random error term associated with the intercept ($\beta = 86.54$, $p < .001$) was significant, suggesting that participants' fatigue scores differed substantially at T1; this variability could be explained by between-individual (i.e., Level 2) predictors.

Changes in fatigue over time. The fixed effects for the linear ($\beta = -11.15$), quadratic ($\beta = 6.11$) and cubic ($\beta = -0.79$) parameters were all significant ($p < .001$) supporting significant changes in fatigue scores over time and changes in the rate of change. This trend is plotted in *Figure 6.4* and suggests that (as higher fatigue scores indicate lower fatigue) fatigue peaked at T2 (after chemotherapy) and subsequently decreased until T4 after which it increased again.

Inter-individual differences in the rate of growth were also investigated. The random error term associated with the linear slope parameter ($\beta = 3.08$, $p > .05$) was not significant, suggesting that there was no significant variation in the initial rate of change across participants. There was no evidence of significant variability in individual change parameters for quadratic or cubic rate of growth between participants ($p > .05$); thus,

these parameters were treated as fixed in the analyses (i.e., time^2 and time^3 were not included as random effects in the model).

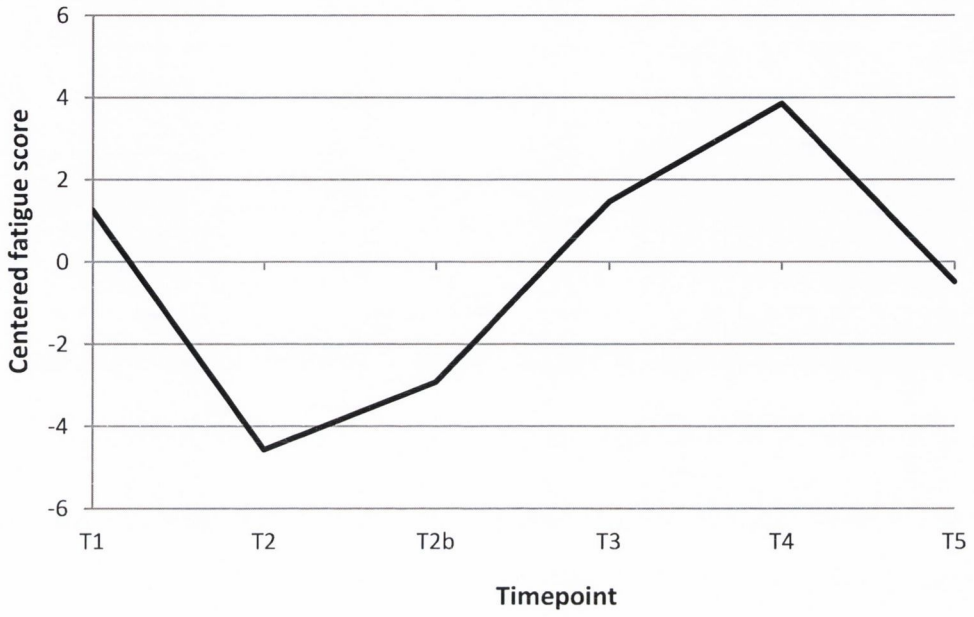

Figure 6.4. Cubic changes in fatigue over time.

Covariance structure of repeated measurements over time. The default Level 1 scaled identity matrix, which assumes a constant variance for all occasions, was used to specify the within-subjects error structure in the analyses detailed above. However, as this type of error structure may not be appropriate for longitudinal data where there may be heterogeneous variances for each measurement occasion and/or significant relationships between the measurements from one occasion to the next, different Level 1 residual covariance structures were also considered using the repeated command in PASW (Heck et al., 2010). However, models that used a covariance structure that allowed heterogeneous variances for difference measurement occasions (i.e., a diagonal covariance structure) and a covariance structure that assumed correlated residual variances between repeated measurements (i.e., an autoregressive error covariance matrix) had a worse fit to the data (output available in Appendix 15). Therefore, the default scaled identity matrix was retained. Heck et al. (2010) note that this simplified within-subject error structure is often sufficient for repeated measurement studies of short duration.

6.3.6 Interindividual differences in fatigue and in the trajectories of fatigue.

6.3.6.1 Demographic and medical predictors. The third research question queried whether demographic and medical characteristics impacted on (a) interindividual

differences in fatigue level and (b) individual rates of change in fatigue over time. Specifically, pain and number of comorbidities were expected to predict individual differences in fatigue levels (part a), and treatment-related factors were expected to influence the rate of recovery from fatigue after treatment (part b). Based on the previous findings presented in this thesis (see Chapter 4), the role of other demographic and medical factors was not explored.

(a) Pain and comorbidities. Pain and number of comorbidities were entered into the cubic growth model as fixed effects (Model E; see Table 6.5). As pain was assessed at each measurement occasion, this variable was entered as a time-varying predictor at Level 1, while number of comorbidities was entered at as a time-invariant predictor at Level 2. The effects of these predictors on the shape of individual growth trajectories were explored by testing interactions with the time parameters. The findings indicated that pain had no effect on the rate of change in fatigue over time; therefore, pain was entered only as a predictor of the intercept in Model E described below.

Model E was a significantly better fit for the data than the unconditional cubic model ($\chi^2(5) = -104.43$, $p < .001$; $\Delta AIC = -94.43$; $\Delta BIC = -74.76$). The intercept was significantly different from the overall centered mean fatigue score when adjusting for pain and number of comorbidities ($p < .001$); thus, the data indicated that participants who had rated their pain as 0 and had no comorbidities had an initial centered fatigue score of 6.05. Pain was a significant predictor of participants' fatigue scores ($p < .001$); the findings suggested that for every one point increase in pain, the fatigue score would decrease by 1.42 points. The parameters for linear ($\beta = -7.83$, $p < .001$), quadratic ($\beta = 3.98$, $p < .001$) and cubic ($\beta = -0.48$, $p < .01$) growth rate all remained significant. Furthermore, number of comorbidities was a significant predictor of linear, quadratic and cubic growth, but was not significantly associated with initial fatigue status ($\beta = -1.87$, $p > .05$). *Figure 6.5* illustrates the effect of number of comorbidities on the rate of change across time using the average, the minimum, and the maximum observed number of comorbidities as prototypical values (Singer & Willett, 2003). Having a greater number of comorbidities resulted in a faster rate of change in linear ($\beta = -3.52$, $p < .05$), quadratic ($\beta = 2.34$, $p < .01$) and cubic growth ($\beta = -0.35$, $p < .01$).

After controlling for the effects of pain and number of comorbidities, there was still significant variance in the initial intercept ($\beta = 60.19$, Wald $Z = 3.93$, $p < .001$) and the variability in the linear growth rate was also significant ($\beta = -3.21$, $p < .05$), indicating that other inter-individual differences could account for these variations. The

predictors pain and comorbidities accounted for 11% of the within-individual variations in fatigue, after the cubic growth pattern was taken into account; however, the remaining residual variance was still significant ($\beta = 60.45$, $p < .001$), suggesting that significant variability within participants over the measurement occasions was not accounted for in the model and thus supporting the merit of exploring the effects of within-individual predictors.

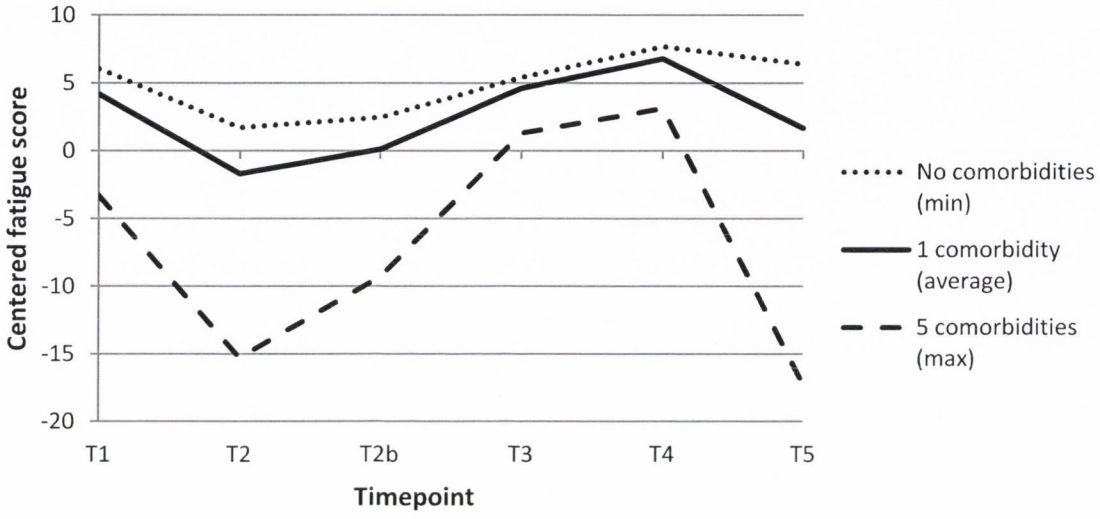

Figure 6.5. Fitted trajectories of the centered fatigue score over time for participants with no comorbidities, one comorbidity and five comorbidities.

(b) Impact of treatment-related factors on the shape of individual growth trajectories. It was hypothesised that (i) receiving RT in addition to chemotherapy and (ii) receiving ongoing treatment with Herceptin after chemotherapy would influence the rate of recovery after treatment. In order to address these hypotheses, the individual change parameters for time must be modelled as a function of the predictors. As the predictors were not expected to influence initial fatigue status at T1 and rate of change over the course of chemotherapy (i.e., T1 to T2), only the post-treatment timepoints were of interest. Thus, to reduce the number of parameters to be estimated in the model and to increase the accuracy of the estimated relationship between fatigue level and time, a separate post-treatment growth curve model was calculated using the actual number of weeks since treatment as the measure of time.

The findings indicated that a quadratic model fit the data significantly better than a linear model ($p < .01$); furthermore, a cubic growth trend did not improve model fit ($p >$

.05; the AIC and BIC increased). The positive effect of linear growth ($\beta = 0.43$, $p < .001$) indicated that fatigue initially decreased after treatment (as higher fatigue scores indicates lower fatigue); however, the negative effect of quadratic growth ($\beta = -0.01$, $p < .001$) indicated a deceleration in the rate of change (see Table 6.6 and *Figure 6.6*). This trajectory of fatigue post-treatment is in line with the growth trend of fatigue between T2 and T5 that was observed in *Figure 6.4*.

Table 6.6. *Comparison of fitting linear and quadratic trajectories to the post-treatment fatigue data and the effects of treatment with radiation therapy (RT) and Herceptin on individual quadratic growth trajectories*

		Linear	Quadratic	RT	Herceptin
Fixed effects					
Composite model	Intercept (T1)	0.23	-2.04	-3.31	-1.14
	Time (linear)	0.07	0.43**	0.77***	0.36*
	Time^2 (quadratic)	-	-0.01**	-0.01*	-0.01
	RT	-	-	1.87	-
	Time*RT	-	-	-0.44	-
	Time^2*RT	-	-	0.01	-
	Herceptin	-	-	-	-5.90
	Time*Herceptin	-	-	-	0.42
	Time^2*Herceptin	-	-	-	-0.02
Variance components					
Level 1	Within person (residual)	55.82***	51.92***	51.26***	53.53***
Level 2	In T1 (intercept)	94.21***	98.05***	99.79***	92.24***
	In linear term (slope)	0.04	0.05	0.05	0.04
	Covariance between linear term & intercept	-1.38	-1.47*	-1.52*	-1.36
No of parameters		6	7	10	10
Goodness of fit	-2LL (deviance statistic)	2001.43	1993.25	1985.98	1939.90
	AIC	2013.43	2007.25	2005.98	1959.90
	BIC	2034.99	2032.42	2041.93	1995.62

*$p < .05$, **$p < .01$, ***$p < .001$.

To test the effect of treatment-related factors on the shape of individual growth trajectories after treatment, the dichotomous variables treatment with RT and treatment with Herceptin were entered individually as predictors of the intercept, linear and quadratic growth parameters. Adding treatment with RT to the quadratic growth model resulted in a small decrease in the AIC; however, the improvement in model fit was not significant ($\chi^2(3) = 7.27$, $p < .05$), the BIC increased and treatment with RT was not a significant predictor of the centered fatigue score at the intercept or linear or quadratic growth ($p > .05$; see Table 6.6). Adding treatment with Herceptin to the cubic growth model resulted in a significantly improved model fit ($\chi^2(3) = 53.35$, $p < .001$; ΔAIC = -

47.35; ΔBIC = -36.80). However, although the linear and the quadratic rate of change appeared to be faster in participants treated with ongoing Herceptin than those who did not receive Herceptin (*Figure 6.6*), treatment with Herceptin was not a significant predictor of initial fatigue status or linear or quadratic growth (see Table 6.6).

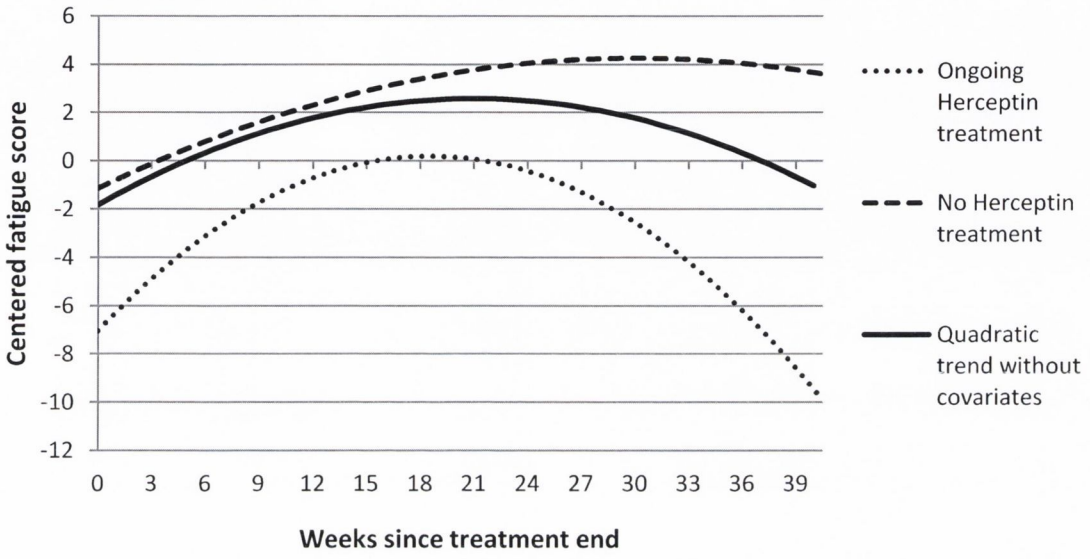

Figure 6.6. Quadratic growth trajectories of all participants post-treatment without the addition of any covariates and fitted trajectories of participants who received ongoing Herceptin treatment compared to those who did not receive Herceptin.

As neither ongoing treatment with Herceptin nor treatment with RT had a clear significant impact on the rate of change in fatigue post-treatment, these variables were not included in further analysis. All subsequent models were based on the six assessment timepoints (T1 to T5) and built on the cubic model presented in Table 6.5.

6.3.6.2 Psychosocial predictors. To address the fourth research question, which queried whether depression, stress, sleep disturbances, and physical activity could account for initial differences in fatigue and changes in fatigue over time, these predictors were entered into the cubic growth model as fixed predictors at Level 1. Since each of these predictors had the potential to change over time, each predictor was initially tested separately (Models F – I) to determine its unique contribution, if any, to baseline fatigue and to changes across the measurement occasions (results presented in Table 6.7). The Level 1 predictors were not entered as random effects as there was no evidence that the impact of the predictors would be different across individuals (Singer & Willett, 2003). However, interactions between the predictors and time were explored. Significant

demographic and medical covariates (pain and number of comorbidities) were retained in the analysis (thus the comparison model, Model E, is included in Table 6.7).

Table 6.7 *Comparison of alternative models for the fatigue data that incorporate psychosocial predictors*

		Model E Pain & no. of comorb.	Model F Depression	Model G Stress	Model H Sleep	Model I Physical activity	Model J All predictors
Fixed effects							
Composite model	Intercept (T1)	6.05***	9.95***	13.72***	11.98***	-11.15	5.85
	Time (linear)	-7.83***	-5.74**	-9.39***	-8.52***	-34.48*	-19.64
	$Time^2$ (quadratic)	3.98***	2.70**	4.47***	4.19***	18.97**	10.88
	$Time^3$ (cubic)	-0.48**	-0.32*	-0.52***	-0.50**	-2.64*	-1.59
	Pain	-1.42***	-0.84***	-0.94***	-1.27***	-1.36***	-0.74***
	Comorbidities	-1.87	-1.01	-1.29	-1.24	-1.63	-0.77
	Time*Comorbidities	-3.52*	-2.94*	-2.88	-3.77*	-3.32	-2.61
	$Time^2$*Comorbidities	2.34**	1.99**	1.95*	2.43**	2.20*	1.78*
	$Time^3$*Comorbidities	-0.35**	-0.30**	-0.30**	-0.36**	-0.33**	-0.27**
	Depression	-	-1.83***	-	-	-	-1.02***
	Stress	-	-	-6.53***	-	-	-3.43***
	Sleep	-	-	-	-1.64***	-	-0.84**
	Physical activity (PA)	-	-	-	-	5.01*	2.83
	Time*PA	-	-	-	-	8.57*	3.69
	$Time^2$*PA	-	-	-	-	-4.82*	-2.28
	$Time^3$*PA	-	-	-	-	0.68*	0.36
Variance components							
Level 1	Within person (residual)	60.45***	44.39***	46.67***	58.80***	51.13***	40.04***
Level 2	In T1 (intercept)	60.51***	32.17**	33.79**	47.85***	66.56***	25.28**
	In linear term (slope)	3.21*	2.60*	1.68	3.81*	3.81*	2.04*
	Covariance btw. linear term & intercept	-9.72*	-5.91*	-4.68	-9.89*	-11.15*	-4.66
No of parameters		13	14	14	14	17	20
Goodness of fit	-2LL	2823.06	2689.49	2694.15	2753.40	2571.22	2419.09
	AIC	2849.06	2717.49	2722.15	2781.40	2605.22	2459.09
	BIC	2900.45	2772.84	2777.46	2836.52	2671.04	2536.42

Note. The HADS depression scale excluding item 8 was used as a measure of depression. The $\log_{10}$ of MET min/wk was used as a measure of physical activity. Participants who reported doing zero levels of physical activity were excluded from the analysis because of concern about the accuracy of such values. *$p < .05$, **$p < .01$, ***$p < .001$.

Depression. There was no evidence that depression had a significant effect on the shape of individual growth trajectories ($p > .05$); therefore, depression was entered only as a predictor of the intercept. When depression was added as a Level 1 predictor (Model

F), the parameter estimates for Time, Time^2, and Time^3 indicated that the rate of change in fatigue, while still statistically significant, had declined (see Table 6.7). This suggests that depression explained some of the observed changes in fatigue over time (Singer & Willett, 2003). This interpretation is supported by (1) the large statistically significant effect of depression – the average centered fatigue score was 1.83 points lower for every one point increase in depression ($p < .001$); and (2) the significantly better fit of the model compared to Model E ($\chi^2(1) = 133.57$, $p < .05$; $\Delta AIC = -131.57$; $\Delta BIC = -127.61$). In addition, adding depression to the model reduced the magnitude of the within-person variance component by 16 points; thus, the time-varying variable depression accounted for nearly 27% of the residual variation in fatigue scores that was not accounted for in Model E. The intercept for this model represents the centered value of fatigue at T1 for participants (i.e., 9.95 points above the overall grand mean of fatigue) with no comorbidities and scores of 0 on the pain rating scale and on the HADS depression measure. *Figure 6.7* illustrates the effect of depression on the fatigue scores across time using a depression score of zero, the average overall depression score observed in the data, and a depression score of 8, which indicates a possible mood disorder (Snaith, 2003), as prototypical values (Singer & Willett, 2003). The graph indicates that patients with higher depression scores had significantly higher levels of fatigue.

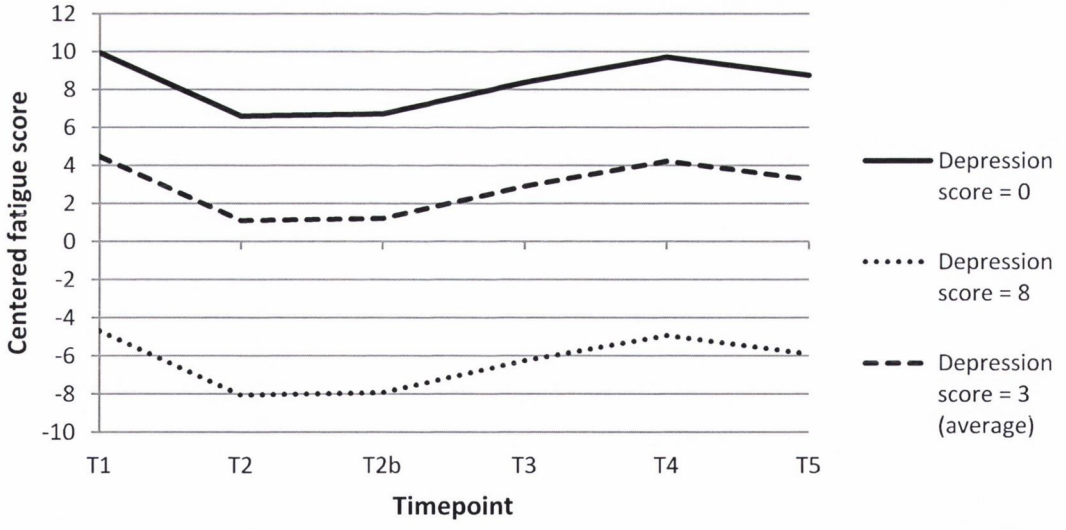

Figure 6.7. Fitted trajectories of the centered fatigue score over time for participants with an average depression score, a depression score of zero, and a depression score of eight.

Stress and Sleep. There was no evidence that either stress or sleep had a significant effect on the shape of individual growth trajectories ($p > .05$); therefore, stress and sleep were entered only as Level 1 predictors of the intercept in Models G and H (see

Table 6.7). Both stress and sleep disturbance had statistically significant fixed effects ($p < .001$); the average centered fatigue score was 6.53 points lower for every one point increase in stress and 1.64 points lower for every one point increase in sleep disturbance. Both models were a significantly better fit to the data in comparison Model E ($p < .001$); the differences in the deviance statistics were 128.91 and 69.66 respectively and the AIC and the BIC for both models decreased by similar amounts. While adding stress to the model accounted for nearly 23% of the unexplained within-person residual variance in Model E, the data suggested that adding sleep disturbance only accounted for approximately 3% of the residual variance.

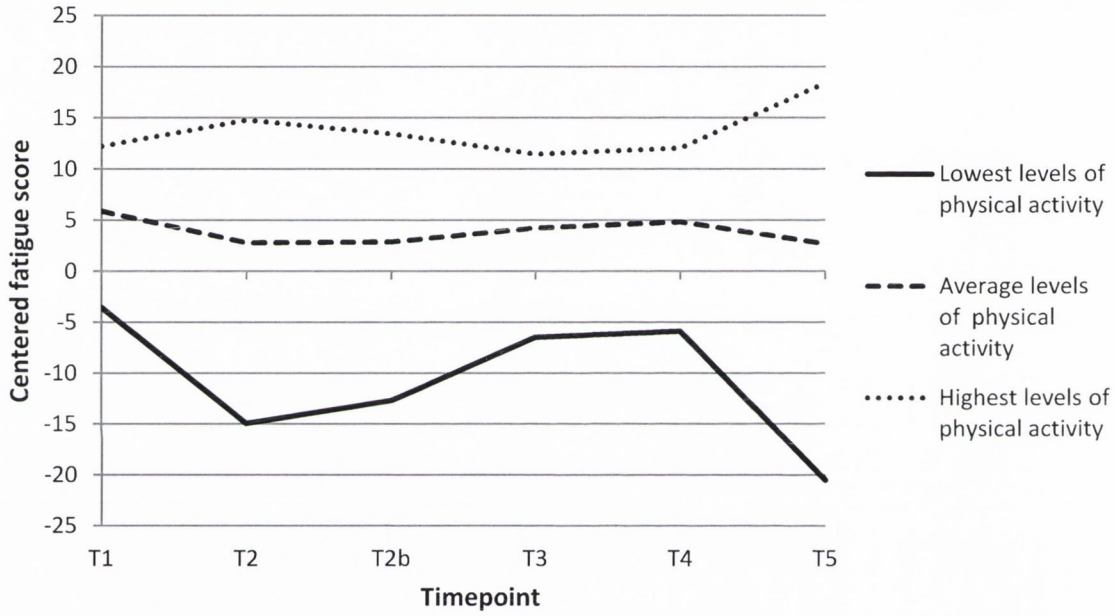

Figure 6.8. Fitted trajectories of the centered fatigue score over time for participants with low, average, and high activity levels.

Note. Low activity levels are based on the lowest reported activity levels in the data (Log_{10} MET min/wk = 1.52), average activity levels represent the mean reported activity levels in the data (Log_{10} MET min/wk = 3.4) and high activity levels are based on the highest reported activity levels in the data (Log_{10} MET min/wk = 4.67).

Physical activity. Physical activity (measured using Log_{10} of MET-mins/week) had a statistically significant fixed effect ($p < .05$) and was also a significant predictor of the linear, quadratic and cubic changes in the centered fatigue score ($p < .05$; see Table 6.7). Adding physical activity to the model explained over 15% of the residual variation not accounted for in Model E. The intercept for this model (11.15 points below the grand mean of fatigue), represented the centered value of fatigue at T1 for participants with no

comorbidities and scores of 0 on the pain rating scale and on the physical activity measure.

The results indicated that the centered fatigue score was 5.01 points higher for every one point increase in Log_{10} MET-mins/week. *Figure 6.8* illustrates the effect of physical activity on the rate of change in centered fatigue across time using the average, the lowest, and the highest reported levels of physical activity as prototypical values. Participants who reported the lowest levels of physical activity showed a faster rate of change over time, while participants who reported physical activity levels close to the overall sample average had little fluctuation in fatigue over time. In addition, the findings indicated that the fatigue levels of participants who engaged in the lowest levels of activity worsened after T4, while the fatigue levels of those who reported the highest levels of physical activity decreased after T4. The goodness of indices indicated that this model was the best fit to the data; the improvement in model fit compared to Model E was statistically significant (χ^2 (4) = 251.84, $p < .001$; ΔAIC = -243.84; ΔBIC =-229.41).

Composite model with all psychosocial predictors. Including all four psychosocial predictors in a composite model (Model J; see Table 6.7) resulted in a better fit to the data than all of the previously presented models; the difference in the deviance statistic from both Model E ($\chi^2(7) = 403.97$, $p < .001$) and Model I ($\chi^2(3) = 152$, $p < .001$) was statistically significant. Furthermore, despite the added complexity in the model, both the AIC and the BIC decreased from the previous models. Depression, stress and sleep had statistically significant fixed effects ($p < .01$ to $p < .001$); however, the parameters for physical activity were no longer significant ($p > .05$). The magnitude of the within-person variance component was reduced by 20.41 points from Model E; thus, the psychosocial variables explained approximately 34% of the residual within-person variation in fatigue scores that was not accounted for in Model E. However, as the within-person variation was still statistically significant, the results indicate that a considerable proportion of intraindividual variation was still not accounted for.

6.3.7 The role of fatigue in inter- and intra-individual differences in quality of life. Changes in QOL over time were examined using unconditional growth models (see Appendix 16 for results from the no change, linear, quadratic and cubic models) before the impact of fatigue on interindividual differences, intraindividual variability, and rates of change in QOL over the measurement occasions were evaluated. The goodness of fit indices indicated that a cubic model was the best fit for the data (χ^2 (1) = -10.16, $p < .01$; ΔAIC = -8.16, ΔBIC = -4.20 from the quadratic model). The fixed effects for the

linear, quadratic and cubic parameters were all significant (p <.05) supporting significant changes in QOL scores over time (see Table 6.8). The trend over time is plotted in *Figure 6.9* and suggests that QOL was lowest at T2 and subsequently increased until T4 after which it decreased again. Although there was significant variation in initial QOL status ($p < .001$), there was no evidence of significant interindividual differences in QOL growth rate based on the individual change parameters ($p > .05$). The within-individual variation in QOL declined from 2.42 ($p < .001$) in the unconditional model to 2.14 ($p < .001$) in the cubic model; thus, just under 12% of variation in QOL was accounted for by a cubic growth pattern. As the within-individual variation remained significantly different from zero, further investigation of the effects of time-variant predictors was supported.

Table 6.8 *Comparison of the cubic growth model for quality of life with a cubic growth model that includes fatigue as a Level 1 predictor (n = 102)*

		Cubic change Unconditional model	Cubic change with Fatigue as Level 1 predictor
Fixed effects			
Composite model	Intercept (T1)	6.82***	2.75***
	Time (linear)	-1.05**	0.27
	Time^2 (quadratic)	0.60***	-0.12
	Time^3 (cubic)	-0.08*	0.01
	Fatigue	-	0.11***
Variance components			
Level 1	Within person (residual)	2.14***	1.51***
Level 2	In T1 (intercept)	2.22***	0.83**
	In linear term (slope)	0.06	0.01
	Covariance between linear term and the intercept	-0.06	0.01
No of parameters		8	9
Goodness of fit	-2LL (deviance statistic)	1574.96	1365.73
	AIC	1590.96	1383.73
	BIC	1622.65	1419.27

*p < .05, **p < .01, ***p < .001.

Fatigue was entered as a Level 1 predictor of QOL. As there was no evidence that fatigue had a significant effect on the shape of individual growth trajectories ($p > .05$), interactions between time and fatigue were not included in the final model. After fatigue was added as a covariate, the parameter estimates for Time, Time^2, and Time^3 were no

longer statistically significant (see Table 6.8). This suggests that changes in fatigue accounted for the observed changes in QOL over time. This interpretation is supported by (1) the large statistically significant effect of fatigue – the average QOL score was 0.11 points higher for every one point increase in the fatigue score ($p < .001$); and (2) the significantly better fit of the model ($\chi^2(1) = 209.23$, $p < .001$; $\Delta AIC = -207.23$; $\Delta BIC = -203.38$). In addition, adding fatigue to the model reduced the magnitude of the within-person variance component by 0.63 points; thus, the time-varying variable fatigue accounted for just over 29% of the residual variation in QOL scores in the unconditional cubic model. The intercept for this model, a score of 2.75, represented the QOL rating at T1 for participants with a score of 0 on the FACT-F (i.e., the highest fatigue score possible). *Figure 6.9* illustrates the effect of fatigue on the QOL scores across time using the lowest reported fatigue score, the average reported fatigue score, and the highest reported fatigue score as prototypical values.

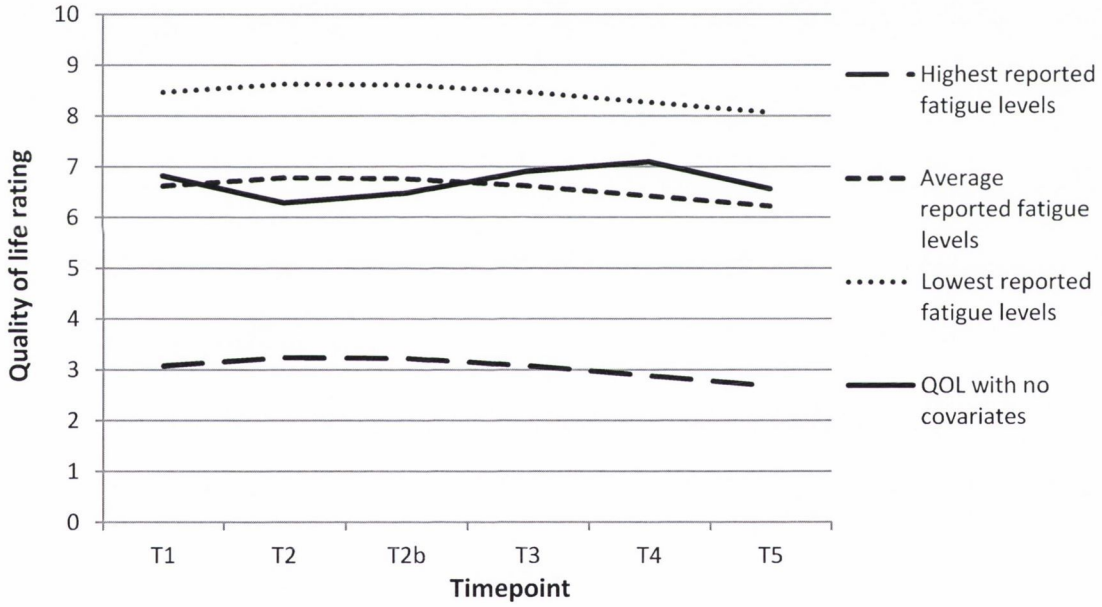

Figure 6.9. Fitted trajectories of quality of life ratings over time in the unconditional cubic model and for low, average, and high fatigue levels when fatigue is included as a covariate.

Note. The high fatigue level is based on the highest reported fatigue score in the data (FACT-F = 3), average fatigue represents the mean reported fatigue score (FACT-F = 35.21) and low fatigue level is based on the lowest reported fatigue score (FACT-F = 52).

6.4 Discussion

The findings indicated that changes in fatigue over time were associated with changes in depression and physical activity. Furthermore, depression, physical activity, stress, and sleep-disturbances significantly predicted interindividual differences in fatigue. Participants' fatigue levels were at their most severe after chemotherapy and although fatigue improved post-treatment, a subsequent increase in fatigue was observed several months after the completion of treatment. Of note, the number of comorbidities that participants suffered from and their self-reported physical activity levels had a significant impact on the rate of change in fatigue over time, whereby patients with greater numbers of comorbidities and lower self-reported activity demonstrated greater fluctuations in fatigue over the measurement occasions. The findings suggest that differences in the number of comorbidities and in self-reported activity levels could contribute to post-treatment increases in fatigue in cancer survivors. The results also highlight the close links between fatigue and QOL in cancer patients. Fatigue and QOL not only covaried over time, but fatigue also accounted for the observed differences in quality of life between the measurement occasions.

6.4.1 Variations in fatigue over time. The results supported the hypothesis that fatigue would vary both within and between participants over time. In line with expectations and previous findings (e.g., Prue et al., 2009), fatigue was greatest after chemotherapy and subsequently improved in the weeks following treatment, reaching pre-chemotherapy levels approximately three months after treatment and showing a further decline thereafter. However, the findings also indicated that there was a subsequent worsening in fatigue levels approximately six months post-treatment (after T4). It is possible that the higher fatigue reported at T5 reflected participants' expectations about recovery timelines and/or attempts to increase activity levels at this stage in their recovery process. While greater fatigue is expected during and shortly after treatment, patients may assume that the side-effects of cancer and cancer treatments will have cleared after six months and many attempt to resume their usual activities by this point in time (Donovan et al., 2007). However, recovery after treatment can be slow and previous activity levels and working patterns may be more taxing than before cancer. Thus, fatigue levels may have increased as participants returned to work or attempted to resume their pre-illness responsibilities. In addition, a discrepancy between perceptions of fatigue status and expectations of a resolution in fatigue by this stage may have influenced self-reported ratings of fatigue. As return to work and expectations of

recovery were not assessed in the current study, it was not possible to test such explanations; however, the observed trends in fatigue and physical activity are in line with this idea as both increases in fatigue and physical activity were observed between T4 and T5. The impact of physical activity on the rate of change in fatigue is discussed in the next section; however, first the role of comorbidities in the trajectory of fatigue post-treatment is considered.

6.4.2 The relationship between fatigue and medical and demographic factors. Previous longitudinal research found no significant effects of time on fatigue among post-treatment cancer patients assessed on a monthly-basis for a year after treatment (Goedendorp et al., 2012). As fatigue was only assessed at approximately three-month intervals in the current study, it is possible that the observed decrease and subsequent increase in fatigue post-treatment did not accurately reflect the underlying trends in fatigue during this time period. However, a possible explanation for the differences in fatigue trajectories may be that Goedendorp et al.'s study excluded patients with comorbidities that could cause fatigue and, perhaps because of this, no effect of comorbidity on persistent fatigue after treatment was observed. The current study did not exclude patients with medical conditions that have been linked with fatigue, and comorbidities did play a role in participants' fatigue trajectories. Nevertheless, the findings suggested that the number of comorbidities was important, not the presence of comorbidities linked to fatigue (see also Chapter 4); participants who had no comorbidities had a flatter fatigue trajectory post-treatment compared to participants with even one comorbidity. Participants with a greater number of comorbidities had a much faster rate of increase in fatigue over the treatment period and, though the rate of decrease in fatigue post-treatment was also faster, fatigue levels remained more severe compared to participants with fewer comorbidities and showed a subsequent sharper increase in fatigue after T4. Thus, comorbidities assessed before the start of treatment explained some of the observed increase in post-treatment fatigue levels.

Although care must be taken in studies on CRF, especially in intervention trials, to exclude participants whose fatigue may not be cancer-related, these findings highlight the potentially misleading conclusions that can be drawn if fatigue is only investigated in groups of cancer patients who meet such inclusion criteria. As cancer is associated with age, the majority of cancer patients suffer from at least one comorbid illness (Ogle, Swanson, Woods, & Azzouz, 2000) and conditions that can contribute to fatigue, such as thyroid problems and arthritis, are common (Berger et al., 2012). If research consistently

excludes such patients, then findings in this area will not be generalisable to a substantial cohort of patients, and the potential effects of cancer treatments on these patients will be overlooked. The current findings suggest that comorbidities have a significant impact on the trajectory of fatigue, and may be especially important in illuminating why some patients experience severe post-treatment fatigue. In line with this, a previous study found that hypertension predicted fatigue in breast cancer survivors five to ten years after diagnosis (Bower et al., 2006). Future longitudinal studies with more frequent follow-up assessments are necessary to examine the interactions between both fatigue- and non-fatigue related comorbidities and CRF over time. In addition, as comorbidities were only assessed pretreatment in the current study, further research should also examine the role of additional comorbid conditions that emerge during or after treatment.

Although pain was not found to impact the rate of change in fatigue, the results supported the hypothesis that pain would contribute to interindividual differences in fatigue. This finding is consistent with previous research (Cavalli Kluthcovsky et al., 2011; Haghighat et al., 2003; Stone et al., 2001). Pain can be distressing, interrupt sleeping patterns, and lead to lower levels of activity, all of which can contribute to fatigue (Oh & Seo, 2011). Pain is also common in cancer patients, affecting approximately 30% of patients irrespective of disease stage (Oh & Seo, 2011), and can occur as a result of surgery or chemotherapy and RT treatments (Fiorentino et al., 2011). The findings suggest that because fatigue and pain often co-occur, particular care should be taken to screen for fatigue in patients who report pain. Previous research has indicated that patients often do not report fatigue to their health care provider (Donovan et al., 2005) and more proactive approaches to assessing and managing fatigue in cancer patients are advocated (Dillon & Kelly, 2003; Reidy, 2011).

The hypotheses that treatment with RT and/or Herceptin would influence the rate of recovery in fatigue after treatment were not supported. There was no indication that receiving RT significantly delayed or impacted on post-treatment improvements in fatigue. A previous study which retrospectively assessed breast cancer patients' ratings of fatigue over different treatment phases also found similar fatigue trends in patients treated with chemotherapy only and patients treated with chemotherapy and RT (Schmidt et al., 2012); nevertheless, although fatigue decreased between chemotherapy and RT in Schmidt et al.'s study, retrospective fatigue rating during RT were still higher than those reported after surgery. Another study on breast and prostate cancer reported that patients' fatigue did not significantly increase after RT, nevertheless the majority of participants

still reported that their fatigue worsened after RT treatment (Stone et al., 2001). However, only a fifth of the participants in Stone et al.'s study had been treated with chemotherapy prior to RT; as all of the participants in the current study had received chemotherapy before RT, it is possible that ratings of fatigue after radiation were influenced by participants' experiences of fatigue during chemotherapy. The profound impact of chemotherapy on fatigue-levels is well known and chemotherapy has been associated with more severe fatigue than RT (Donovan et al., 2004). Research has indicated that patients can adapt to fatigue over the course of their treatment, leading them to redefine how they evaluate fatigue severity (e.g., Andrykowski, Donovan, & Jacobsen, 2009; Jansen, Stiggelbout, Nooij, Noordijk, & Kievit, 2000; Visser, Smets, Sprangers, & de Haes, 2000). Thus, the parallel post-treatment fatigue recovery trends among both participants who received additional RT and those who did not in the current study, may have been due to a response shift in self-reports of fatigue after chemotherapy. This is consistent with previous research that found that fatigue only increased during RT among breast cancer patients who had not received chemotherapy beforehand (Donovan et al., 2004). This proposed explanation requires further investigation; however, based on the current findings, there was no evidence that receiving RT in addition to chemotherapy impacted on patients' post-treatment recovery in fatigue.

The effect of Herceptin treatment on fatigue post-treatment was less clear. Ongoing treatment with Herceptin was not a significant predictor of fatigue or of post-treatment rate of change in fatigue; nevertheless, including these parameters in the model resulted in a significantly better model fit and the graphical representation of these results supported some role for Herceptin treatment in patients' recovery patterns. As Herceptin treatment had no clear significant impact, its inclusion in the subsequent models described in this study was not justified; however, it may need to be considered in future studies. Clear trends may not have emerged in the current study as only 15% of participants were treated with Herceptin.

6.4.3 The relationship between psychosocial factors and fatigue. All of the hypothesised psychosocial variables were significant predictors of interindividual differences in fatigue; in line with previous research (see Oh & Seo, 2011; Prue et al., 2006), patients with higher levels of depression, greater sleep disturbance and stress, and lower levels of physical activity reported more severe fatigue. In addition, depression, stress and physical activity also accounted for substantial proportions of the variation in

within-individual changes in fatigue scores over time. Depression demonstrated a very similar trajectory to fatigue. The current study thus supports previous research that reported that changes in fatigue were associated with changes in depression (Stone et al., 2001; Tchekmedyian et al., 2003). However, although depression and fatigue covaried over time, there was no evidence that depression impacted on the rate of change in fatigue scores and no conclusions can be drawn regarding the directional nature of the relationship between these variables. Nevertheless, as the current study consisted of multiple timepoints spread across the treatment trajectory and the initial post-treatment recovery period, and excluded fatigue-like symptoms in the measurement of depression, the findings add weight to the argument that these symptoms are closely related. Although treatment of depression alone is not sufficient for treating CRF (Morrow et al., 2003), the co-occurrence of these symptoms supports a multidimensional approach in the management of fatigue in cancer patients.

Like depression, stress and sleep-disturbances also did not impact on the rate of change in fatigue over time. Furthermore, sleep-disturbances explained little of the within-individual variation in fatigue scores and the trajectories of these variables displayed quite different trends. This result is in line with the idea that CRF is unresponsive to sleep or rest and supports the independence of fatigue and sleep-related factors (National Comprehensive Cancer Network, 2012a). The current findings thus do not support the contention that treating poor sleep quality may be effective in decreasing or preventing CRF. Nevertheless, as in previous studies (e.g., Banthia et al., 2009; Cavalli Kluthcovsky et al., 2011; Fagundes et al., 2012), sleep-disturbance significantly predicted interindividual differences in fatigue and the co-occurrence of these symptoms indicates the importance of screening for sleep-disturbances along with fatigue. Although stress accounted for a substantial proportion of the within-person residual variance in fatigue, examination of the trends in fatigue and stress over time suggested that there was little covariance in these factors over the measurement occasions. Whereas fatigue increased from before to after chemotherapy, stress levels showed little change; the only period during which similar trends were evident was shortly after chemotherapy when reductions in both stress and fatigue were observed, otherwise increases in stress occurred alongside decreases in fatigue and vice versa. The nature of the association between these factors requires further investigation. As stress can impact on immune response and interfere with the functioning of physiological circadian rhythms that have been associated with CRF (Payne, 2004; Wu et al., 2012), increases in stress, and

particularly prolonged periods of stress, may lead to subsequent changes in fatigue through such physiological mechanisms. Delayed effects of stress on such biological processes may account for the observed differences in time trends.

Physical activity not only explained inter- and intraindividual differences in fatigue, but also impacted on the rate of change in fatigue levels over time. The finding that higher fatigue was associated with less physical activity is in line with previous findings (e.g., Donovan et al., 2007; Gerber et al., 2010). Donovan et al. (2007) reported that fatigue gradually decreased over time in the six months following treatment in both breast cancer patients with high and low fatigue and that activity level at the end of treatment was a significant predictor of greater fatigue over this follow-up period. However, in this study activity was only assessed at one point in time and the impact of activity levels on the rates of change in fatigue was not examined. Results from the current study indicated that participants who reported the lowest physical activity levels showed a much steeper increase in fatigue over the treatment period as well as a marked increase in fatigue after the initial post-treatment recovery period (i.e., after T4). In contrast, participants who consistently reported physical activity levels close to or above the average levels reported displayed little fluctuation in fatigue over time, and the fatigue levels of those with the highest reported physical activity levels showed a decreasing trend after T4. These findings suggest that the trajectory of fatigue is substantially different for patients with low and high levels of physical activity and support reports of the effectiveness of exercise interventions for CRF (Cramp & Daniel, 2008). However, it is important to note that physical activity in this study was self-reported and therefore the observed relationships were between fatigue and perceived activity levels rather than actual activity levels. It would be interesting to examine to what extent these patterns map on to objective measures of physical activity. If the same patterns were observed then such data could be used to develop guidelines about optimal physical activity levels during and after treatment. Furthermore, such findings could be used to inform optimal times for activity-based interventions with the aim of preventing such fluctuations in fatigue over time. In the current study, however, physical activity and interactions between physical activity and time did not remain significant in a composite multivariate model of fatigue that incorporated all of the hypothesised psychosocial predictors.

Despite the complexity of the final multivariate model, the results indicated that differences in fatigue between participants and changes in fatigue over time were best

described in a model that included both the fixed effects of pain, comorbidities, depression, stress, sleep-disturbance, and physical activity and the interaction effects of comorbidities and physical activity with time. This composite model was a significantly better fit to the data than previous models with fewer predictors and supports a multidimensional approach to understanding and treating CRF. As interrelationships are thought to exist between the contributing factors to fatigue in cancer patients, it is possible that associations between the predictors limited the physical activity parameters from emerging as significant in the final model. Additional research is required in order to explore these associations and to test causal relationships over time.

6.4.4 Fatigue and quality of life. The final hypotheses that QOL changes over the course of the cancer trajectory and that both inter- and intraindividual difference in QOL can be explained by fatigue were also supported. Fatigue and QOL demonstrated highly similar patterns over time, and fatigue was a significant predictor of QOL that explained a substantial proportion of the variance within individuals. Furthermore, although QOL showed significant changes over time, the observed linear, quadratic and cubic time trends were no longer significant once fatigue was entered as a predictor, suggesting that fatigue accounted for the observed decreases and increases in QOL over the measurement occasions. These findings build on previous cross-sectional (e.g., Alexander, Minton, Andrews, et al., 2009; Cavalli Kluthcovsky et al., 2011; Gupta et al., 2007) and retrospective studies (Schmidt et al., 2012) on the relationship between CRF and QOL and reinforce the importance of continuously screening for fatigue in cancer patients and survivors so that adequate and timely support can be delivered.

6.4.5 Theoretical implications. Findings from the current study are in line with many of the relationships identified in the cognitive-behavioural model of fatigue (see Chapter 3). The role of the proposed predisposing factors (i.e., pain and comorbidities) was supported as both significantly predicted interindividual differences in fatigue levels. Furthermore, the results suggested that the presence of comorbidities may influence the rate of change of fatigue over the course of the cancer trajectory. Thus, comorbidities may also feed into the self-perpetuating cycle of persistent fatigue. The role of a number of the psychosocial perpetuating factors outlined in the cognitive-behavioural model were examined and supported; depression, sleep disturbance, stress, and physical activity all significantly predicted fatigue levels. Furthermore, the findings indicated that changes in depression, stress, and physical activity accounted for within-individual changes in fatigue across the timepoints; thus, supporting the idea that such factors could help to

maintain fatigue over time. The role of physical activity may be particularly important in this context, as significant interactions between self-reported activity levels and rates of change in fatigue levels were observed. The findings also suggested that depression, stress and sleep might precipitate fatigue as these variables appeared to play a role in determining participants' initial fatigue status at T1, before chemotherapy. Thus, such factors might contribute to both the development and maintenance of fatigue over time. Finally, the multifactorial approach of the cognitive-behavioural framework was also supported as differences in fatigue were captured more fully when the complete range of psychosocial predictors and predisposing factors were included in the model. The AIC and BIC goodness of fit indices penalise models with a greater number of parameters and, in the case of the BIC, smaller sample sizes (Singer & Willett, 2003); however, despite the added complexity of the composite model, it was a much better fit to the data compared with the models that focussed on any one psychosocial predictor. Thus, the findings support a multidimensional approach to understanding the development of CRF.

6.4.6 Limitations. The sample on which these findings are based did not reflect the incidence of malignancies or the demographic characteristics of cancer patients in the Irish population. Thus, reported severity levels of fatigue and other symptoms should not be generalised beyond the study sample. The focus of this study was on examining relationships between established predictors of fatigue over time and not determining incidence or prevalence rates; nevertheless, further research with more representative samples of patients is necessary to replicate these results.

The analysis reported imposed an oversimplified structure on complicated treatment trajectories in order to analyse the data in a logical manner. Although every effort was made to assess patients at corresponding stages of their treatment plan, this was not always possible. As a result, the actual time since treatment varied somewhat within each timepoint for participants and this would have contributed to the measurement error in the model. In addition, as time was defined as the occasion of assessment, which located participants in terms of where they were in their treatment trajectory, questionnaires that were completed outside the assessment time-frames had to be excluded from the analysis. This contributed to the missing data in the study and the different numbers of questionnaires available across the study timepoints. Nevertheless, the ability to handle longitudinal data of this sort is one of the advantages of using MLM for data analysis and, despite the missing and excluded questionnaires, the overall questionnaire response rate was still good.

6.4.7 Conclusion. Few studies to date have investigated the course of fatigue over the different cancer treatment phases and the initial post-treatment recovery period. The current findings illustrate not only how fatigue varies over the cancer trajectory, but also the extent to which fatigue differs between patients as a function of psychosocial predictors, such as depression, stress, sleep-disturbance and physical activity. Furthermore, the results indicate how the trajectory of fatigue can vary between different patient groups. As patients with a greater number of comorbid conditions and the lowest levels of physical activity appeared to experience greater fatigue in response to chemotherapy and a less favourable fatigue trend post-treatment, the results suggest that such patient groups are especially vulnerable to the side-effects of cancer treatment and ongoing post-treatment problems with fatigue. Nevertheless, as self-report questionnaires were used to assess physical activity, and participants' perceptions of how much physical activity they are engaging in may not be an accurate reflection of their actual activity levels, these results should be interpreted with caution. Finally, fatigue was also associated with lower quality of life throughout the treatment stages and post-treatment recovery period. Health professionals must be mindful of this and fatigue screening and management should be integrated into routine clinical care.

Chapter 7: Fatigue and Inflammatory Activity in Breast Cancer Patients Before Chemotherapy Treatment.

"Fatigue seems to begin with the Chemo treatments because of the beating that the cells in your body take. Same with Radiation. But beats the heck out of the other option... death." – Martin

7.1 Introduction

Activation of immune responses is increasingly implicated in the development of behavioural alterations in both healthy and medically ill individuals (Miller et al., 2008). Administration of proinflammatory cytokines is known to induce "sickness behaviour", which includes many of the common side-effects experienced by cancer patients such as depression, fatigue, impaired sleep, and cognitive dysfunction (Miller et al., 2008). Several reviews have documented relationships between inflammatory markers and fatigue in cancer patients (Bower, 2007; Bower & Lamkin, 2012; Kurzrock, 2001; Saligan & Kim, 2012; Schubert et al., 2007), and the idea that heightened levels of proinflammatory cytokines is the underlying biological mechanism for the development of cancer-related fatigue (CRF) has become popular. Inflammation has also been implicated in depression (Raison, Capuron, & Miller, 2006) and consequently proinflammatory cytokines have been proposed as a potential common cause of both fatigue and depression, thus accounting for the strong correlations observed between these symptoms (Brown et al., 2012).

In addition to direct effects on the brain, inflammatory cytokines may also contribute to behavioural changes by impacting on the metabolism of neurotransmitters such as serotonin, noradrenaline, and dopamine (Bull et al., 2009; Miller et al., 2008; Raison et al., 2006). Alterations in the functioning of these neurotransmitters play a central role in the regulation of several behaviours and they are also primary targets for psychopharmacologic treatments of depression, anxiety and fatigue (Miller et al., 2008). Proinflammatory cytokines such as interleukin (IL)-1β, interferon-gamma (IFN)-α IFN-γ, IL-6 and tumour necrosis factor alpha (TNF)-α can stimulate the enzyme indoleamine 2,3-dioxygenase (IDO; Wichers & Maes, 2002; Zunszain et al., 2012), which drives the kynurenine pathway (KP; Capuron et al., 2003; Raison et al., 2006). The KP is the major metabolic pathway for the amino acid tryptophan (TRP); increased activation of this pathway increases the degradation of TRP into kynurenine (KYN), leaving less TRP available for other metabolic processes (Chen & Guillemin, 2009). As the synthesis of serotonin is dependent on the availability of TRP (Russo, Kema, Bosker, Haavik, & Korf,

2009) and a deficit of serotonin is implicated in the aetiology of depression (Cryan & Leonard, 2000; Owens & Nemeroff, 1994), KP activation and subsequent TRP depletion is a potential mechanism through which inflammation can contribute to the development of depressive symptoms (Widner, Laich, Sperner-Unterweger, Ledochowski, & Fuchs, 2002). Depression associated with cytokine therapy has been linked to TRP depletion and increased KP activation (Capuron et al., 2002; Maes, Leonard, Myint, Kubera, & Verkerk, 2011; Raison et al., 2010). However, lower levels of TRP have also been observed in the absence of increased KP activation in depressed patients (Hughes et al., 2012). Thus, the role of IDO in mediating the relationship between inflammation and depression symptoms is not clear.

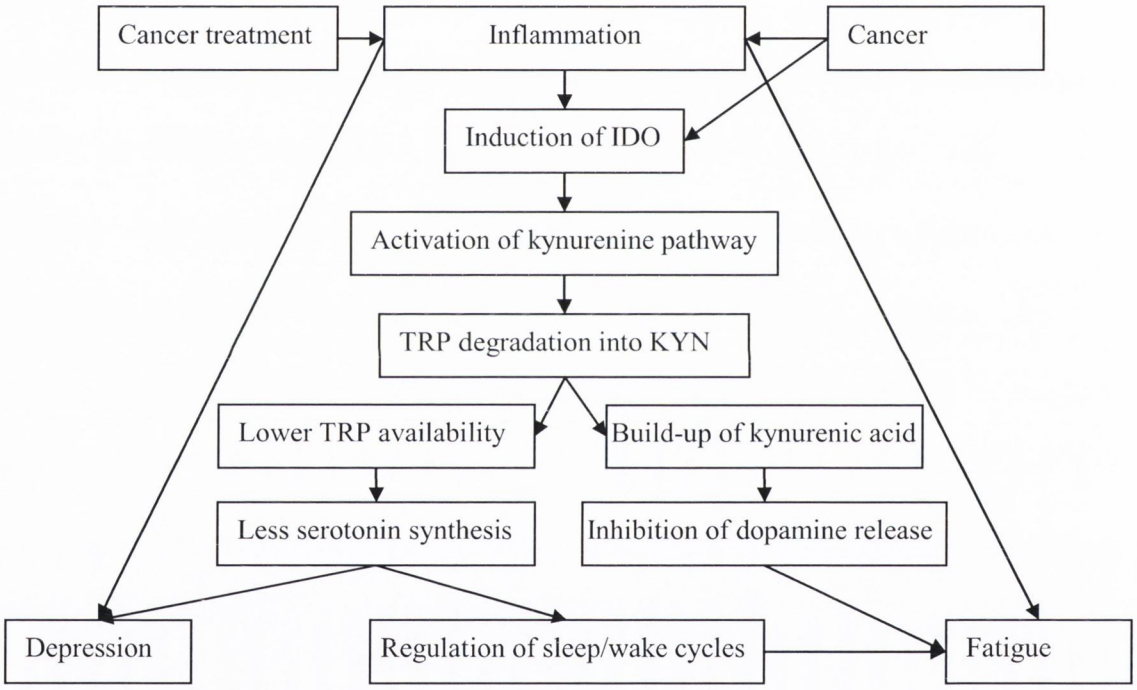

Figure 7.1. Potential mechanisms through which inflammatory cytokines and kynurenine pathway activity might contribute to fatigue and depression in cancer patients.
Note. IDO = indoleamine 2,3-dioxygenase, TRP = tryptophan, KYN = kynurenine.

TRP breakdown may also play a role in CRF. In addition to inflammation, KP activation may be increased in cancer patients because IDO is overexpressed in many cancer cells and is activated by cancer cells as a strategy for immune escape (Muller, DuHadaway, Donover, Sutanto-Ward, & Prendergast, 2005). The ratio of KYN to TRP is indicative of IDO activation, and elevated KYN/TRP ratios as well as lower TRP and

higher KYN concentrations were predictive of increased fatigue in a sample of mixed cancer patients (Schroecksnadel et al., 2007). In addition, more severe fatigue has been linked to lower TRP concentrations and a higher degree of immune activation in advanced lung cancer patients (Kurz et al., 2012). Altered serotonergic neurotransmission has also been implicated in the development of fatigue in a number of chronic illness groups (Meeusen, Watson, Hasegawa, Roelands, & Piacentini, 2006; Swain, 2000). As serotonin is a precursor to melatonin, and serotonin and melatonin regulate the body's sleep wake cycles, such neuroendocrine processes may impact on fatigue in part by influencing sleep regulation (Payne, 2004).

Increased activation of the KP can also influence the functioning of other neurotransmitters associated with fatigue. The production and build-up of kynurenic acid inhibits the release of glutamate and dopamine (Wichers et al., 2005). Dopamine is linked to fatigue through drug trials that support the use of the psychostimulant methylphenidate for the treatment of CRF (Meeusen et al., 2006). Methylphenidate works in a fashion similar to amphetamines; it increases the levels of dopamine in the central nervous system by blocking dopamine breakdown in the synaptic cleft and inhibiting its uptake back into the cell. Furthermore, it stimulates neurotransmitter production, thus making greater levels of dopamine available to bind to active receptors (Minton, Richardson, Sharpe, Hotopf, & Stone, 2011). Therefore, inflammation and alterations in neurendocrine activity may contribute to the development of fatigue in cancer patients in a variety of interconnected ways (see *Figure 7.1*).

Bower and Lamkin (2012) noted that although there is increasing evidence linking inflammation to CRF, longitudinal studies that include the psychological risk factors for fatigue are necessary to examine the relationship between inflammatory activity and fatigue in patients treated for cancer. Furthermore, few studies have investigated links between inflammation and fatigue before cancer treatment and the findings to date have been mixed (e.g., Fagundes et al., 2012; Von Ah et al., 2008). The current study investigated the association between fatigue and inflammatory cytokines and TRP metabolism in breast cancer patients prior to chemotherapy. The hypothesis that greater fatigue severity would be associated with increased inflammation (elevated levels of IFN-γ, IL-1β, IL-6, TNF-α and CRP) and KP activation (lower concentrations of TRP, higher concentrations of KYN, and elevated KYN to TRP ratio) before chemotherapy was tested. In addition, changes in inflammatory markers and TRP metabolism over the course of cancer treatment and after the completion of treatment were explored in a

subset of participants using growth curve modelling, and associations with changes in fatigue were examined. Finally, given the links among inflammatory activity, fatigue and depression, the relationship between depression and cytokines was also investigated. Specifically, as inflammation has been proposed as a common cause of both fatigue and depression in cancer patients, patterns of associations with cytokines and TRP were compared across these symptoms.

7.2 Method

7.2.1 Participants. Participants for this study were drawn from a larger prospective longitudinal study of CRF, previously described in Chapter 4. Ethical approval for the study was obtained from the institutional research ethics committees in both the hospital and the university (see Appendix 2) in which the research was carried out and all participants provided written informed consent. The current report focuses on the questionnaire and immune data from the 61 participants with breast cancer from whom a blood sample was available from before the start of chemotherapy treatment (of a total of 77 breast cancer patients in the larger study). Although no participants declined to give a blood sample as part of the study it was not always possible to obtain a sample, in some cases because of the short time span between referral for chemotherapy and start of treatment and in others because the participants went on to have their treatment in another hospital and therefore did not attend the hospital again between giving consent and starting treatment. Furthermore, it was not possible to obtain samples for all participants at the post-treatment follow-up assessments due to problems with blood draws and scheduling difficulties; for example, blood samples could only be collected during scheduled clinical hospital appointments and hospital appointments were not always scheduled within the study follow-up time, were sometimes changed without notification and/or often took place in another hospital. Thus, changes in inflammatory and KP activity were only investigated in a subsample of participants. There were no significant differences on any demographic, medical or treatment characteristics between participants who gave a blood sample for analysis and those who did not ($p < .05$).

7.2.2 Procedure and measures. Self-report data and blood samples were collected from participants at three assessment points: before the start of chemotherapy treatment (T1), after the completion of cancer treatment (T2; within six weeks of finishing the final treatment of either chemotherapy or radiation therapy; *M* number of days since treatment = 19.53, *SD* = 11.07) and at a follow-up assessment several months post-treatment (T3; *M* number of days since treatment = 157.97, *SD* = 52.45). At each

assessment timepoint, participants met with the researcher in the hospital during a scheduled hospital appointment. They were given a set of questionnaires to complete and a nurse collected the blood sample for immune analysis.

The questionnaires used to collect sociodemographic information and the scales used to assess fatigue (FACT-F; Yellen et al., 1997) and depression (HADS; Zigmond & Snaith, 1983) have been previously described in Chapter 4. Item 8 of the HADS ("I feel as if I am slowed down") was excluded from the measure of depression to minimize symptom overlap with fatigue. The internal reliability of each of the subscales at the three timepoints was good ($\alpha > .75$). Medical data including type of cancer, disease stage, tumour grade, type of treatment (e.g., surgery, radiation therapy, chemotherapy, hormone treatment) and treatment regimen, time since diagnosis and time of treatments, comorbid medical conditions, and height and weight were collected from hospital medical charts.

7.2.3 Blood sampling. Two 5ml blood samples were collected by venipuncture using VACUETTE® Z Serum Sep Clot Activator Serum tubes. Serum was obtained from the whole blood by centrifugation after completion of the coagulation process. Ascertained serum samples were labelled with a unique identifier code and stored in the freezer at -72°C for subsequent batch analysis. All samples were frozen within one and a half hours from collection. Mean time from questionnaire to blood sampling was 3.54 days ($SD = 11.02$).

7.2.4 Inflammatory markers. Serum concentrations of CRP were measured using the validated commercially available enzyme-linked immunosorbent assay (ELISA) Duoset (R&D Systems, UK), according to the manufacture's protocols. Absorbance was read at 450nm using a microplate reader (Sunrise Tecan, Reading, UK) and was then recalculated as a concentration (mg/L) using standard curves derived using GraphPad Prism Software Version 5.00 (GraphPad software, Inc.). The limit of detection for CRP was 5pg/ml. Concentrations of IFN-γ, IL-1β, IL-6, and TNF-α (pg/ml) were determined using the Meso scale discovery (MSD) multi-spot assay system. The plates were analysed using the Sector Imager 2400 and the MSD Discovery workbench software (Meso Scale Diagnostics, Gaitherburg, MD). The lower limits of detection for the kit were 0.4 pg/ml for IFN-γ, 0.5 pg/ml for IL-1β, 0.22 pg/ml for IL-6, and 0.49 pg/ml for TNF-α. All samples were processed in the same batch and run in duplicate; mean assay levels were used in all analyses. Of the 116 samples collected for IFN-γ, IL-1β, IL-6, and TNF-α, concentrations of IL-1β were undetectable in 17 samples (15%) and

therefore no results were reported for this cytokine. Three samples were below the limits of detection of IFN-γ and these were assigned scores of 0. Concentrations of IL-6 and TNF-α were detected in all samples. Concentration of CRP was not detected in 7 samples.

7.2.5 Measurement of tryptophan and kynurenine. Serum concentrations of TRP and KYN were measured by high performance liquid chromatography (HPLC). KYN metabolite concentrations were assessed using the Shimadzu ADVP HPLC system coupled to PDA-UV dector (Shimadzu SPD-M10A VP) set to integrate at 230 and 250nm, while TRP was measured fluorometrically at an excitation wavelength of 254nm and an emission wavelength of 404nm (Shimadzu RF-20A XS prominence). Homogenisation buffer prepared with mobile phase containing 10% perchloric acid to deproteinise the samples, was spiked with 200ng/20µl of N-methyl 5-HT (Sigma Chemicals Co., UK) as internal standard. The mobile phase contained 50nM glacial acetic acid, 100 mM zinc acetate and 3% acetonitrile at pH 4.9. A 1:1 ratio of serum and homogenisation buffer was centrifuged at 12,800 rpm for 20 min at 4°C before being passed through a 0.45µm syringe filter (Antech, Ireland). A 20µl-sample of the resultant filtrate was injected onto a C-18 reverse phase Kinetex core–shell technology column (Phenomenex, UK) for separation of the metabolites. Standards (200ng/20µl) of TRP and KYN were prepared in mobile phase, and standards and samples were run with a continuous flow rate of 0.8ml/min and acquisition time of 18 minutes. Chromatograms were generated using Class VP software and peak heights and retention times of TRP, KYN and internal standard (N - methyl-5-HT) were used to calculate metabolite concentrations expressed as ng/ml of serum. The KYN/TRP ratio was used as an indicator of KP activation.

7.2.6 Analysis. Descriptive statistics were used to describe participants' clinical and demographic characteristics. Pearson correlations were used to examine associations between self-report measures, inflammatory markers and KP activation before chemotherapy. As the distribution of IL-6, IFN-γ, CRP, and KYN were non-normal and skewed, the data were transformed before analysis by calculating the square root of the values for IL-6, and carrying out $\log_{10}$ transformations on the values for IFN-γ, CRP, KYN and the KYN/TRP ratio. Since some participants had values of less than one for IFN-γ, CRP and the KYN/TRP ratio, a value of one was added to all values prior to transformation. As transformation of the data did not sufficiently improve the distribution of CRP or the KYN/TRP ratio, Spearman *rho* (denoted as *rs* in the results)

was used to examine correlations that involved these variables. Hierarchical multiple linear regression was used to investigate whether biological markers were significant predictors of fatigue. Demographic and medical factors that were significantly related to fatigue before chemotherapy (i.e., pain and number of comorbidities; see Chapter 4) as well as depression, were included in step 1 of the multiple regression analyses, and biological predictors were entered in step 2. Biological predictors of depression were also investigated using hierarchical multiple repression, with pain, number of comorbidities and fatigue entered in step 1.

The mixed model procedure in PASW 18 was used to examine changes in fatigue and immune markers over time; multilevel growth models (MLM) were fitted to the data to model linear and quadratic growth trends in fatigue and biomarkers of inflammatory and KP activity, and to explore whether changes in fatigue and depression were related to inflammatory cytokine concentrations and/or KP activation. Time was defined as the occasion of measurement (T1 = 0, T2 = 1 and T3 = 2). MLM does not require a balanced design with an equal number of assessments for each participant (Shek & Ma, 2011). All participants gave blood samples at T1; however, blood samples were available from only 32 participants at T2 and from 23 participants at T3. As the sample sizes were small, and goodness-of-fit statistics for the entire model were not examined, regression coefficients were estimated using restricted maximum-likelihood estimation (Singer & Willett, 2003). In line with recommendations by Singer and Willet (2003), prototypical values representing the extremes in the data were used to demonstrate the effect of predictor variables on initial status and on rate of change across time.

7.3 Results

7.3.1 Participants. Demographic characteristics of participants are reported in Table 7.1. The mean age of participants was 50.15 (*SD* = 9.87). The majority of participants were married or living with a long-term partner and had children. Approximately half of the sample were currently working and 60% had completed at least higher second level education. Just over half of participants suffered from at least one comorbidity. The most common types of comorbidities were hypertension (n = 10), high cholesterol (n = 9), and hypothyroidism (n = 5); all other comorbidities were experienced by less than five participants. The average BMI was 27.27 (*SD* = 5.18), whereby more than half of participants were classed as overweight using the WHO BMI classification system. The majority of participants had lymph nodes positive for cancer at the time of diagnosis and over a third had stage III disease. Two participants had grade 1

tumours, 30 participants had tumours of grade 2, and 29 had grade 3 tumours. Just under a quarter of participants received neo-adjuvant treatment, whereby chemotherapy was followed by surgery and radiation therapy. Only six participants did not receive radiation as part of their treatment and all but five were treated with additional hormonal therapy. Twelve participants were treated with chemotherapy combined with Herceptin, which was continued in three-weekly cycles after the completion of chemotherapy. The most common type of chemotherapy was AC-T.

Table 7.1 *Participants' demographic and clinical characteristics (n = 61)*

Demographic characteristics	n	%	Clinical characteristics	n	%
Marital status			Comorbities		
Married/Partnered	41	67.21%	No comorbidities	28	45.90%
Single	9	14.75%	1 comorbidity	15	24.59%
Separated/Divorced	5	8.20%	2 comorbidity	14	22.95%
Widowed	6	9.84%	≥ 3 comorbidities	4	6.56%
Children			Disease stage		
Has children	47	77.05%	I	11	18.03%
Children living at home	37	60.66%	II	27	44.26%
Employment status			III	23	37.70%
Employed	30	49.18%	Positive lymph nodes present	45	73.77%
Housewife	15	24.59%	Treatments received		
Retired	6	9.84%	Surgery before chemotherapy	47	77.05%
Resigned for health	4	6.56%	Surgery after chemotherapy	14	22.95%
Unemployed	5	8.20%	Radiation Therapy	55	90.16%
Student	1	1.64%	Hormonal treatment	56	91.80%
Highest educational level			Herceptin (Trastuzumab)	12	19.67%
Primary (≤ 8 years)	9	14.75%	Type of surgery		
9 - 11 years	16	26.23%	Wide local Excision (WLE)	17	44.26%
12 - 14 years	19	31.15%	WLE and axillary clearance	16	1.64%
Third level education	12	19.67%	Unilateral Mastectomy	27	27.87%
Postgraduate	5	8.20%	Bilateral Mastectomy	1	26.23%
Menopausal status			Chemotherapy regimen		
Premenopausal	32	52.46%	Doxorubicin, Cyclophosphamide & Paclitaxel (AC-T)	36	59.02%
Perimenopausal	12	19.67%			
Postmenopausal	17	27.87%			
BMI (kg/m2) class[a]			Docetaxel Carboplatin (TC)	20	32.79%
Underweight (< 18.5)	1	1.64%	Doxorubicin & Cyclophosphamide (AC)	4	6.56%
Normal (18.5 - 24.9)	23	37.70%			
Overweight (25 - 29.9)	23	37.70%	Paclitaxel	1	1.64%
Obese (>30)	14	22.95%			

[a]Based on World Health Organisation (WHO) BMI classification.

7.3.2 Relationships among inflammatory biomarkers, kynurenine pathway activity, fatigue and depression before chemotherapy. More severe fatigue was strongly associated with greater depression (r = -.62, n = 61, p < .001) and concentrations of proinflammatory cytokines were related to KP activation. Specifically, higher levels of KYN were significantly associated with greater concentrations of IL-6 (r = .42, n = 61, p < .001), TNF-α (r = .37, n = 61, p < .01) and CRP (rs = .33, n = 54, p < .05), while lower levels of TRP were significantly associated with greater concentrations of TNF-α (r = -.28, n = 61, p < .05). The KYN/TRP ratio was significantly correlated with IL-6 (rs = -.43, n = 61, p < .001), TNF-α (rs = .40, n = 61, p < .01) and CRP (rs = .34, n = 54, p < .05).

7.3.2.1 Correlations between fatigue and circulating inflammatory markers and kynurenine pathway activity. Fatigue was not significantly correlated with IFN-γ (r = .10, n = 61, p > .05), IL-6 (r = -.18, n = 61, p > .05) or TNF-α (r = -.07, n = 61, p > .05) before chemotherapy; however, more severe fatigue was significantly associated with higher levels of CRP (rs = -.36, n = 54, p < .01). No significant correlations were observed between fatigue and KYN (r = -.10, n = 61, p > .05), TRP (r = .07, n = 61, p > .05), or the KYN/TRP ratio (rs = -.02, n = 61, p > .05).

A hierarchical multiple regression analysis was carried out to test whether levels of CRP (using transformed $\log_{10}$ values) could independently predict fatigue severity in a model that included depression and established demographic/medical predictors of fatigue (i.e., pain and number of comorbidities) in step 1. Assumptions regarding normally distributed and independent residuals and multicollinearity were met; however, one residual outlier was excluded from the analysis. In the final model, depression (standardised β = -.51, p < .001), pain (standardised β = -.31, p < .01), number of comorbidities (standardised β = -.08, p > .05) and CRP (standardised β = -.22, p < .05) explained a total of 51% of the variance in fatigue scores (F(4,48) = 14.30, p < .001; ΔR^2 = .05 for step 2, p < .05).

7.3.2.2 Correlations between depression and circulating inflammatory markers and kynurenine pathway activity. Depression was not associated with concentrations of IFN-γ (r = -.13, n = 61, p > .05), IL-6 (r = 0.14, n = 61, p > .05), or TNF-α (r = .02, n = 61, p > .05); however, more severe depression was significantly correlated with higher levels of CRP (rs = .36, n = 54, p > .01). In addition, no significant associations were observed between depression and levels of KYN (r = .03, n = 61, p > .05), TRP (r = -.02, n = 61, p > .05) or the KYN/TRP ratio (rs = -.02, n = 61, p > .05).

CRP was a significant predictor of depression, explaining 11.5% of the variance in a simple linear regression; $F(1,50) = 7.61$, $p < .01$. However, CRP did not make a significant contribution in a hierarchical multiple regression analysis of depression that included fatigue, pain and number of comorbidities in step 1. Four residual outliers were excluded from the analysis. In the final model, fatigue (standardised $\beta = -.45$, $p < .01$), pain (standardised $\beta = -.01$, $p > .05$), number of comorbidities (standardised $\beta = .16$, $p > .05$) and CRP (standardised $\beta = .17$, $p > .05$) explained a total of 29% of the variance in depression scores ($F(3,46) = 5.91$, $p < .001$; $\Delta R^2 = .02$ for step 2, $p > .05$).

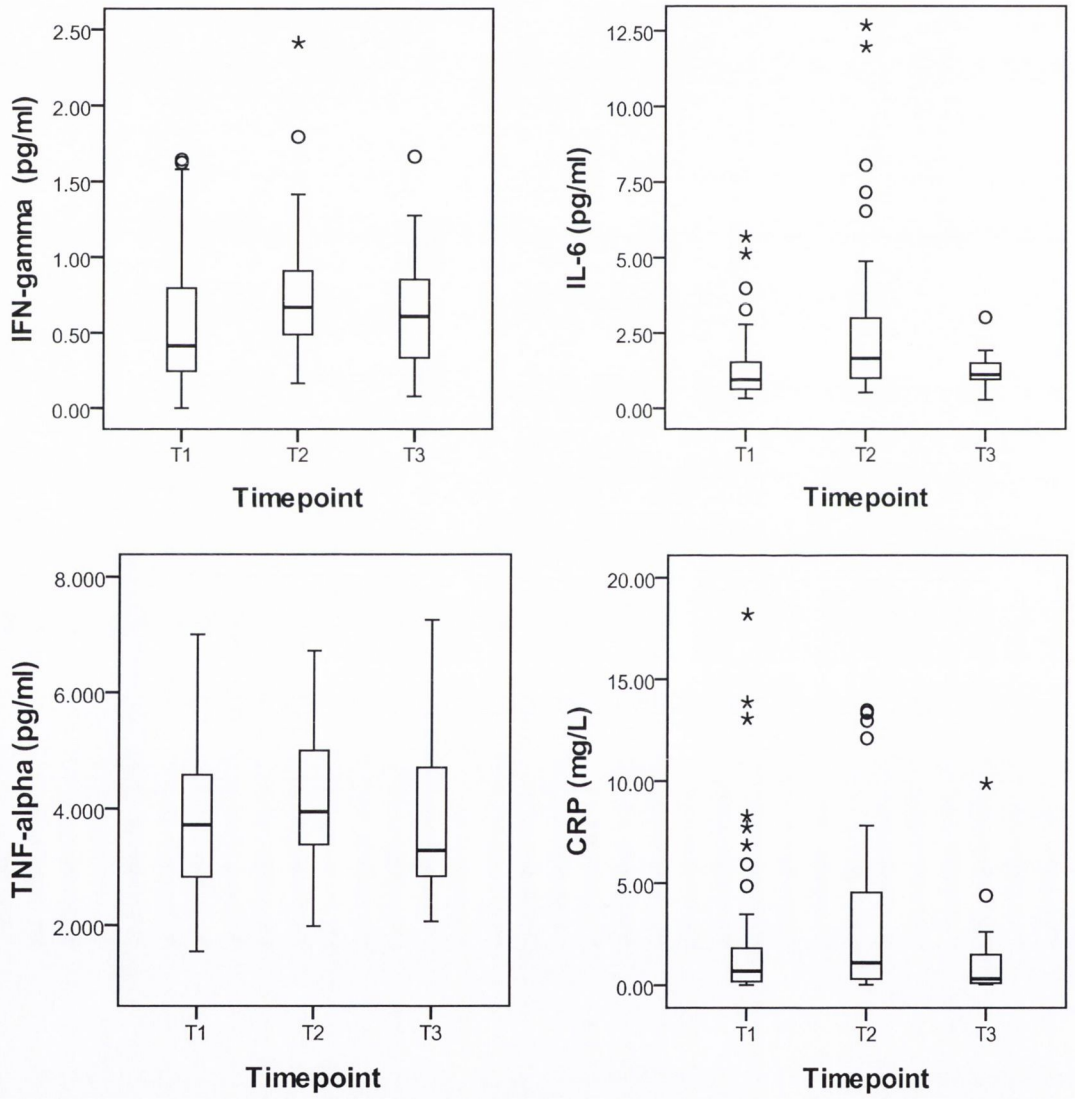

Figure 7.2. Concentrations of circulating inflammatory markers at each timepoint.

Note. Boxes represent data ranging from the 25th to the 75th percentile of the observed distribution of values; horizontal lines represent the median levels of biomarkers; whiskers range from the minimum and maximum observed data values; and outliers are identified by open circles or, in the case of extreme outliers, asterisks.

7.3.3 Changes in fatigue, depression, inflammatory activty and kynurenine pathway activation over time. Multilevel models were used to explore changes in the levels of the inflammatory cytokines, CRP, KYN, TRP, depression and fatigue over the three measurement occasions. Significant linear and quadratic trends were observed for fatigue, depression, and all of the inflammatory markers except CRP over time (see Table 7.2; see *Figure 7.2* for boxplots of the observed concentrations of IFN-γ, IL-6, TNF-α and CRP at each timepoint on the untransformed scales. The results indicate that levels of IFN-γ, IL-6, TNF-α, depression, and fatigue all increased between T1 and T2 and subsequently decreased between T2 and T3. No significant changes were observed in levels of KYN over time but there was a significant linear trend for TRP (see Table 7.2; *Figure 7.3* illustrates boxplots of the observed concentrations of KYN and TRP at each timepoint using the untransformed scales. The results suggest that levels of TRP increased across the three timepoints. Boxplots demonstrating the distribution of the transformed values that were used for these analyses are presented in Appendix 17.

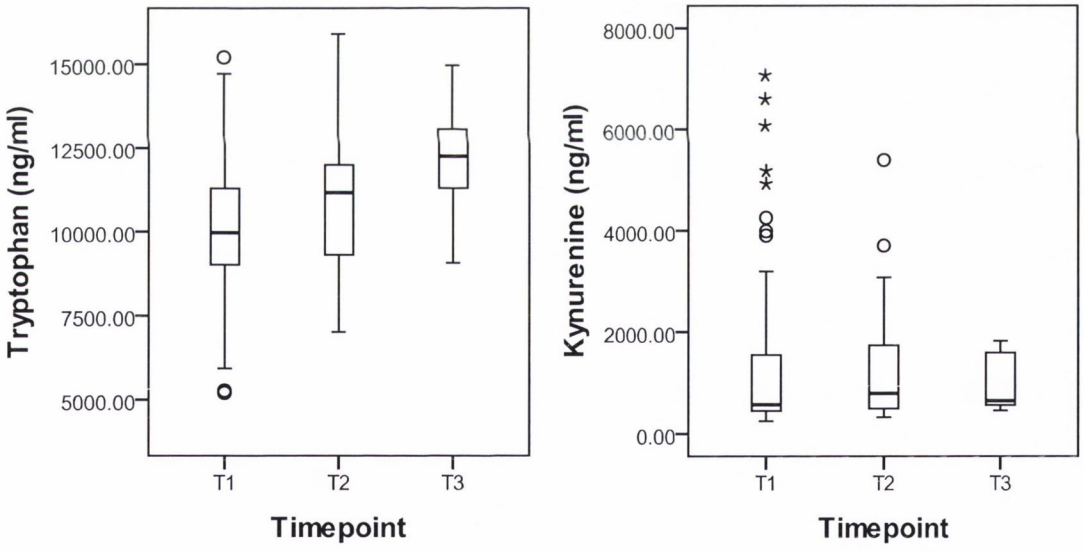

Figure 7.3. Levels of KYN and TRP observed at each timepoint.

Note. Boxes represent data ranging from the 25th to the 75th percentile of the observed distribution of values; horizontal lines represent the median levels of biomarkers; whiskers range from the minimum and maximum observed data values; and outliers are identified by open circles or, in the case of extreme outliers, asterisks.

Table 7.2 *Linear and quadratic trends in fatigue, depression and inflammatory cytokines*

	Linear trend (SE)	Quadratic trend (SE)
Fatigue	-21.48 (3.47)***	10.75 (1.80)***
Depression	3.57 (1.09)**	-1.88 (0.56)**
IFN-γ	0.12 (0.04)**	-0.05 (0.02)*
IL-6	0.94 (0.19)***	-0.46 (0.10)***
TNF-α	0.81 (0. 30)**	-0.38 (0.15)*
CRP	0.20 (0.13)	-0.13 (.0.07)
KYN	0.09 (0.14)	-0.05 (0.07)
TRP	884.30 (206.03)***	-

Note. Higher scores on the FACT-F indicate lower fatigue. *$p < .05$, **$p < .01$, ***$p < .001$.

7.3.4 Associations between inflammatory and kynurenine pathway activity and fatigue over time. MLMs were used to examine the relationship between fatigue and inflammatory markers and KP activity. There was no evidence that levels of IFN-γ, IL-6, TNF-α, CRP, KYN or TRP predicted fatigue severity, nor was there any indication that levels of these markers were associated with changes in fatigue over time (all $p > .05$).

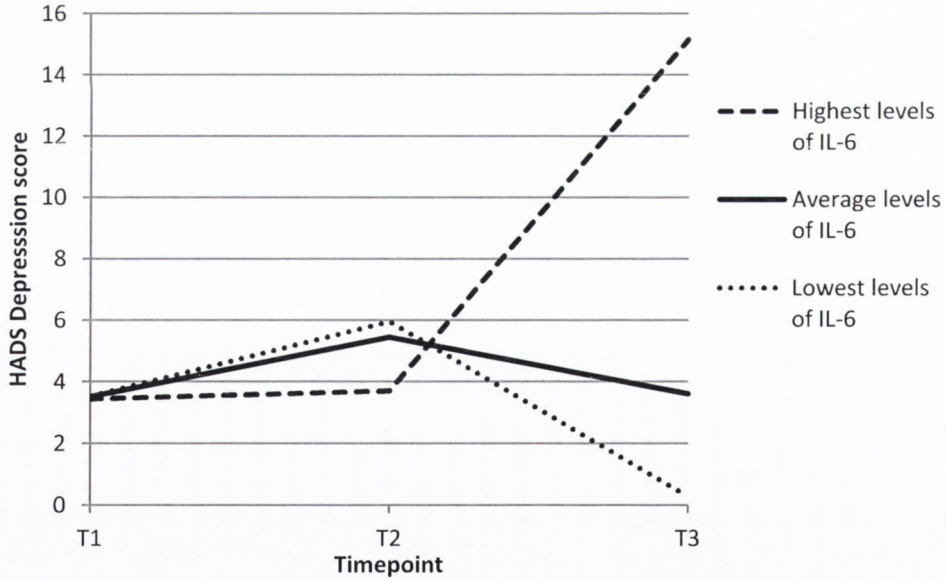

Figure 7.4. Fitted trajectories of depression scores over time for participants with the highest, the average and the lowest observed concentrations of IL-6.

Note. Values represent the square root of IL-6 levels. The low IL-6 level is the minimum concentration (√IL-6 = 0.52), the average level is the mean concentration (√IL-6 = 1.20) and the high IL-6 level is the maximum concentration (√IL-6 = 3.56) of IL-6 observed in the data.

7.3.5 Associations between inflammatory and kynurenine pathway activity and depression over time. There was no evidence that levels of any of the inflammatory markers, KYN or TRP predicted depression (all $p > .05$); however, there was a significant interaction between time and both IL-6 and KYN. Specifically, IL-6 was a significant predictor of quadratic changes in depression ($\beta = 3.17$, $SE = 1.53$, $p < .05$), whereby participants with higher levels of IL-6 showed a faster rate of change in depression after T2. *Figure 7.4* demonstrates different trajectories of depression as a function of IL-6 using prototypical values based on the maximum, minimum and mean concentrations of IL-6 observed in the data. Participants with consistently higher levels of IL-6 showed a sharp increase in depression between T2 and T3, while participants with consistently low levels of IL-6 showed a decrease in depression over the same time period.

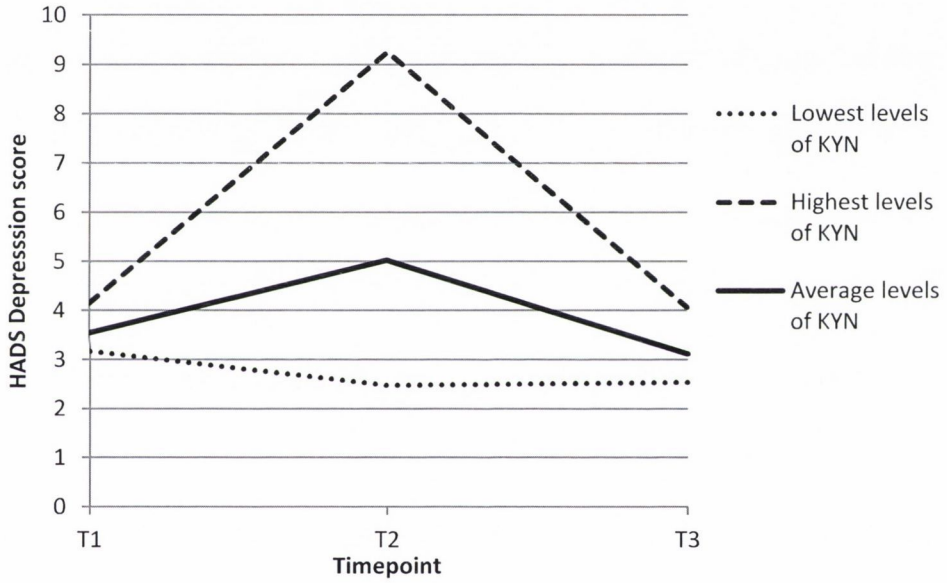

Figure 7.5. Fitted trajectories of the centered depression scores over time for participants with the highest, the average and the lowest observed levels of KYN.

Note. Values represent the $\log_{10}$ KYN levels. The lowest KYN level is the minimum value ($\log_{10}$ KYN = 2.39), the average level is the mean value ($\log_{10}$ KYN = 2.94) and high level is the maximum value ($\log_{10}$ KYN = 3.85) observed in the data.

KYN was a significant predictor of linear change in depression ($\beta = 7.75$, $SE = 3.79$, $p < .05$), whereby participants with higher levels of KYN showed a faster rate of change in depression after T1. *Figure 7.5* demonstrates differences in the trajectory of depression as a function of KYN using prototypical values based on the maximum, minimum and mean observed levels of KYN in the data. While participants with

consistently high levels of KYN showed a sharp increase in depression between T1 and T2, participants with consistently low levels of KYN showed a slight decrease in depression over the same time period.

7.4 Discussion

The findings support the hypothesis that low-grade inflammation plays a role in fatigue before the start of chemotherapy. Higher concentrations of CRP were significantly associated with both fatigue and depression; nevertheless, CRP predicted fatigue severity independently of depression. No significant relationships were observed between either fatigue or depression and levels of IFN-γ, IL-6, or TNF-α. Although evidence of KP activation was observed, and markers of KP activity were correlated with increased immune activation, there was no evidence that increased activation of the KP, or indeed levels of TRP or KYN, played a role in fatigue or depression before chemotherapy. Nevertheless, the findings indicated that levels of KYN pre- to post-cancer treatment and levels of IL-6 after the completion of treatment significantly predicted changes in depression.

7.4.1 Inflammation, the kynurenine pathway and fatigue before chemotherapy.

Physiological theories of CRF suggest that increased inflammatory activity, and associated neuroendocrine changes, contribute to the development of fatigue in cancer patients. The results of the current study provide some support for this idea and suggest that inflammation may contribute to fatigue even before the start of systemic treatment for breast cancer. More severe fatigue was associated with greater concentrations of serum CRP, a downstream marker of inflammation. Furthermore, CRP was a significant independent predictor of fatigue severity in a multivariate model that included depression, pain rating and number of comorbidities. No significant correlations were observed between fatigue and any of the other inflammatory markers examined in this study. Nevertheless, as CRP is an acute phase protein that is produced by hepatocytes upon stimulation by IL-6 (Gabay & Kushner, 1999), it is an indicator of cumulative IL-6 activity (Jager et al., 2008). IL-6 is produced in smaller quantities and is harder to detect in serum than CRP, which is thought to be a more sensitive and reliable indicator of systemic inflammation (Bower et al., 2009; Myers et al., 2004). Thus, the significant association between CRP and fatigue in the current study may also signify that IL-6 plays a role. Indeed, the observed magnitude of the correlation between IL-6 and fatigue, though not significant, is in line with previous research that reported a significant relationship between these factors and is larger than the composite correlation coefficient

between IL-6 and fatigue reported in a review of studies on inflammatory markers and CRF (Schubert et al., 2007). The trends in the data are thus consistent with the idea that increased inflammatory activity could play a role in fatigue before systemic treatment for breast cancer.

A number of previous studies have reported significant relationships between higher levels of CRP and CRF; however, these have largely been based on breast cancer survivors (e.g., Orre et al., 2011; Reinertsen et al., 2010) and have examined persistent CRF rather than levels of fatigue on a continuum (e.g., Alexander, Minton, Andrews, et al., 2009). Few studies have explored inflammatory activity and fatigue before cancer treatment. Meyers et al. (2005) reported that higher levels of IL-6, IL-1 receptor antagonist, and TNF-α levels were related to ratings of fatigue in patients with acute myelogenous leukemia and myelodysplastic syndrome before chemotherapy. CRP was not assessed in this study, but the finding that IL-6 was related to fatigue is consistent with the current results. Associations between higher levels of IL-6 and greater vegetative symptoms of depression (including fatigue) have also been found in pre-surgery ovarian cancer patients with advanced disease (Lutgendorf et al., 2008). Fagundas et al. (2012) found no evidence of an association between CRP and fatigue in breast cancer patients who were newly diagnosed or awaiting a positive diagnostic result; however, the relationships between fatigue and other inflammatory markers were not assessed in this study. Elevated levels of CRP have also been associated with increased fatigue severity in patients undergoing cancer treatment (Kurz et al., 2012; Schroecksnadel et al., 2007). Furthermore, findings from these two studies supported the idea that inflammatory activity impacts on fatigue by influencing the activity of the KP.

There was no evidence in the current study that fatigue was associated with increased activation of the KP; no correlation was observed between fatigue severity and levels of KYN, TRP or the KYN/TRP ratio. It is possible that such relationships did not emerge because most participants did not experience inflammatory activity above the normal clinical range (above 6 mg/L). The median concentration of CRP in the current study was 0.7 mg/L (M = 2.1 mg/L, SD = 3.7), which is in line with the median concentrations (0.8 mg/L) found in healthy young adults (Pepys & Hirschfield, 2003). During inflammation CRP can rise to more than 500mg/L; however, in the current study, the highest CRP concentration at T1 was 18.2 mg/L and only 6 participants had values about 6 ml/L. Both the studies by Kurz et al. (2012) and Schroecksnadel (2007), which support a role for TPR degradation in the aetiology of CRF, included patients with

advanced disease and collected data during the active treatment phase, when inflammatory activity may be more pronounced. Indeed, Kurz et al. reported elevated concentrations of CRP compared to reference ranges and concentrations in both studies were substantially higher than in the current study. As heightened inflammatory activity is thought to lead to KP activation via the induction of IDO, it is possible that TRP and KYN play a greater role later in the cancer trajectory after sustained inflammation and/or in response to above normal inflammatory activity. Research suggests that low-grade inflammatory activity may not be sufficient to elicit the KP or the behavioural responses that have been observed in patients treated with cytokine therapies (Hughes et al., 2012). Nevertheless, increased inflammation was related to KP activation in the current study. Concentrations of inflammatory markers were significantly associated with decreased levels of TRP, increased levels of KYN, and an elevated KYN/TRP ratio, thus supporting the connection between these physiological processes.

7.4.2 Changes in inflammation, kynurenine pathway activity and fatigue over time. The findings indicated that levels of fatigue and cytokine concentrations increased from pre- to post-treatment assessments and subsequently decreased again. These results are in line with the idea that cancer treatment can induce inflammatory activity and suggest that fatigue and inflammatory cytokines follow similar patterns over time. Nevertheless, there was no evidence that increases in inflammation were significantly related to changes in fatigue. Furthermore, no significant changes in levels of CRP or KYN were observed over the assessment timepoints, and there was no indication that changes in these markers were linked to increases in fatigue over time. Few longitudinal studies have examined associations between proposed physiological contributing factors and CRF. Bower et al (2009) reported that changes in serum markers of CRP and IL-1 receptor antagonist were positively associated with increases in fatigue symptoms in breast and prostate cancer patients undergoing radiation therapy. However, these findings were only based on a subsample of 22 participants and thus require replication. Reinertsen et al. (2010) reported that increased CRP levels in long-term breast cancer survivors were associated with chronic fatigue but not persistent fatigue across two assessment points 2.5-3 years apart. Nevertheless, changes in CRP levels were not examined in this study.

7.4.3 Evidence for common physiological mechanisms for depression and fatigue. The pattern of results was similar across depression and fatigue; both were significantly correlated with higher CRP, and the magnitude of the nonsignificant

correlation coefficients with the other biomarkers for inflammation and KP activation did not vary hugely between these symptoms. These findings are thus in line with the idea that common physiological mechanisms underlie both depression and fatigue; however, given the strong relationship between fatigue and depression, one could argue that the positive association between CRP and fatigue was simply due to depression. Of note, CRP predicted fatigue independently of depression; whereas CRP was not a significant predictor of depression in a multivariate model that included fatigue. Thus the data do not support the idea that depression accounted for the significant relationship between fatigue and CRP. Similar findings have been reported in a study of breast cancer survivors (Orre et al., 2011).

Although inflammation was also implicated in the experience of depressive symptoms in the current study, the results suggest that fatigue may account for this relationship. As the link between inflammatory activity and KP activation is more established in the literature for depression than fatigue, it is somewhat surprising that stronger relationships did not emerge for depression. It is possible that the measurement of depression in the current study, which consisted of a non-somatic scale of depression from which items similar to fatigue were excluded, impacted on the strength of the observed relationships. Furthermore, stronger relationships may not have emerged because both inflammation and overall depressive mood disturbance were low at the pre-chemotherapy assessment point (57% of the sample had a score of 3 or below on the HADS).

7.4.4 Relationships between inflammation, kynurenine activity and depression over time. Although there was no evidence that depression was related to levels of cytokines, KYN or TRP, the findings indicated that changes in these factors may impact on changes in depression. Significant interactions were observed between time and both IL-6 and KYN in multilevel growth models of depression over the assessment timepoints. The results suggest that changes in depression after treatment are associated with levels of IL-6, whereby higher levels of IL-6 were linked to increases in depression post-treatment, while decreases in depression were linked to lower levels of IL-6 over the same time period. Such findings support the inflammatory explanatory model of depression (Maes, 2008; Raison et al., 2006). Furthermore, they are in line with the cognitive-behavioural model of CRF, which suggests that interrelations between psychological and physiological factors could contribute to the persistence of CRF by helping to maintain one another. Although research supports the idea that inflammation

precedes depression, there are plausible mechanisms for bidirectional relationships between these factors (Gimeno et al., 2009). Larger samples and more frequent follow-up assessments are required to test the nature of the relationships between these variables in the context of CRF. Nevertheless, the results of the current study are in line the idea that depression and inflammation are interrelated, and that such factors are also linked to fatigue, thus supporting the multifactorial explanatory framework of CRF outlined in the cognitive-behavioural model.

Levels of KYN were also significantly associated with changes in depression. The findings indicated that participants with higher levels of KYN showed a greater increase in depression between the pre- and post-treatment assessments, while participants with lower levels of KYN showed a less pronounced increase, or even a slight decrease, in depression over the same time period. These trends support the idea that increased KP activation, and hence greater TRP degradation into KYN, can lead to depressive symptoms (Maes et al., 2011; Widner et al., 2002). Nevertheless, no corresponding relationship between decreases in TRP and increases in depression was found. Previous studies have also reported associations between cytokine-stimulated KYN in the absence of TRP depletion (Raison et al., 2010) and findings from animal studies suggest that peripheral administration of KYN alone can lead to depressive-like symptoms (O'Connor et al., 2009). Thus, the behavioural changes connected to increased IDO activation may not be dependent on TRP depletion (Raison et al., 2010).

7.4.5 Limitations. Although the sample size at T1 was moderate, blood samples were only available for a small number of participants at the follow-up timepoints. Previous studies on inflammation and CRF have been carried out on similarly small samples (e.g., Bower et al., 2009; Cameron et al., 2012; Von Ah et al., 2008); nevertheless, the sample size means that the results from longitudinal analyses should be interpreted with caution. In addition, considering the number of tests that were carried out without adopting a more stringent *p*-value, it is possible that the significant relationships observed were due to a Type I error. The findings thus require replication in larger samples.

Although blood samples were generally taken mid-morning in the hospital, there was some variation in the time of day that samples were collected. However, as CRP is not responsive to diurnal rhythm and is unaffected by eating prior to collection (Myers et al., 2004; Pepys & Hirschfield, 2003), it is unlikely that the results were affected by such factors. The time gap between assessment of fatigue and blood sampling also varied

somewhat between participants and this could have reduced the opportunity to detect associations between fatigue and IFN-γ, IL-6, and TNF-α, as these proinflammatory markers are more unstable than CRP levels (Myers et al., 2004; Schubert et al., 2007). However, no significant associations were found between the biological markers and number of days between self-reports and blood sampling; furthermore, controlling for this variable in the analyses had no impact on any of the results (data not shown). Finally, medication effects on the physiological variables were not investigated or controlled for.

7.4.6 Conclusion. Concentration of serum CRP was independently associated with levels of fatigue severity in breast cancer patients before the initiation of chemotherapy. This finding provides some support for the idea that low-grade inflammation plays a role in the development of CRF. In addition, the results indicated that levels of IL-6 and KYN predicted the trajectory of depression, and strong associations between fatigue and depression were observed. These findings are thus in line with the cognitive-behavioural model of CRF, which suggests that physiological responses to cancer and cancer-treatment play a role in the pathogenesis of fatigue and that interrelationships between psychological and physiological factors related to fatigue may help to maintain symptoms post-treatment. Based on the current findings, there was no evidence that activation of the KP plays a role in fatigue before commencement of chemotherapy, nor was there any indication that changes in markers of KP activity or inflammation over the treatment trajectory are linked to changes in fatigue.

Chapter 8: Post-Treatment Cancer-Related Fatigue and Diurnal Cortisol Patterns

"Fatigue isn't something that comes and goes from week to week. Its more of a contunual post treatment condition that has to be handled hour by hour and day by day." – Linda

8.1 Introduction

Prolonged inflammatory processes are thought to contribute to persistent fatigue in cancer survivors (Bower & Lamkin, 2012; Schubert et al., 2007); however, the mechanisms underlying ongoing inflammatory activity are not clear (Bower, Ganz, Dickerson, et al., 2005). One potential mechanism for enhanced inflammatory cytokine activity in fatigued cancer survivors is through alterations in immune regulatory processes and, in particular, through dysregulation of hypothalamic-pituitary-adrenal (HPA) axis function, including altered diurnal cortisol secretion and decreased cortisol response to stress (Bower, 2007; Miller et al., 2008).

The hypothalamus and the pituitary gland, along with the adrenal glands, constitute the primary neuroendocrine axis responsible for maintaining homeostasis in the body by regulating major physiological processes including metabolism, reproduction, development and growth, and responding to physiologic or psychological challenges (Payne, 2004). The HPA axis is activated by stress and mediates the body's stress response by releasing hormones that stimulate the secretion of glucocorticoids including cortisol (Wu et al., 2012). Such HPA activation is adaptive and helps to protect and restore the body. However, when stress is chronic, the functioning of the HPA axis can become altered and the ensuing dysregulation of the stress response can lead to abnormalities in HPA regulated circadian rhythms. Circadian rhythms are endogenous physiological patterns that run on approximately 24-hour cycles and include rhythms of hormonal secretion, sleep-wake cycles and activity patterns (Payne, 2004). Desynchonisation of such rhythms can result in sleep disruptions, concentration problems, depressive symptoms, and irritability, all of which may influence fatigue (Payne, 2004). Aberrations in HPA functioning, such as glucocorticoid deficiencies and insufficient glucocorticoid signalling, have been reported in patients with chronic fatigue syndrome (CFS) and fibromyalgia (Demitrack et al., 1991; Raison & Miller, 2003), the onset of which have been linked to emotional and physical stressors (Demitrack, 1997). As glucocorticoids are potent anti-inflammatory hormones that act to suppress the production and activity of proinflammatory cytokines during stress exposure and restore homeostasis after stress, hypocortisolism and decreased glucocorticoid signalling may

contribute to persistent inflammatory activity in such patient groups (Raison & Miller, 2003).

The stress associated with cancer diagnosis, physiological and psychological adjustment to cancer and its treatments, and disruptions to social and occupational functioning as a result of cancer may lead to similar alterations in the circadian function of the HPA axis in cancer patients (Wu et al., 2012). For example, Dedert et al. (2012) reported that maladaptive psychological responses to breast cancer diagnosis were related to disrupted rest/activity rhythms and patients with disrupted rest/activity cycles also had disrupted cortisol rhythms. Furthermore, cancer treatments may also directly or indirectly result in changes to the neuroendocrine system that could contribute to alterations in HPA functioning (Wu et al., 2012). Research on breast cancer survivors has found that women with persistent fatigue had significantly lower levels of morning serum cortisol (Bower et al., 2002) and a blunted cortisol response in response to a stressor when compared to women without persistent fatigue (Bower, Ganz, & Aziz, 2005). Furthermore, blunted cortisol responses were significantly associated with increased intracellular production of the inflammatory cytokine interleukin-6 (IL-6) following stimulation with lipopolysaccharide (LPS), suggesting that CRF is associated with a functional alteration in innate immune responses (Bower et al., 2007). Thus, there may be a similar pathophysiology underlying the fatigue experienced by cancer patients and patients with CFS (Wu et al., 2012).

Research by Bower et al.'s group, using salivary measures of cortisol, also suggests that there are disruptions in the circadian patterns of cortisol secretion in fatigued cancer survivors. Cortisol has an established diurnal rhythm in healthy adults, which peaks following awakening and then decreases over the course of the day (Edwards, Clow, Evans, & Hucklebridge, 2001). The rate of decline is thought to be an important indicator of HPA functioning. Saliva provides a more feasible and practical approach to collecting multiple samples for cortisol measurement than blood, and research indicates that salivary cortisol is an accurate index of free plasma cortisol (Kirschbaum & Hellhammer, 1994). A significantly flatter cortisol slope has been observed in breast cancer survivors with persistent fatigue than non-fatigued survivors (Bower, Ganz, Dickerson, et al., 2005), whereby those with persistent fatigue had a slower rate of decline in the evening hours. Studies that have used actigraphy to investigate the circadian rhythms of cancer patients have also reported associations between fatigue and disruptions in sleep/activity patterns (Roscoe et al., 2002), which are

thought to be indicative of circadian dysregulation and have also been associated with the incidence, progression and prognosis of cancer (Wu et al., 2012). Furthermore, significant associations have been found between actigraphy-measured circadian activity patterns, high serum levels of inflammatory cytokines, performance status, and dampened cortisol rhythms in patients with advanced cancer (Rich et al., 2005). Such findings thus also support the idea that dysregulation in HPA functioning plays a role in the aetiology of CRF by promoting inflammatory responses. Nevertheless, few studies to date have investigated cortisol patterns in cancer survivors and the role of HPA dysregulation in post-treatment CRF is still not clear.

The current study sought to build on previous work by assessing diurnal cortisol rhythms and the awakening cortisol response (ACR) in cancer survivors and examining whether there is any evidence that alterations in cortisol patterns are associated with greater fatigue. No previous studies have explicitly investigated the ACR and its association with CRF. The ACR refers to the sharp increase in cortisol release that is stimulated by awakening (Fries, Dettenborn, & Kirschbaum, 2009). Research suggests that cortisol levels rise by approximately 50-75% within the first 20-30 minutes of wakening (Pruessner et al., 1997; Schmidt-Reinwald et al., 1999). This increase is distinct from the diurnal variation in HPA axis activity (Wilhelm, Born, Kudielka, Schlotz, & Wust, 2007) and furthermore, is independent of time of awakening, sleep duration and sleep quality (Pruessner et al., 1997). The ACR is thus thought to be a useful indicator of dysregualtion in the HPA axis (Pruessner et al., 1997; Schmidt-Reinwald et al., 1999; Wüst, Federenko, Hellhammer, & Kirschbaum, 2000), and may be used to reveal subtle changes in HPA (re)activity due to prolonged psychosocial stress or clinical symptoms influenced by the HPA axis (Schmidt-Reinwald et al., 1999). It was hypothesised that greater fatigue would be associated with lower levels of morning salivary cortisol, a less pronounced ACR, and a flatter diurnal cortisol slope, indicating a disturbance in HPA axis functioning.

8.2 Method

8.2.1 Participants and design. Participants were drawn from a larger prospective longitudinal study of CRF (previously described in Chapter 4), in which recently diagnosed cancer patients referred for chemotherapy were recruited through outpatient oncology clinics in a large Dublin Hospital. Ethical approval for the study was obtained from the institutional research ethics committees in both the hospital and the

university (see Appendix 2) in which the research was carried out. All participants provided written informed consent.

The current report focuses on a subsample of participants from the larger study who were asked to provide saliva samples for assessing diurnal cortisol at a follow-up assessment several months after the completion of cancer treatment. All participants (n = 74) who were asked to provide saliva samples as part of the study agreed to do so. However, only 68 provided analysable data (three did not return saliva samples and three did not provide sufficient saliva for assessment purposes).

8.2.2 Measures. The measures and procedures used to collect sociodemographic information (age, gender, menopausal status, marital status, number of children, employment status, and educational level) and assess fatigue (FACT-F; Yellen et al., 1997), and possible confounders of circadian rhythms and cortisol patterns included in the analyses (i.e., depression, stress, pain, and sleep disturbance), have been previously described in Chapter 4. The internal reliability of each subscale was good (α = .74). Medical data including type of cancer, disease stage, type of treatment (e.g., surgery, radiation therapy, chemotherapy, Herceptin and hormonal treatment) and treatment regimen, time since diagnosis and time of treatments, comorbid medical conditions, and height and weight were collected from hospital medical charts.

8.2.3 Saliva collection procedure. Participants were posted a saliva collection kit that contained written instructions (with illustrative pictures) for saliva collection (see Appendix 18), a saliva collection log for noting times of collection and times since wakening (see Appendix 19), five labelled SARSTEDT Salivette® collection tubes (including one spare tube), and packaging and a padded stamped addressed envelope for returning the samples. Participants were instructed to collect saliva four times over the course of a day (upon wakening, 15 minutes after wakening, 45 minutes after wakening, and at 5pm) so that ACR and circadian cortisol patterns could be assessed. Participants were asked not to eat or drink for one hour before saliva collection and to store their samples in the refrigerator until all samples had been collected. When saliva samples were returned by post they were stored in a freezer at -20°C until analysis. Research suggests that collecting samples outside the laboratory and then returning them by mail is feasible, and that short-term delays in freezing and/or analysing samples do not adversely affect cortisol concentrations (Clements & Parker, 1998; Garde & Hansen, 2005). Previous studies have indicated that saliva samples are stable at room temperature for at least 7 days with no changes in cortisol values (Bower, Ganz, Dickerson, et al., 2005);

however, others have noted that saliva can be stored at room temperature for at least 4 weeks without significant reductions in cortisol concentrations (Kirschbaum & Hellhammer, 2000). In the current study most samples were received within 7 days of collection (M = 4.52, SD = 2.26); however, eight samples were returned and frozen between 8 and 18 days after collection.

8.2.4 Cortisol measurement. For saliva sample preparation, swabs were centrifuged in the Salivette collection tubes at 2000rpm for 10mins, and resulting saliva samples were diluted at a ratio of 1:2 with standard diluent. Cortisol levels were assessed by enzyme-linked immunosorbent assay (ELISA) kits (Enzo Life Sciences, Exeter, United Kingdom) according to the manufacturer's instructions. This assay has a sensitively of 56.72 pg/ml (range 156 - 10,000 pg/ml; 0.156nmol/l). All samples from a participant were analysed in the same assay to minimize variation. Absorbance measurements were read at 405nm using a microplate reader (Sunrise Tecan, Reading, UK). Final concentrations of cortisol (in pg/ml) were determined using spline analysis in Graph Pad Prism Software Version 5 (Graphpad Software Inc), and then converted to nanomoles/L (nmol/L) for analysis.

8.2.5 Analysis. As raw cortisol values are typically skewed (Bower, Ganz, Dickerson, et al., 2005), the data were transformed using $\log_{10}$. The correlation between fatigue and wakening levels of salivary cortisol were examined with Pearson product moment correlations. Analyses (Pearson correlations and t tests) was first conducted to identify whether there were significant associations between wakening cortisol levels and any potential confounding variables (e.g., time since wakening, actual time of collection, age, depression, stress, pain, sleep disturbance, cancer treatments received, and time since treatment) so that variables that were significantly related to cortisol levels could be controlled using partial correlations.

The mixed model procedure in PASW 18 was used to examine the ACR; multilevel growth models (MLM) were fitted using the first three cortisol measurements (approximately at time of wakening, and 15 and 45 minutes after wakening) to model linear and quadratic growth trends in cortisol. As participants were asked to note the exact number of minutes since wakening for each sample collected, this was used as the time variable in the analysis. In line with recommendations (Clow, Thorn, Evans, & Hucklebridge, 2004), the effect of actual time of awakening was controlled in the analysis. Furthermore, the effects of other potential confounding variables (as above) were also examined to assess whether they had a significant impact on the observed

cortisol slope. The impact of fatigue on the cortisol trajectory was then investigated by adding this variable as a between-individual (level 2) predictor of both the intercept and time coefficients. Regression coefficients were estimated using restricted maximum likelihood estimation.

The same procedures were followed to examine the diurnal cortisol rhythm using all four measures of cortisol. Time was expressed in hours for this analysis. In line with recommendations by Singer and Willet (2003) prototypical values representing the extremes in the data were used to demonstrate the effect of the predictor variable on initial status and on rate of change across time.

8.3 Results

Table 8.1 *Participants' demographic and clinical characteristics (n = 68)*

Demographic characteristics	n	%	Clinical characteristics	n	%
Gender			Cancer Type		
Male	5	7.40%	Breast Cancer	56	82.40%
Female	63	92.60%	Colorectal Cancer	8	11.80%
Menopausal status			Endometrial Cancer	2	2.90%
Premenopausal	34	54.00%	Lymphoma	1	1.50%
Perimenopausal	9	14.30%	Cervical Cancer	1	1.50%
Postmenopausal	20	31.70%	Disease stage		
Marital status			I	14	20.60%
Married/Partnered	44	64.70%	II	29	42.65%
Single	15	22.10%	III	25	36.76%
Separated/Divorced	4	5.90%	Positive lymph nodes present	44	64.70%
Widowed	5	7.40%	Treatments received		
Children			Surgery	66	97.06%
Has children	52	76.50%	Radiation Therapy	52	76.50%
Children living at home	42	62.00%	Hormonal treatment	51	75.00%
Employment status			Herceptin (Trastuzumab)	13	19.10%
Employed	38	56.00%	Comorbities		
Housewife	11	16.20%	No comorbidities	35	51.50%
Retired	10	14.70%	1 comorbidity	16	23.50%
Resigned for health	2	2.90%	2 comorbidity	11	16.20%
Unemployed	5	7.30%	≥ 3 comorbidities	6	8.80%
Student	2	2.90%	BMI (kg/m2) class[a]		
Highest educational level			Underweight (< 18.5)	0	0%
Primary (≤ 8 years)	8	11.80%	Normal (18.5 - 24.9)	29	42.60%
9 - 11 years	11	16.20%	Overweight (25 - 29.9)	25	36.80%
12 - 14 years	24	35.30%	Obese (>30)	14	20.60%
Third level education	18	26.50%			
Postgraduate	7	10.30%			

[a]Based on World Health Organisation (WHO) BMI classification.

8.3.1 Participants. Demographic characteristics of participants are reported in Table 8.1. The mean age of participants was 50.28 (*SD* = 11.66). The majority of participants were married or living with a long-term partner and had children. Over half of the sample was currently working and nearly three-quarters of participants had completed at least higher second level education. Approximately half of participants suffered from at least one comorbidity. The most common types of comorbidities were hypertension (n = 7), high cholesterol (n = 7), asthma (n = 5), osteoarthritis (n = 5) and hypothyroidism (n = 5); all other comorbidities were experienced by less than five participants. The average BMI was 26.58 (*SD* = 4.54), whereby more than half of participants were classed as overweight using the WHO BMI classification system. The majority of participants had lymph nodes positive for cancer at the time of diagnosis and over a third had stage III disease. All participants were treated with chemotherapy and all but two also had surgical treatment. Over three-quarters of the sample received radiation and hormonal adjuvant treatments and 13 participants also had treatment with Herceptin.

8.3.2 Fatigue and morning cortisol levels. No significant associations were observed between awakening cortisol level and any of the potential confounding variables identified ($p > .05$). There was also no evidence that fatigue severity was correlated with wakening cortisol levels ($r = .03$, $p > .05$).

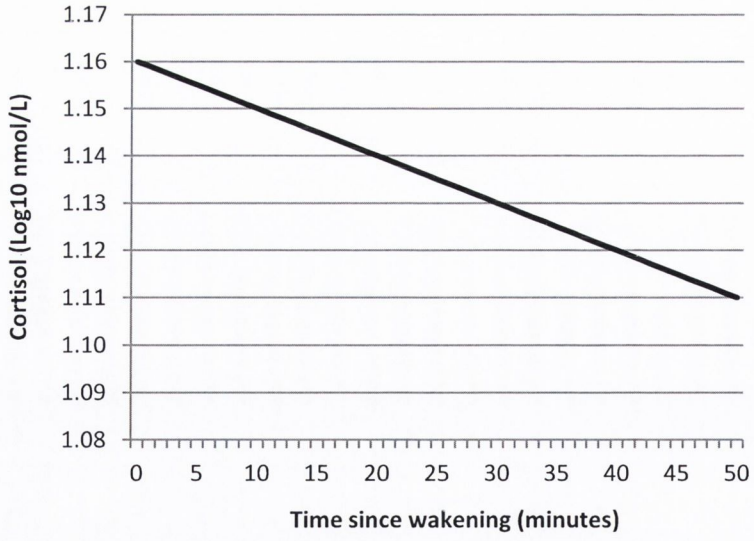

Figure 8.1. Fitted trajectory of the awakening cortisol response based on the first three cortisol measurements.

Note. As participants deviated from the specified collection times, and the actual self-reported minutes since wakening were used in the analysis, the time trend is presented on a continuum.

8.3.3 Fatigue and the ACR. A significant negative linear pattern was observed in cortisol levels over the awakening measurements (β = -0.06, *SE* = .03, $p < .05$). Actual time of awakening did not make a significant contribution to the model ($p > .05$). Thus, the findings indicated that cortisol levels decreased over the course of the first 45 minutes after wakening (see *Figure 8.1*). Potential demographic, medical, and psychological confounding factors and fatigue did not significantly predict cortisol levels or changes in the trajectory of cortisol over time ($p > .05$).

8.3.4 Fatigue and diurnal cortisol rhythm. A significant negative linear trend was observed for cortisol over time (β = -0.034, *SE* = .003, $p < .001$), suggesting that cortisol decreased over the course of the day. Additional analyses were conducted to control for demographic and medical factors, pain, depressed mood, sleep disturbance and stress; however, none of these factors influenced the trend observed in cortisol over the four measurement occasions. Fatigue was also not a significant predictor of linear changes in cortisol ($p > .05$). However, the observed trends were in line with the hypothesis that participants with higher levels of fatigue had flatter cortisol slopes (see *Figure 8.2*).

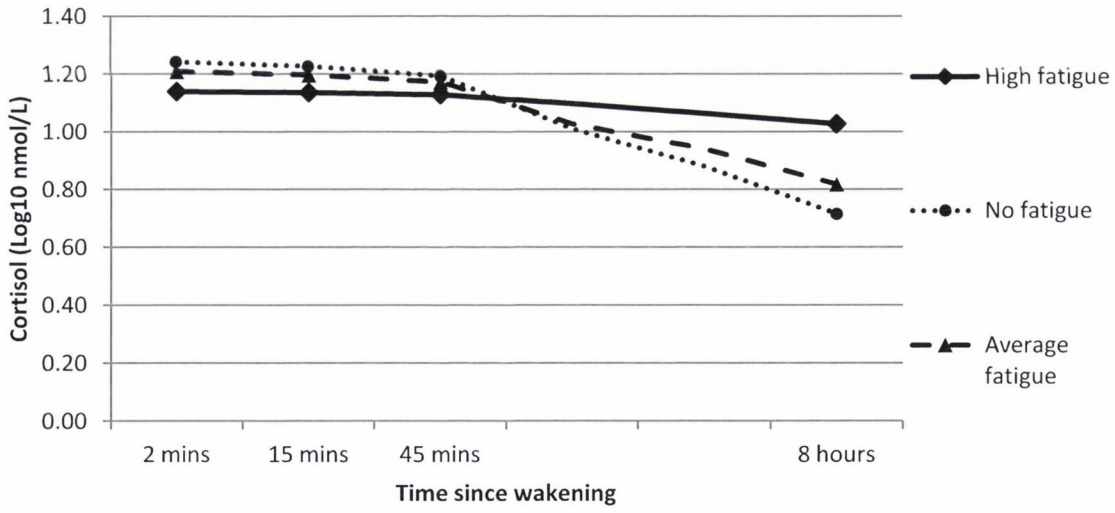

Figure 8.2. Fitted trajectories of the cortisol values ($\log_{10}$ nmol/L) over the four measurement times using prototypical values of no fatigue (FACT-F score = 52), high fatigue (FACT-F score = 0) and average fatigue (FACT-F = 35).

Note. The graph presents the approximate time at which samples were given (2, 15 and 45 minutes after wakening and 8 hours after wakening to represent the 5pm sample) to aid interpretation; however, the actual self-reported time since wakening (in hours) was used as the measure of time in the analysis.

8.4 Discussion

The findings did not support the hypothesis that greater fatigue is associated with lower levels of morning salivary cortisol. In addition, contrary to expectations, fatigue severity was not significantly associated with a flatter diurnal cortisol slope. Although no ACR was observed in the data, there was no indication that fatigue impacted on the pattern of cortisol during the initial period after wakening. Thus, based on the current results, there was no evidence that fatigue was linked to a disturbance in HPA axis functioning in this sample of post-treatment cancer patients.

8.4.1 Morning cortisol levels. The finding that fatigue was not associated with lower morning cortisol levels contrasts the results reported by Bower et al. (2002) and research on fatigue in other illness groups, such as CFS (Cleare et al., 1995; Jerjes et al., 2006). However, a second study by Bower, Ganz, Dickerson et al. (2005) also found no significant differences in morning cortisol levels between fatigued and nonfatigued breast cancer survivors. As Bower et al. (2002) measured cortisol in serum samples that were collected in the same two hour timeframe for all participants, and both the current study and the study by Bower, Ganz, Dickerson et al. (2005) measured salivary cortisol collected upon wakening, differences in the timing and method of collection may explain differences in the results. For example, wakening times varied greatly between participants in the current study (e.g., 4.30am to 12.30pm) and this may have impacted on the initial awakening cortisol values obtained. Nevertheless, even when time since wakening and actual time of collection were controlled in the analyses, there was no indication that cortisol levels were linked to fatigue.

It is possible that other methodological differences impacted on the observed results. Both studies by Bower's group were based on participants with enduring and severe fatigue after cancer treatment, and cortisol levels were compared to cancer survivors with no fatigue. As the current study investigated fatigue on a continuum based on one assessment, the design may not have accurately differentiated between participants with severe CRF and those who had transient fatigue on the day of assessment. Nevertheless, even when participants were categorised according to whether or not they had experienced significant fatigue for at least the previous two weeks, and when they were categorised as having either ongoing or transient fatigue based on whether they also had significant fatigue at the previous assessment point from the larger longitudinal study, there was no evidence of differences in cortisol levels between groups

(results not presented). Furthermore, as the size of the correlation coefficient was close to zero, the lack of a significant association cannot be attributed to the sample size.

8.4.2 Awakening cortisol response. There was no evidence of an ACR in the current study. The ACR refers to a sharp increase in cortisol levels in the period immediately after awakening; however, in the current study cortisol levels decreased over the three awakening measurements. Furthermore, fatigue was not a significant predictor of initial cortisol level or the morning trajectory of cortisol levels. To our knowledge, the ACR has not been previously investigated in the context of CRF; however, the results are inconsistent with studies on CFS that have reported lower cortisol responses to awakening in such patients compared to control samples (Nater et al., 2008; Roberts, Wessely, Chalder, Papadopoulos, & Cleare, 2004). Nevertheless, as the ACR was not observed in the current study, the results relating to fatigue should be interpreted with caution.

Although participants were given careful written instructions for giving saliva samples, with emphasis on the importance of collecting samples at the specified times, it is possible that non-adherence to collection protocols contributed to the observed results. Indeed, the times since wakening recorded by participants deviated substantially from the specified collection times (e.g., the minimum and maximum recorded values for time since wakening were one to 60 minutes for sample 1, 15 to 75 minutes for sample 2 and 40 to 135 minutes for sample 3; though the mean collection times were in line with the protocol). However, as the analyses were based on the reported time since wakening rather than the specified sample collection time, such deviances should not have unduly influenced the results. Furthermore, even when only samples that strictly adhered to the specified collection times were included, the observed trends remained the same. Nevertheless, it is possible that participants did not accurately record the times of collection. The reliability of leaving participants to collect their own samples at home has been questioned (Clow et al., 2004). Nonadherence with sample collection times has a significant impact on the response to wakening where, because of the fast rate of change within the first 40 minutes after awakening, even small deviations from the protocol can have a substantial effect on the values obtained (Clow et al., 2004; Kudielka, Broderick, & Kirschbaum, 2003). Unfortunately, the use of alarms with preprogrammed reminders and/or electronic devices to track when participants used the sampling tubes was not feasible in the current study, and so it was not possible to ascertain whether the results were attributable to nonadherence.

Other methodological factors may also have impacted on the results. For example, although the ACR is thought to be independent of time of wakening (Pruessner et al., 1997), some studies have found a larger ACR in early risers (Clow et al., 2004). Furthermore, there is evidence that the ACR is sensitive to light manipulation (Clow et al., 2004). Thus, differences in the time of wakening and in environmental conditions during wakening may have influenced the observed cortisol concentrations. Although time of wakening was controlled in the analysis and did not appear to impact on the results, information about lighting was not assessed. There is also evidence that a greater ACR is observed on weekdays compared to weekends (Clow et al., 2004). Participants were not instructed to collect their samples on a particular day of the week (e.g., on a weekday or over the weekend) in the current study; therefore, the days on which samples were given were not consistent across participants. Furthermore, other potential confounding factors such as gender differences, menopausal differences, and medication and contraceptive use were not investigated. The failure to account for medication use is especially important, since some participants suffered from asthma and may therefore have been on corticosteroid medication. Future studies should be mindful of this.

Although the dynamic nature of the ACR makes it an attractive focus of study in research linking psychological responses to physiological processes, the many potential factors that may influence it means that great care needs to be taken in its measurement. As the ACR is more sensitive to minor deviations in timing than the diurnal cortisol rhythm, overcoming the practical problems that home sampling presents is challenging. In addition, while research on the ACR has increased substantially, the main role of the ACR and the impact that psychological factors might have on this response pattern are still not clear. For example, it is uncertain whether positive affect and health are related to larger or smaller awakening responses. Contradictory findings have been reported in studies on perceived stress and burnout whereby both have been associated with blunted and elevated ACRs (Clow et al., 2004). Furthermore, an elevated ACR has been linked to a variety of psychological factors that were not documented and excluded in the current analyses, but which might nevertheless affect people who have recently finished treatment for cancer, such as loneliness and social recognition (Clow et al., 2004). Thus, while the sensitivity of the ACR to such psychosocial variables makes it is a promising area of research in the context of conditions like CRF, where psychological factors are thought to interact with physiological functioning to maintain symptoms, these characteristics also make it difficult to quantify. The findings from the current study

were limited further because cortisol measurements were only taken on one collection day. Future studies investigating the ACR should aim to collect saliva over at least two consecutive days in order to increase the validity of the findings.

8.4.3 Diurnal cortisol rhythms. The finding that fatigue was not significantly associated with a flatter cortisol slope is inconsistent with the results reported by Bower, Ganz, Dickerson et al. (2005). Nevertheless, the trends observed in the data were in line with their results. As participants in the current study were instructed to collect their final sample at 5pm, it is possible that the diurnal pattern was not sufficiently captured. In Bower et al.'s study the final collection time was at 10pm, at which point fatigued survivors had significantly elevated cortisol levels compared to nonfatigued controls. Thus, the observed trends were driven to a large extent by this final assessment point, as no significant differences were observed at wakening, 12pm or 5pm. In the current study the trends in cortisol patterns between awakening and 5pm were very similar to those reported by Bower et al. for the corresponding timeframe, thus it is possible that clearer distinctions in the slopes would have been observed if later collection points had been included. However, of note, the trends in the current study were only based on two time periods (the three samples in the awakening period and one sample at approximately 5pm), and thus do not capture patterns over the full day.

The idea that altered diurnal cortisol secretion patterns are linked to fatigue in cancer patients and survivors has a strong theoretical basis and is supported by research on the effects of cancer treatment and the functioning of glucocorticoids and immune cells. Research has demonstrated that cancer and cancer treatments, as well as the stress associated with diagnosis and treatment, can disrupt circadian regulatory processes (Payne, 2011); circadian cortisol patterns are known to be important for regulating immune functioning, and research has documented that decreased glucocorticoid signalling can disrupt the suppressive effects of cortisol on proinflammatory activity (Raison & Miller, 2003). The role of proinflammatory cytokines in turn, in contributing to symptoms of fatigue, has received strong empirical support in a variety of patient groups and research areas (Bower & Lamkin, 2012; Ryan et al., 2007). Furthermore, there is evidence that the links between inflammation, behavioural changes and cortisol rhythms are bidirectional; daytime fatigue and altered rest/activity patterns may disrupt evening cortisol decline (Roscoe et al., 2002), and inflammatory cytokines can also stimulate the HPA axis (Ryan et al., 2007). Thus, although insufficient research to date has documented altered circadian cortisol patterns in the context of CRF, the theoretical

basis for linking such physiological processes to fatigue in this population is clear. Although the current findings did not demonstrate that fatigue was a significant predictor of diurnal cortisol pattern, the results suggest that the trends were in line with expectations and thus further research, that is mindful of the methodological concerns raised in the current study, is warranted.

8.4.4 Conclusion. There was no evidence that fatigue was linked to HPA axis dysregulation in the current study. Although no consistent ACR was observed in the data, there was no indication that fatigue impacted on the pattern of cortisol during the initial period after wakening. Furthermore, no significant associations were observed between fatigue and cortisol levels at any stage of the day. Nevertheless, although fatigue was not a significant predictor of diurnal cortisol trajectory, the diurnal cortisol trends observed were in line with the idea that fatigue may be linked with a slower rate of decline in cortisol over the course of the day. Such findings are consistent with previous studies on CRF and the theoretical basis linking subtle dysregulation in HPA axis functioning to fatigue. Further research is necessary to establish whether such mechanisms play a significant role in the experience of fatigue in people treated for cancer.

Chapter 9: "I'm not Complaining Because I'm Alive": Constructing a Discourse of Cancer-Related Fatigue

"I try not to get too worried about my fatigue because it is a small price to pay to be healthy" – Natasha

9.1 Introduction

Cancer-related fatigue (CRF) is a common and distressing side-effect of cancer and cancer treatment (Hofman et al., 2007). Between 50-90% of cancer patients report fatigue and persistent CRF continues to affect many patients for months or even years after treatment is completed (Campos, Hassan, Riechelmann, & Del Giglio, 2011a). Patients are often left to make sense of and manage CRF by themselves; CRF and its treatment are frequently not discussed by doctors and many patients do not report fatigue to health care professionals (Donovan et al., 2005; Stone, Richardson, et al., 2000). Insufficient dialogue about CRF in clinical practice might at least partly occur because it is not yet fully understood (Mustian et al., 2007). Although diagnostic criteria are established, there are multiple proposed definitions and subcategories, and there is debate about whether CRF is a symptom, a side-effect, a syndrome or a disorder (Ahsberg & Furst, 2001). Furthermore, no specific aetiology is agreed and therefore treatment is problematic. CRF is multidimensional and multifaceted, with many biological, psychological and behavioural contributing factors that are likely to vary between individuals (Ryan et al., 2007).

Although CRF is widely acknowledged as a prevalent and debilitating condition, there is no coherent discourse of CRF in the academic literature and inadequate discourse of CRF in medical settings (Ahsberg & Furst, 2001; Mustian et al., 2007). However, few researchers have explored where this has left patients themselves, how they conceptualise their CRF and their discourse about CRF. The present study contributes to the emerging literature on CRF by reporting on patients' own experiences and narratives of CRF. Furthermore, because the findings presented are based on an analysis of 'additional comments' from the end of a quantitative questionnaire, this chapter also makes a methodological contribution.

Quantitative surveys often end with 'additional comments' sections that provide the opportunity to leave remarks about the study or questionnaire items. However, such data are rarely analysed or discussed in research publications (O'Cathain & Thomas, 2004). Additional comments are a rich source of data that give context to results and lead

to novel findings and research ideas (Garcia, Evans, & Reshaw, 2004). Furthermore, providing comment sections gives participants an opening to voice concerns or raise issues that they believe are inadequately addressed in quantitative surveys or in clinical practice. Thus, by attending to such comments in this article, this paper demonstrates the value of seeking data through such unconventional means.

9.2 Methods

9.2.1 Analytic Approach. This study attempted to construct a psychological understanding of CRF based on the lived experiences of patients with CRF. A pluralist approach to analysis was adopted that followed good practice guidelines described by Willig (2012) where different cycles of analysis were conducted that led to data driven shifts in perspective. The rationale for this approach is the amplification of meaning through consideration of diverse perspectives, thereby gaining access to different aspects of participants' experiences, rather than deriving meaning according to one epistemological stance (Willig, 2012). Although a specific hypothesis or question was not formulated in advance, engaging with the data led to the formulation of a series of questions that progressed the analysis and resulted in a multilayered understanding of the data.

Initially, a realist approach was used to capture and systematically represent experiences by inductively identifying themes very closely linked to the respondents' comments. A more focused research question evolved from this process, which led to a shift in analytical focus and a more detailed analysis using a constructionist approach. This marrying of epistemologies is akin to the 'contextualist' method (Braun & Clarke, 2006): how individuals make sense of their experiences is acknowledged and permitted to remain rooted in their professed reality while the influence of the wider social context on those meanings is also acknowledged. Thus, the initial thematic analysis was complemented by applying elements of discourse analysis to question the assumptions, ideologies and meanings that might underpin what was articulated and the language that was used. A critical discourse analytic approach and, to a limited extent, Foucauldian discourse analysis informed the interpretation of the themes. Although critical discourse analysis is a broad term used to describe a heterogeneous array of approaches, it considers how social domination and control are manifested in language and how the discourses that people draw on or actively resist when describing their experiences can position them within power structures (Wodak & Meyer, 2009).

9.2.2 Participants. Data were derived from people who completed a questionnaire study on CRF (described in Chapter 2), and who elected to leave 'additional comments' in a space provided for this purpose. The unexpected volume and richness of these comments provided the impetus for the present analysis (O'Cathain & Thomas, 2004). Seventy-three participants (80% of whom were women) provided data. The mean age was 51 years (*SD* = 11.5) and the average time since treatment was 3 years and 4 months (*SD* = 22 months). Participants had a variety of cancer diagnoses: 21 had breast cancer (28.8%), 16 had ovarian cancer (21.9%), 14 had lymphoma (19.1%), 10 had leukemia (13.7%), six had prostate cancer (8.2%), two had colon cancer (2.7%) and the remaining four participants had lung cancer, sarcoma, gastric cancer and cervical cancer (1.4%). Although some participants wrote very little in the additional comments section, others wrote at length about their CRF; the average number of words per comment was 86 (*SD* = 81, *Min* = 2, *Max* = 366). Quotes are presented as they were written by the participants themselves with original spelling and punctuation. All names were changed and the names of any organisations were removed.

Ethical approval was obtained from the Research Ethics Committee of the researchers' university (see Appendix 2). From January to July 2010, cancer support groups and associations in Ireland and the United Kingdom were contacted and asked whether their members would participate in a questionnaire study on CRF. Flyers, information sheets, consent forms and questionnaires were posted to the 22 groups that agreed to facilitate recruitment. The research was also advertised on cancer association websites with a link to an online version of the questionnaire. The research was introduced as a questionnaire study on people's beliefs about the nature and causes of their CRF and the strategies used to manage fatigue. Cancer patients and survivors who self-reported 'significant fatigue or reduced energy' were eligible to take part.

The questionnaire contained scales to assess participants' beliefs regarding CRF (Pertl et al., 2012) and the coping strategies they used for managing fatigue (Ray et al., 1993). Participants also completed a fatigue severity questionnaire (The Functional Assessment of Cancer Therapy Fatigue subscale; Yellen et al., 1997) and answered questions about whether their doctor had spoken to them about CRF, they had received management recommendations for CRF, and they had requested advice from their doctor about managing CRF. Perceived social support for CRF was assessed using three items: participants rated whether those closest to them provided adequate support, understood their fatigue experience, and understood how fatigue affects them. Space was provided at

the end of the questionnaire for comments in response to the statement "If you have any thoughts about the questionnaire or about any other issues related to your fatigue please leave your comments in the space below". The findings presented in this chapter are based on the 73 participants (47% of the original sample of 155 participants) who left comments.

Recruitment was carried out online and through cancer groups; thus, selection bias might have occurred because those with more fatigue problems might have been more likely to come across the research and participate. Furthermore, the context of the additional comments, a CRF belief questionnaire, is likely to have influenced the data (Howitt, 2010). For example, participants might have commented on topics that featured in the questionnaire rather than aspects of CRF that were absent (O'Cathain & Thomas, 2004). Although the comments reflected questionnaire topics such as the causes of CRF, coping with CRF, social support and medical management of CRF, several topics raised were not included. For example, comment topics such as satisfaction with medical management, the extent and nature of communication with others regarding CRF, others' reactions to CRF, and impact of CRF on quality of life did not feature in the questionnaire. Nevertheless, the questions may have primed comments on related topics. For instance, questions on whether their doctor had spoken to them about CRF may have led participants to write about their satisfaction with medical support. Participants with strong beliefs or especially bad or good experiences might have been more motivated to leave comments or to comment in greater detail than those who were ambivalent about their CRF experiences. No differences were found between participants who left a comment and those who did not regarding clinical and demographic data, medical management of CRF, social support, or fatigue severity. Nevertheless, the issues participants raise in additional comments sections depend on their circumstances at the time of participation (Garcia et al., 2004). Just under half of participants provided comments and therefore the data are unlikely to be representative of all the original questionnaire respondents and it cannot be assumed that the current themes reflect the most important issues facing people with CRF. However, the analysis highlights some of the issues for people with CRF and provides an initial interpretation of the wider systems of meaning and discourses that might underlie these issues.

9.2.3 Analysis. Analysis proceeded in several phases. Initially an inductive thematic analysis was carried out following guidelines by Braun and Clarke (2006). Comments were read repeatedly and initial themes were identified, which focused on the

content of what was written. Potential themes were listed in a spreadsheet; Themes that addressed similar issues were then grouped together, checked for recurring patterns and variability, and given provisional definitions. Comments were reread and relevant participant phrases that reflected these definitions were categorised under one (or several) themes. During this process, new themes were added as they were identified. Themes were then sorted again and expanded, the initial definitions were refined and the text examples categorised under each theme were checked for consistency. Interpretation of themes involved reading and rereading, discussion with colleagues, and consultation with relevant literature. Consideration of themes, their broader meaning and implications led to one overarching theme, from which a specific research question emerged (see *Figure 9.1.*); this moved the analysis forward to the next stage where a more theoretical thematic analysis was used to question the conceptualisations underlying the semantic content of the data.

The themes and excerpts identified were analysed to address the research question: 'how is the absence of a discourse on CRF constructed and maintained?' A full discourse analysis was not possible given the limited text available; however, critical discourse analysis and Foucauldian discourse analysis informed how the research question was addressed by exploring the availability of discursive repertoires of CRF and the social and cultural understandings of health and illness that facilitated the construction of participants' realities (Wiggins & Riley, 2010). A social constructionist discourse analytic approach was used to interrogate the themes generated phase 1 of the analysis in a bid to explore how they resonate with discourses available in the wider culture; the discourses and subject positions available to participants and how these were adopted (or resisted); as well as the responsibilities, expectations and implications involved in taking up such positions (Wiggins & Riley, 2010). The themes were combined under two overarching explanatory themes, each comprising two secondary subthemes or discourses. Comments exemplifying a particular theme were extracted, identified using the participants' pseudonyms, and categorised under that theme. Themes within and between categories were examined to identify underlying systems of meaning. No specialised software packages for qualitative analysis were used to organise the data.

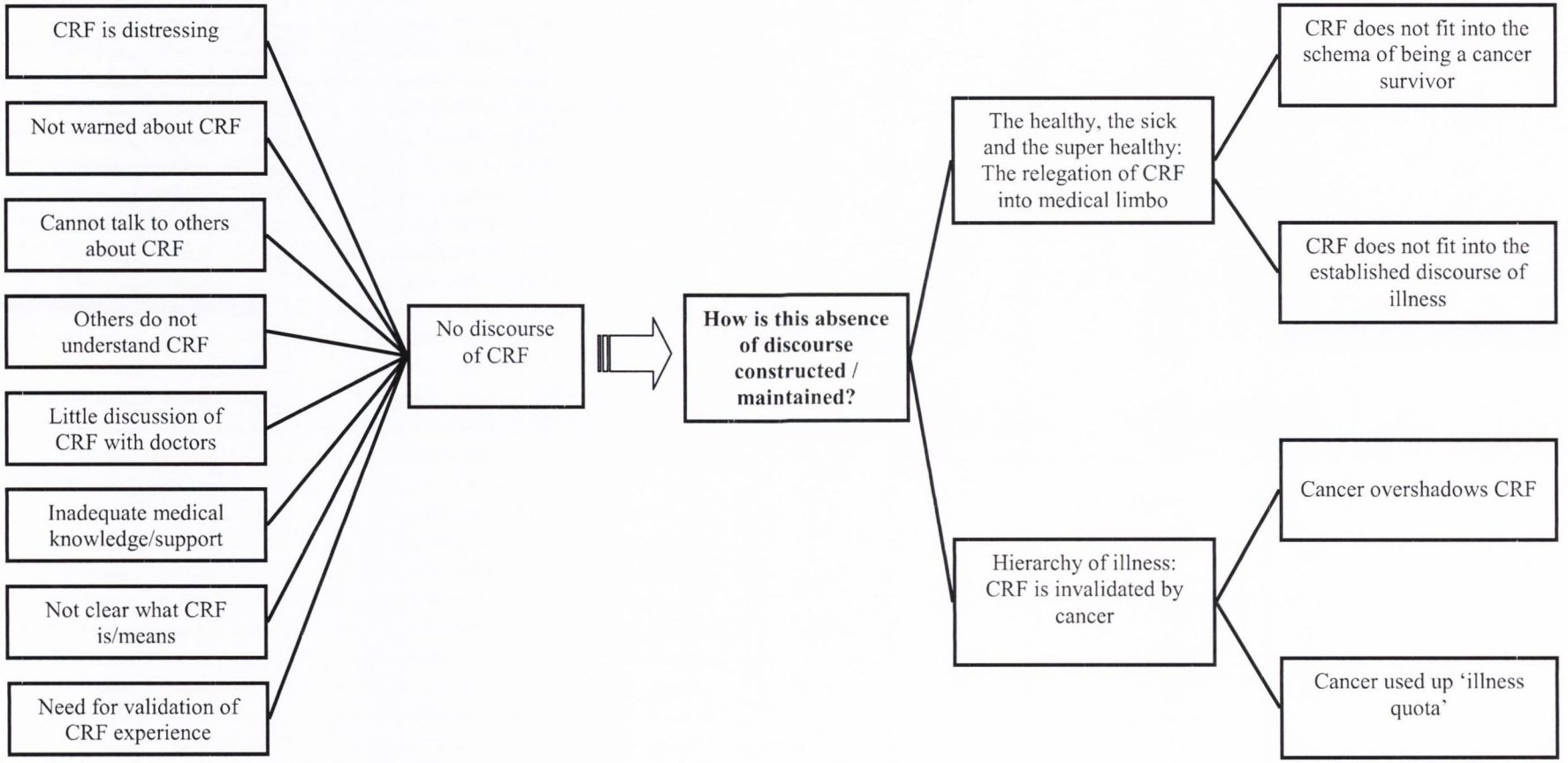

Figure 9.1. Thematic map showing the initial themes from the first phase of the analysis, the development of a specific research question, and the final latent themes that emerged in the latter stages of analysis.

9.3 Results and Discussion

9.3.1 CRF "is a serious issue that needs to be addressed". The overarching pattern in the semantic themes was that there is often little discussion and inadequate communication regarding CRF. This was evidenced in participants' comments in relation to both social and medical discourse. Participants reported that they were not warned about CRF (e.g., Martha: "I wasn't expecting the fatigue. I found it a big shock") and that they did not understand their continued fatigue or what it meant for them (e.g., Hannah: "Maybe I'm expecting too much of myself... Just wondering how long these symptoms will last and when I will be back to myself again."). Some participants sought justification for their continued symptoms (e.g., Jane: "I find it frustrating that no one can explain what fatigue is and why some people suffer from it") or reassurance that they were not alone (e.g., Catriona: "I really just want someone to tell me that the dizziness and the fatigue are normal reactions for this and not just me."). Many participants indicated dissatisfaction and frustration at the lack of interest, support and knowledge regarding CRF from the medical community (e.g., Jackie: "The GP has no idea how to respond and is offering no aftercare... There seems to be a complete lack of understanding of fatigue by the medical professionals and by other health related folks/voluntary organisations."). Inadequate communication regarding CRF in clinical practice is noted in previous research; less than half of patients talk about CRF to a health care professional (Passik et al., 2002; Stone, Richardson, et al., 2000). Furthermore, the unexpectedness of ongoing problems after cancer and the sense of isolation that accompanies persistent post-treatment symptoms and concerns has also previously been raised (Sinding & Gray, 2005).

A small number of participants indicated that they were coping well with fatigue. Their comments indicated that fatigue had been expected, that the causes (i.e., cancer treatment) were clear, and/or the expectation that fatigue would improve in time; e.g.:

> Maureen: They had drilled it into me that you can get very tired during the treatment and for up to a year after it – so I was expecting it. I was warned not to fight it. If you get too tired you just need to rest.
>
> Melissa: I am aware that it is a side effect of the chemo and that in time it will get better.

Participants who felt informed and prepared for CRF might have been better able to deal with fatigue, but persistent, unexplained fatigue was distressing and led some

participants to catastrophise. For example, some feared that it might indicate a cancer recurrence (e.g., Laura: "Sometimes fear would take over me with the fatigue as the only symptom I had of breast cancer originally was fatigue. This fear is that the cancer has returned.").

Participants frequently described their fatigue as overpowering (e.g., Karen: "it grinds me down") and leaving them with little or no sense of control (e.g., Anne: "As if all the power and energy had been taken out of your body and you're just left with this body."). They thus sought recognition and validation for their experience; e.g.:

> Sinead: I actually feel more positive within myself since discovering this study was taking place. It is almost like there is someone out there who understands the condition may exist and understands that I do actually feel the immense fatigue.

Participants suggested that family and friends could not appreciate the extent of their fatigue (e.g., Catriona: "I'm not sure anyone but someone having been through this type of fatigue can understand it") and that even when others were aware of their condition, they did not always provide them with adequate support (e.g., Kim: "People around me know i [sic] am tired but do not seem to help much around the home!").

Distress and uncertainty surrounding CRF, dissatisfaction with medical and social support, the lack of reporting of CRF, and the need for validation suggest that there is inadequate discourse of CRF in clinical practice and between patients and their family and friends. However, broader discourses of health, illness and cancer are further hampering communication regarding this side-effect. The findings suggest that the absence of a discourse of CRF is maintained because CRF falls in a medical limbo between sickness and survivorship, and also because the perceived enormity of cancer invalidates patients' post-cancer experiences. These explanatory themes are now considered.

9.3.2 The healthy, the sick and the super healthy: The relegation of CRF to medical limbo. Kaiser (2008) describes the dominant image of cancer "survivors" as being triumphant and happy, and demonstrating exceptional health and strength in the face of adversity. Such images, and the language of survivorship in which cancer has been "beaten" or "conquered", are consistent with the medical model of disease and testify to the power of medicine to triumph over cancer and restore health (Kaiser, 2008). This conceptualisation of survivorship supports Frank's (1995) "restitution narrative" of illness, wherein healthy people become sick, are diagnosed, treated and then return back to health. Just as the sick role is associated with a set of rights and

duties that govern how a patient is expected (and allowed) to act, being healthy and a "survivor" also places moral expectations on a person's behaviour (Frank, 2003). Cancer survivors are not just back to normal, they are even better than they were before.

The themes in the current study suggest that a discourse of CRF is hindered because CRF falls into a medical limbo between sickness and health, where the established discourses of becoming ill and "surviving" cancer overrule patients' own narratives regarding fatigue. Although fatigue is an accepted part of being a cancer patient, it is inconsistent with the conceptualisation of a cancer survivor that emphasises self-improvement and heroics. CRF also does not qualify as an illness or fit into the idea of how you lay claim to the sick role. Consequently, for people who have lived through cancer, fatigue falls outside the established illness process; it is neither a legitimate ongoing side-effect of a cured disease nor an independent medical condition.

9.3.2.1 CRF does not fit into the schema of being a cancer survivor. Patients typically experience fatigue during cancer treatment; however, when fatigue persists after treatment, patients generally continue to view their fatigue in the context of their cancer, even when it continues long after treatment has been successfully completed. For example, participants talked about their fatigue in relation to how long they had finished treatment:

> Alan: I really wasn't prepared for the side effects, not the length of them. They tell you 6-8 months (post-treatment) but I tell you it can be a couple of years really. I'm 14 months post-treatment.
>
> Mandy: I'm a year after treatment but I still have fatigue.

Participants thus reinforced the connection between their treatment and their fatigue, keeping it as part of their cancer experience. However, others might not accept a cancer survivor with ongoing fatigue; as patients move from treatment to recovery to cure, recognition of CRF by others gradually declines.

Social discourses of cancer survivorship: the dichotomy between illness and health. For family and friends, the end of treatment often signifies the end of cancer. Participants reported how those around them presumed that the side-effects would resolve after treatment and that consequently they would regain their former level of functioning; e.g.:

> Melany: Once I finished chemo, radiation, and herceptin my family and friends seem to think that I would be back to my 'old self'. Instead I feel like my body has been through so much that it's going to take time to recover from all that's happened.

Thus, although patients themselves might feel fundamentally changed or think that getting back to normal is a long way off, significant others' outlooks endorse the 'restitution narrative' of disease, where illness is transitory and treatment returns the patient to full health (Frank, 1995). Thus, problems post-treatment are distanced from the disease. This was apparent in the way others tried to divorce participants' current condition from their previous illness by equating CRF with everyday tiredness, thereby normalising it; e.g.:

> Daniel: People often say to me 'We all get tired'. This really annoys me, because I know what the differance [sic] between a long day at work and THIS feels like! and they (thankfully) DON'T.

CRF was perceived as a legacy of cancer that can only be understood by those who have gone through it, creating conflict between participants' own experiences and the expectations of those around them. Other people's views are informed by a schema of what is means to be a cancer survivor and wider social discourses around cancer. Upbeat accounts of the medical breakthroughs in the "war on cancer" and restitution narratives of individuals who overcame cancer, recovered, and continued with their lives, permeate the media and send clear messages about what "survivors" are like (Batt, 2007; Frank, 2003; Kaiser, 2008). Even the word "survivor" evokes images of a strong and positive individual who has battled and prevailed, rather than someone who, like Melany, has gone through a difficult ordeal that has left them weakened or with continuing problems.

Although survivorship stories can be inspirational, such narratives do not ring true for everyone and can therefore alienate those who are still grappling with ongoing disease-related physical or psychological problems, or those who do not equate their experience with a "heroic" struggle for survival (Kaiser, 2008). Survivorship discourses can thereby place unrealistic expectations and social pressure on patients to live up to these ideals. Sinding and Gray (2005) point out that patients who violate the socially prescribed timeframe for cancer by not "getting over it" are stripped of the accomplishment of survivorship that society bestows on them. Others' expectations that cancer should be over can mean that such individuals are seen as hypochondriacs

who are overreacting and refuse to move on. Patients might therefore feel blamed for continuing problems and frustrated at the lack of understanding; e.g.:

> Jackie: The 'think positive' brigade are irritating as are the 'it will get better in time' lot as I would prefer it if they would just admit they don't have a clue.

The idea that others are already divided into camps based on pre-existing notions of what recovery from cancer should involve also means that Jackie's experience is isolating; the use of clichés denies her the opportunity to construct and tell her own illness story. The difficulty of deviating from the well-established narrative of the positive cancer survivor has been highlighted previously by several writers (Ehrenreich, 2001; Hozman, 2005; Segal, 2010) and is so ubiquitous in the breast cancer culture that Ehrenreich equates it to a cult or a religion rather than a culture. The mandatory cheerfulness means that dissent is seen as a subversive action and negativity or anger are not deemed to be legitimate or permissible responses for survivors of this life-threatening illness (Ehrenreich, 2001). Similarly, Segal (2010) refers to the coercive "code of optimism" that is forced upon cancer patients and the almost obligatory acknowledgement that is expected from patients that cancer ultimately led to a self-improvement of some kind. The prescriptive formula for recovery that clearly segregates 'the sick' and 'the cured' means that there is little room for individual experiences to be heard if they deviate from this narrative or if they exist somewhere in between.

Dissident narratives of survivorship and fatigue: the grey area between health and illness. In contrast to the restitution narrative evident from others, many participants' accounts reflected Frank's (1995) "chaos narratives", where there are never-ending problems and little control. This was highlighted in participants' expressions of hopelessness (e.g., Anne: "you're literally an invalid in your own home. I can manage nothing – everything needs to be done for me. Will this ever go away? I so want to get relief") and loss of control (Hillary: "your body won't do what it's being told. Can't do what it's being told. It's too heavy, too tired"), frustration at the loss of career plans (e.g., Jackie: "I have had to give up a well paid job with responsibility and returned to a job well below my capabilities and part-time due to the fatigue") and limits on functioning (e.g., Linda: "Its [sic] frustrating being unable to keep up with everyday things or activities your peers seem to find quite normal"), which were contrasted against their 'precancer' selves (e.g., Melany: "I went from feeling like a young forty something to an old woman"). Instead of the acute model of illness

inherent in survivor/restitution narratives where cancer is "beaten", participants were still engaged in an ongoing battle. Similar findings have previously been reported whereby cultural definitions of survivorship clashed with some women's ongoing struggles with fears of breast cancer recurrence (Kaiser, 2008).

The ongoing impact of cancer, after the immediate effects of the disease and its treatments, could also be viewed in the context of Frank's (1991) reflections on how the experience of cancer can be seen as a series of losses; loss of the future that was imagined or expected prior to cancer, loss of the body's continuity with the past through distortion or injury by treatments, loss of innocence about one's vulnerability to cancer, loss of the predictability of energy, loss of self-esteem and the belief in one's ability to function, the loss of normality. Such losses are minimised in a culture where the focus is on adjustment and getting over illness. Patients are dissuaded from dwelling on losses; instead they are encouraged to conceal them until they return to "normal". Even more widely acknowledged and tangible losses, such as the loss of a breast or hair loss, are actively camouflaged with inserts and wigs to present the appearance of not only a whole and normal body, but also a whole and normal person that belies the experience of cancer and the possibility that it can result in any permanent (negative) change (Batt, 1994). While many patients take comfort from such measures that allow them to present an outwardly healthy appearance, the pressure to conceal the effects of cancer denies others the opportunity to mourn their losses and openly acknowledge that they do not feel like they are back to normal.

In the current study participants were frustrated by others' narrow conceptualisation of cancer, which contained cancer within the boundaries of diagnosis and the end of treatment, implying that outside these boundaries illness ceased to exist. Participants indicated that they wanted others to understand the continued effect of cancer on their lives; e.g.:

> Maura: It would be very helpfull [sic] to have after care on a regular basis to help cope with fatigue. And also awarness campaing [sic] so people who don't have cancer may be able to understand that cancer doesn't end when chemo ends.

However, equally, they recognised that their own conceptualisation of CRF was shaped by their experience; e.g.:

> Sile: It is nearly impossible for a person who has not gone through several months of intensive chemotherapy (or similar) to understand the condition because there is

> nothing in normal life to compare it with. I would definitely not have understood this condition before I had it.

The idea that CRF is beyond description also supports the chaos narrative, where "the suffering is too great for a self to be told" (Frank, 1995, p.115); as Anita notes it is the "type of exhaustion where it's hard to speak clearly". Differences in participants' and others' conceptualisations of their condition therefore denied participants a social discourse of their fatigue. The restitution narrative can be a form of social control that pushes people to return to health and thereby denies them their own illness experience; however, people's own illness stories must be acknowledged to deliver care (Frank, 1995).

Medical discourse of cancer survivorship: Eschewing responsibility for the grey area. The prescription of survivorship is not just social but also medical; health care professionals also endorse the view that cancer can be over (Sinding & Gray, 2005). After the acute phase of treatment, patients' functional status is no longer a primary concern for oncology professionals, and patients can feel that their concerns are dismissed or seen as inconsequential. In the current study, participants' illness narratives of CRF were often not recognised or closed-off during exchanges with medical professionals. While participants attributed their fatigue to cancer treatment, the medical profession frequently distanced the condition from cancer after treatment was completed; e.g.:

> Melany: Yes I see my oncologist every 3 months but I feel that it is more to make sure that the cancer isn't back, not to deal with the problems I may be having as a result of cancer treatments. Every time I try to bring up any problems my Dr. says it's from menopause not cancer treatments.

Professionals' failure to take clinical responsibility for symptoms that participants believe were caused by their treatments is difficult because patients spend prolonged intensive time with such professionals (e.g., Alan: "You spend months being seen by the cream of oncology treatment and then bam you finish and you can go. I'm feeling very frustrated."). Thus, when this period is over and they are deemed to be disease free, the sudden lack of support from medical specialists is difficult to deal with and may leave patients feeling abandoned (Sinding & Gray, 2005). The absence of medical validation for CRF is also isolating; fatigue symptoms form part of their cancer experience, yet there is no forum for its expression or amelioration; e.g.:

> Jackie: The nurse had no idea how to provide any support and no understanding that fatigue could be part of the cancer experience, though he had attended a [medical group named] workshop/seminar on cancer.

When medical professionals' understanding of their condition was not in line with their own participants questioned the expertise of medical staff; e.g.:

> Catherine: I wish Oncologists would educate themselves on this as the last year has been worse than the cancer treatments. I was told I was just "getting older now" and probably just getting arthritis and should just exercise for the fatigue.

The repeated use of the word "just" suggests that Catherine felt dismissed by her doctors; her symptoms were not only distanced from cancer but also trivialised. Thus, even though participants to some extent accepted why friends and family could not understand their CRF, many participants felt their doctors had a responsibility of care and an obligation to inform themselves because fatigue was a problem that came "as a result of cancer treatments" (Melany). The lack of support and shared dialogue regarding CRF led some to reject medical accounts of their condition.

> Reena: I have received very little support to cope with this from both my oncologist and gp. The only thing I have been offered is valium - which I refused as I don't think it is an appropriate medication for my symptoms.

Previous research on medically unexplained symptoms suggests that patients are more likely to accept medical explanations when the reality of their suffering is acknowledged (Peters, Stanley, Rose, & Salmon, 1998). However, it is not clear where the responsibility for delivering such acknowledgement lies in respect to the late effects of cancer and its treatment. Cancer presents a unique problem because it fits poorly into the dominant conceptualisations of disease as either chronic or acute (Tritter & Calnan, 2002). While it is now categorised as a chronic illness, the emphasis on "beating cancer" and "surviving" implies that cancer can be over. The delivery system of cancer care is fragmented and the majority of the multiple specialists (e.g., surgeons, medical oncologists, and radiation oncologists) that contribute to the treatment of cancer operate during acute episodes of the disease where intensive intervention is necessary; it is not clear who is responsible for dealing with the aftermath. Furthermore, there is often poor coordination between primary care providers and cancer care providers (Hewitt, Greenfield, & Stovall, 2006). The absence of a locus of responsibility for follow-up care to deal with the ongoing effects of cancer treatment is

an issue that is increasingly being acknowledged, and the divergence between patients' expectations and physicians' perceptions of cancer follow-up has been documented (Hewitt et al., 2006). However, the majority of cancer research is still focused on the acute phases of the disease, while the capacity of cancer to be a chronic stressor that can have a persistent effect on people's quality of life has received insufficient attention (Deimling, Sterns, Bowman, & Kahana, 2005). Little is known about what kind of follow-up care patients actually want and it is not clear why patients' expectations are not being met; however, it is likely that a combination of a lack of recognition of the importance of such care, barriers to communication, and the absence of clear guidelines regarding medical responsibility for follow-up care are all contributing factors (Hewitt et al., 2006).

Participants' accounts position fatigue as a legacy of cancer that continues to impact on their quality of life. However, this discourse of CRF is denied when it is ignored by family, friends, and/or medical professionals in favour of restitution stories of cancer, which were actively resisted by many participants. Pressure to conform to the image of "spunky survivorship" can thus obscure the lived experience of cancer's ongoing impact and exacerbate the issues that face people who have lived through cancer (Sinding & Gray, 2005). Conflict between medical and patient conceptualisations of fatigue can thus impede not only social and medical dialogue but also medical care.

9.3.2.2 Fatigue after cancer does not fit into the established discourse of illness. CRF is not seen as a medical condition in its own right; to obtain illness status a person should look unwell, have physical symptoms or biological markers of disease, there should be documented causes for their condition and a diagnosis. These criteria are not always met and therefore CRF does not fit into the medical model and the established discourse of illness.

The importance of visible symptoms. Symptoms are used by medical professionals as markers of specific disease; however, they also denote an individual's illness status for self and others (Radely, 1994). Symptoms act as a guide for social discourse because they signify the individual's right to be treated as a sick person; because CRF manifests only in an individual's self-reported fatigue, others might not appreciate the significance of fatigue for the patient (e.g., Jackie: "My family are pretty good but they can easily forget how tired I can get as this is not obvious"). The absence of symptoms means that the patient's illness status is not always apparent and

acknowledged. Sinding and Gray (2005) highlight the sense of isolation that accompanies the hiddenness of survivors' continued experience of cancer, which leaves them outside a circle of shared understanding and meaning. Furthermore, in the current study some participants indicated that their status was challenged because they had no outwardly signs of illness (e.g., Karen: "I very often wonder if people think I'm faking it because I'm not bed-ridden"). This comment not only implies that others do not consider her fatigue to be real, but suggests that she is fabricating her ill health. Accounts of chronic pain and fibromyalgia also raise issues of moral and social legitimacy because the invisibility of these conditions cause the illness and the person's credibility to be questioned (Sim & Madden, 2008).

The recognition of a bodily sign as a symptom is not straightforward; its context determines whether it is seen as warranting attention (Radely, 1994). Fatigue is a common side-effect of cancer treatment and thus the most obvious manifestations of CRF, physical tiredness and the inability to carry out usual activities, are not necessarily seen as abnormal. One participant commented that "everbody [sic] just expects it and you to deal with it along with all the other side-effects that are not visible" (Madge). Not only is fatigue not seen as a major concern because it is *not seen*, it is also not viewed as something requiring attention. Cancer is the illness and issues like fatigue are seen as temporary side-effects, not new medical problems.

When common physical side-effects (e.g., hair loss, skin problems) resolve after cancer treatment is completed, it can appear as though the patient's health status is improving. Others equated 'looking well' with 'being well' (e.g., Melissa: "Because I look so much better then [sic] when I was having treatment, people think that I am back to prior fitness"). Misunderstanding and/or lack of concern from others as a result of dissonance between an individual's appearance and their professed ability to engage in activities has also been reported in the context of fibromyalgia (Sim & Madden, 2008).

No cause, no cure. Lack of clear-cut indicators for CRF complicates diagnosis. Like fibromyalgia (Sim & Madden, 2008), CRF could be viewed as a "diagnosis of exclusion", which is only given after other potential causes of fatigue are ruled out. Participants suggested that because biological markers for CRF were lacking, doctors became unconcerned; e.g.:

> Daniel: The doctors cannot find anything wrong with me so that's often enough for them to dismiss it as irrelivent [sic].

Similar views were reported by patients with CFS, where the absence of well defined, organic causes can lead doctors to downplay the importance of symptoms (Guise, McVittie, & McKinlay, 2010). Frank (1991) noted how the existence of a medical problem is contingent on the availability of a treatment. The focus on curing suffering means that simply acknowledging suffering is seen as a medical failing and thus its continued existence is denied. As a result, patients are not allowed to experience symptoms that cannot be treated (Frank, 1991). Participants' comments suggested that doctors dismissed fatigue when there were no obvious diagnostic signs; e.g.:

> Conor: I was referred to a general physician because I kept mentioning my tiredness and lack of energy and he referred to it as a general malaise. He did some blood test but they showed nothing abnormal so he said there was no more he could do.

The necessity of a sign to "announce" what has happened, what is now taking place, and what will happen next is discussed by Foucault (1973, p. 90). Although symptoms are a map to the truth by allowing disease to show through, a sign is a symptom "in its original truth" and it alone enables clear and complete reading (p. 94). Thus, while fatigue may be a symptom that is perceived by patients, "medical gaze" is necessary to make what is visible expressible, and without clear signs the truth of a patients' condition cannot be known.

The need for medical validation. The necessity of medical certification is apparent in Foucault's (1973) discussion of the medical gaze. Although symptoms are a signifier of a disease, they cannot be interpreted by anyone; medical gaze is necessary to bring meaning to what is seen and even then clinical descriptions can only be understood by "those initiated". In the clinic the sovereignty of the gaze is established. Medical gaze "has the power to bring a truth to light" (p. xiii); it is not the gaze of an observer but that of a doctor who has the power to make decisions and intervene with the support and validation of an institution. Thus the gaze is an elite language that is "the master of truth" (p. 115). The lack of biological markers, coupled with the absence of visible symptoms, meant that the participants' fatigue status was not validated by a medical authority and thus it was challenged by others and mistrusted by participants themselves. Patients often try to cope with legitimacy issues by projecting healthy identities and hiding their actual experiences. Women with chronic pain frequently developed uncertainty over their own bodily feelings when these were questioned by others and consequently, their own illness experiences were invalidated (Werner,

Isaksen, & Malterud, 2004). Similarly, the absence of a diagnosis led some participants to doubt the reality of their own experiences; e.g.:

> Eilis: I have not been told that I have fatigue but I seem to be living with it- it varies a lot but I do believe it interferes with my daily life and the sense of needing to "keep going" because "it must be all in my head" because I've not really had any diagnosis, and this makes me feel worse when I am tired, because I feel silly.

The repeated use of the word "*believe*" means that Eilis stopped short of actually saying that she *has* these symptoms and experiences and she states that her fatigue has not been certified by a medical authority. Previous research on patients with ambiguous chronic conditions suggests that the main motivation for seeking medical help is to legitimate the condition in both their own and other people's eyes (Brown, 1995; Peters et al., 1998), and that such acknowledgement outweighs any tangible returns that might follow. Many participants lacked feelings of solidarity with their doctors (e.g., Eilis: "Have found that health professionals tend not to try and deal with this issue, neither my consultant nor my GP, and you get passed back and forth between the two."). Eilis' experience of being passed between doctors illustrates how fatigue after cancer falls between the cracks of medical discourse; it is neither in the realm of general medicine nor in the realm of cancer, at odds with both sickness and survivorship.

Little (2002) argues that while cancer has a strong public profile, there is no appropriate discourse available for cancer survivors; instead the experiences of survivors are pushed into the ill-fitting paradigms of the normal or the chronically ill, cast in the role of cancer heroes or victims. Survivors are patients who have been "made normal" again, as in Frank's restitution narrative, which presents the culturally preferred and institutionally prescribed model for how illness stories should unfold (Frank, 1995; Sinding & Gray, 2005). The only identity other than "normal" that is open to people who have lived through cancer is 'better than normal'. Through this identity patients can embrace the "makeover opportunity" that cancer presents (Ehrenreich, 2001) and ostensibly become more effective, more loving, more positive, and more courageous in line with the heroic cancer survivor crusade (Sinding & Gray, 2005). The responsibility of what it means to be a cancer "survivor" is thus clear; however, the burdens of survival are not.

9.3.3 Hierarchy of illness: Cancer-related fatigue is invalidated by cancer.

The term cancer is synonymous with serious illness; it evokes strong emotional reactions and profoundly negative cognitive representations; indeed, it is often not even

named, but just referred to as 'C'. Cancer has been described as the "the dread disease" (Patterson, 1987); it is seen as such a threatening illness that it dwarfs everything else and trivialises any experience that is not as sensational. Consequently, by virtue of having gone through cancer, patients may feel un-entitled to entertain 'smaller' health problems: they have survived and therefore should be happy and grateful. Being cured and becoming "normal" again may come at a price; however, where cancer is concerned no price is considered too great and therefore there is little sympathy or acknowledgement of problems or stresses that face survivors (Little et al., 2002). Thus, the emphasis on being positive is coupled with pressure to hide the effects of cancer, ongoing suffering, or negativity after cancer (Batt, 1994; Hozman, 2005).

Findings from the current study suggest that a discourse of CRF is prevented because cancer is top of the hierarchy of illnesses and therefore, after cancer, fatigue was rendered insignificant either by participants themselves or by others. Furthermore, for participants who had completed treatment and were now considered "cured", there was a perceived pressure to shed the sick role and to embody their precancer healthy selves. Thus in a sense, the enormity of cancer had absorbed participants' 'illness quota' and therefore a discourse of CRF was blocked.

9.3.3.1 Cancer overshadows CRF. A number of participants trivialised their fatigue by overtly comparing the severity of their current condition to cancer (e.g., Martin: "Beats the heck out of the other option... death"). Thus, CRF was a price worth paying for undergoing treatment and surviving cancer; consequently, they did not need the right to be unhappy about their fatigue because they themselves felt that cancer overshadowed CRF (e.g., Mandy: "I'm not complaining because I'm alive"). Therefore, to report fatigue would mean "*complaining*" about a trivial issue rather than reporting a medical problem. Other participants internalised the view that surviving cancer invalidated fatigue but found it harder to enact this concept in practice (e.g., Jeremy: "I should try to practice the gratitude a bit more, I would love to be more greatful [sic] but I am trying"). Thus, although they struggled to cope with fatigue, they felt un-entitled to be negative about their condition and silenced themselves to embody the image of the cheerful, grateful cancer survivor.

In contrast, other participants expressed frustration that others tried to push the view of CRF as insignificant on them. In their responses to patients' reports of fatigue, some doctors almost implied that they were naive in thinking that they could be cured of something so serious and not suffer any ill consequences. Such responses conveyed

the message that one is not entitled to complain about the side-effects of lifesaving treatments; that health problems such as fatigue are a small price to pay for surviving, e.g.:

> Jackie: Now the GPs and hospital doctors already expect may [sic] to say I am tired so do not look into this at all - just nod as if I should expect/accept this. . . There almost seems to be an attitude of 'be grateful that you are alive' without consideration for quality of life.

Health professionals therefore trivialised patients' CRF experiences by putting them in the cancer context, thereby making it difficult for patients to discuss this condition (e.g., Conor: "it is difficult to talk about without it sounding fairly trivial") and making them feel ungrateful or demanding for raising it.

9.3.3.2 Cancer uses up the 'illness quota'. Some of the themes that emerged suggest that, because of the enormity of cancer, patients had used up their 'illness quota'. When cancer had been successfully treated, there was a perceived expectation from others that they should now be healthy again; e.g.:

> Eilis: When you're told you're going to be well (as I have been) you then feel you *have* to be and you feel you aren't allowed to have problems.

As such, patients are not entitled to continue to experience the side-effects that characterised their treatment (e.g., Catherine: "most people believe since treatment is over I should be 'back to normal'"). This is in line with the previously discussed theme that others tried to trivialise participants' fatigue by normalising it; treating CRF like 'everyday tiredness' downplays its significance and attempts to move patients from their 'cancer self' back to their "old self" (Melany). When cancer has been cured and there is no clear medical reason for continued fatigue, patients might also perceive more direct pressure from others to cease being sick and to move on after cancer. For example, Karen commented: "my mum basically accused me of not trying hard enough to get over it". This conveys the perception that others think she is herself to blame for her continued fatigue and also implies that she is relishing her persistent illness. The image of having to actively engage in battle to become well is a cancer cliché that may well extend to the side-effects of cancer treatment. The discourse on cancer suggests that cancer can be controlled through an effort of will or through possession of the right attitude (Seale, 2002). Whereas people with other diseases are simply sick, people with cancer have to "fight" it (Frank, 1991); the implication of this is that those who fare

poorly simply did not fight hard enough. The pressure to be well and acceptance that others cannot understand their fatigue, may thus shut patients in and create a barrier between them and anyone who has not experienced CRF (e.g., Eilis: "I don't talk to my friends or colleagues about the symptoms because they expect me to be ok now"). Thus, dialogue is closed off, depriving patients of validation or recognition for their lived experience and leaving them to cope by themselves.

Although patients might perceive an expectation to be well from others, patients might also feel pressure to be well *for* others. In the current study, some participants actively hid their fatigue because they did not want to continue to burden others; e.g.:

> Reena: I try very hard not to let my family see how tired I can be. They have been fantastic over the last 10 months and I don't want them to go through more than they have to.

Thus, patients might also enforce an 'illness quota' on themselves and strive to be well after treatment. The language of battle that participants used to describe efforts to cope with fatigue (e.g., Lilly: "fight it", May: "force myself", Miriam: "hit me", Kate: "push myself") is consistent with the dominant image of survivorship that emphasises *fighting* illness and reflects the ongoing struggle participants experienced. Some participants also put pressure on themselves to be upbeat and to resist the dominance of their symptoms (e.g., Jeremy: "I'm trying to be positive but being unable."). However, failing to maintain this positive front can have negative implications, which might lead people to wonder whether their own attitude is contributing to their condition and to blame themselves (e.g., Jill: "I thought it was just me not recovering quickly enough"). This supports the idea that people might feel unentitled to be ill after they have been "cured" and are in recovery.

9.3.4 Conclusion. This study examined cancer patients and survivors' lived experiences of CRF. The findings indicate that established discourses of cancer and illness play a powerful role in shaping these experiences. The dominance of such discourses overshadows CRF and inhibits the emergence of an identity for a person who has lived through cancer that permits the existence of persistent problems such as fatigue. Furthermore, because others view cancer through dominant social discourses, they can fail to recognise individual narratives of CRF when these deviate from or oppose established conceptualisations. "Restitution narratives" and dominant images of "survivors" thus override patients' own accounts of fatigue as a legacy of cancer. Although there is currently no discourse available for cancer survivors that

acknowledges the lingering presence of cancer in people's lives, the current findings indicate that patients internalise subject positions from dominant survivor discourses, or actively resist such subject positions, to communicate their experience. Nevertheless, the enormity of cancer can trivialise ongoing health concerns and contest continued access to medical and social support.

The findings contribute to the literature on recovery from illness by identifying some of the issues and difficulties that face patients whose illness experiences are seen as medically ambiguous or trivial. The results demonstrate the complexity of seeking medical and social support when there is a perception that the legitimacy and significance of the health concern is questioned. The importance of recognising patients' own representations of a health threat when delivering care is apparent from the results. Furthermore, the findings illustrate the difficulties facing patients whose experiences do not conform to dominant discourses of illness and recovery, and the extent to which established and accepted illness narratives can inhibit or override patients' own illness stories. The findings are therefore relevant to the literature on any illness groups that fall between the cracks of medical discourse, and diseases or conditions for which dominant discourses circumscribe 'normal' recovery or adjustment (e.g., bereavement or initiation of palliative care).

The findings also have practical implications for managing CRF. A clearer conceptualisation of CRF is required in clinical practice to facilitate the emergence of a narrative of CRF that acknowledges the potentially enduring effects of cancer. If patients are adequately informed before treatment that persistent fatigue is a possibility and alerted to the characteristics of CRF after treatment, patients would be better prepared and equipped to manage fatigue should it occur. Having a diagnosis would allow patients to frame their fatigue as part of cancer illness and serve a social function by giving credibility to their experience, thereby opening a social discourse of CRF.

Much of the distress associated with CRF arises from the lack of validation of patients' experiences. Although the causes of CRF are not yet clear and there is still considerable debate about how to assess and treat such fatigue, current levels of knowledge should not prevent the discussion of CRF in clinical practice. Acknowledging that CRF is different from regular tiredness might alleviate much unnecessary distress. Furthermore, although many factors not related to cancer treatment can contribute to fatigue in cancer survivors, conceding that sometimes treatments can have long-term effects is important. The lack of follow-up care and

support is an issue that clearly goes beyond CRF and relates to the ambiguities of cancer itself. The failure of cancer to fit into an acute or a chronic model of illness and the implications of this for survivorship care are outlined in the aptly named Institute of Medicine report 'From Cancer Patient to Cancer Survivor: Lost in Transition', which documents how a wide variety of patients' psychosocial needs post-cancer are not met (Hewitt et al., 2006). The findings from this study are thus in line with the increasingly acknowledged wider issue in cancer care that patients' needs go beyond curing cancer.

Although the focus in medical practice is on clinical investigations and treating symptoms, such approaches are unlikely to be effective when they clash with patients' own conceptualisations and concerns. The common sense model (CSM) outlines how peoples' cognitive and behavioural responses are shaped by their own representations of the problem (Leventhal et al., 1998). Thus, discrepancies between such representations and medical interpretations may lead patients to challenge medical expertise. Appreciation of patients' narratives and validation of their experience can result in better therapeutic relationships and more collaborative treatment approaches; patients are likely to be more accepting of alternative investigations and interventions that are not in line with their original conceptualisations when their experiences have been recognised and acknowledged.

Finally, the findings from the current study illustrate that, more than giving respondents the opportunity to voice their opinion, 'additional comments' sections are a rich source of data that can be analysed qualitatively and can lead to insight into important issues facing patients. Although the study attends to a limited set of comments from a small group of cancer survivors, it draws further attention to the emerging recognition of how dominant social discourses of cancer can drown out individual cancer stories. In addition, based on these findings, the use of a pluralistic analytic strategy is encouraged. Few researchers to date have adopted such an approach; the present article illustrates the merits of considering different perspectives to facilitate and deepen understanding.

Chapter 10: General Discussion

"The impact of fatigue has mostly been frustration and impatience at this stage of my recovery. It is I think probably one of the daily reminders of my cancer diagnosis and the consequences of my treatment. Leaves a feeling of guilty that I should be back to "normal" at this stage." – Alice

10.1 Summary of Empirical Chapters

This thesis examined the factors that contribute to fatigue in individuals treated for cancer, using a cognitive-behavioural model of illness as a conceptual framework. This work thus combines two important and increasingly recognised areas of research: 1) documenting and addressing survivorship issues in cancer care and 2) understanding illness through a multifactorial aetiological framework that considers how a diversity of factors, and interrelationships between them, can contribute to the development and experience of symptoms. Cancer survivorship is not a new area of research; however, adequate recognition of cancer as a potentially chronic illness that can have lasting physical, psychological, social and economic consequences for people who have been successfully treated for this disease has only materialised in recent years (Hewitt et al., 2006). As increasing numbers of people are living after cancer, following improvements in screening, diagnosis and treatment, the long-term consequences of cure demand greater attention in the research agenda and in clinical care. The focus on cancer-related fatigue (CRF), one of the most common, distressing and persistent health concerns after cancer treatment, was thus appropriate. The use of a cognitive-behavioural framework for understanding this symptom reflects the increasing application of integrated aetiological models of illness that not only go beyond psychology, biology and behaviour, by recognising the role of cognitive processes and beliefs in contributing to symptoms, but also explicitly consider the mechanisms through which different types of contributing factors can interact and impact on illness outcomes. Such models have long since been applied to conditions with medically unexplained or ambiguous symptoms. However, the value of exploring psychological, social and cognitive contributing factors, even in the context of diseases and symptoms where there are clear physical and/or physiological causes or contributing factors, is increasingly recognised. This chapter identifies the main themes that emerged from the empirical findings presented in this thesis and discusses them in relation to the cognitive-behavioural model of CRF.

10.1.1 The role of cognitions in CRF.

10.1.1.1 Assessing cognitions about CRF. In order to examine the role that individuals' thought processes and beliefs may play in the experience of symptoms, such cognitions must first be reliably assessed. Chapter 2 described the validation of a measure for assessing such beliefs in the context of CRF, adapted from a widely used and reliable measure of illness representations, the Illness Perception Questionnaire (IPQ). The importance of tailoring this measure to different illness groups to accurately reflect patients' perceptions regarding a particular condition has been noted (Moss-Morris et al., 2002). The common sense model (CSM), on which the questionnaire is based, outlines how people's illness representations are shaped by their experience of symptoms, their personal history and the sociocultural context in which they occur (Leventhal et al., 1998). Indeed, the findings presented in Chapter 9 illustrate how the distress caused by the experience of symptoms of fatigue can lead people to catastrophise about their condition (e.g., by worrying whether symptoms are an indication of cancer recurrence), how the context in which the symptoms emerged (i.e., cancer treatment) can shape how people continue to view their condition, and how the sociocultural discourses surrounding cancer survivorship can impact on and/or restrict how people conceptualise their condition. CRF thus has a unique set of cultural and contextual influences that can contribute to individuals' cognitive and behavioural responses to symptoms.

The adapted version of the IPQ for CRF presented in Chapter 2 exhibited good psychometric properties, supporting its use for the assessment of patient perceptions regarding CRF. The scale could thus be helpful in clinical practise to explore people's representations of fatigue in a cancer context. Although the IPQ alone may not be sufficient to give full and in-depth insight into individuals' precise understanding of their condition (French & Weinman, 2007), it can provide a useful starting point for eliciting more specific beliefs that can then be used to form the basis of tailored interventions. Furthermore, the scale may be useful for research exploring the mechanisms underlying changes in CRF, both over time and in response to interventions.

10.1.1.2 Evaluating the role of cognitions in CRF. The cognitive-behavioural model stresses the central importance of patients' beliefs in maintaining both symptoms and the contributing factors to symptoms over time. The findings presented in Chapter 5 support the idea that cognitive processes play such roles in the context of CRF.

Nearly all of the cognitive representations specified by the CSM were significantly related to fatigue severity and together accounted for 58% of the variance in post-treatment fatigue. Only treatment-control, timeline-cyclical and causal attributions were not correlated with fatigue. It is possible that the treatment-control items were ambiguous for respondents as there are no clearly defined treatments for CRF, and treatments for cancer are known to cause fatigue. Thus, modification of the treatment-control construct in the context of CRF may be necessary.

Refinement of some of the measures used to assess causal attributions may also be helpful. Physical and psychological causal attributions have previously been linked to CRF (Servaes, Verhagen, et al., 2002c) and challenging unhelpful cancer- and treatment-related causal attributions is a key component of cognitive-behavioural therapy (CBT) interventions for CRF (Collier & O'Dwyer, 2011; Gielissen, Verhagen, et al., 2007). However, there was no indication in the current study that such attributions were associated with more severe fatigue. As only three items were used to assess such beliefs, further development of these scale dimensions may reveal a role for such factors. Nevertheless, findings on CFS, a condition in which the tendency to attribute fatigue to physical causes is also thought to be unhelpful, suggest that such attributional cognitions play a less important role in determining outcomes than other cognitive factors such as negative representations of fatigue and attentional processes (Deale, Chalder, & Wessely, 1998; Knoop et al., 2010). It is possible that the same is true for CRF. Nevertheless, dysfunctional attributions could feed into other cognitive factors that are important in the context of CRF, such as fear of cancer recurrence. The qualitative findings presented in Chapter 9 suggested that ambiguity over the meaning of fatigue and previous experiences of fatigue led some participants to attribute their fatigue to a cancer recurrence; such thinking patterns could thus exacerbate fatigue by contributing to emotional distress or catastrophising. Indeed, findings from Chapter 5 indicated that fear of cancer recurrence was indirectly associated with fatigue through catastrophising, stress and depression. Thus, the role of causal attributions may be more indirect than other cognitive processes.

Although the composite negative representation construct described in Chapter 5 was an independent predictor of fatigue severity in a multivariate model of CRF, the idea that beliefs can impact on psychosocial contributing factors to fatigue and thereby add to a cycle of perpetuation was also supported by the findings. The negative representation construct was significantly associated with almost every psychological

and behavioural predictor of fatigue severity. For example, a more negative representation of CRF was significantly associated with greater anxiety, depression, and stress; lower self-reported physical activity; less social support regarding fatigue; and increased use of symptom focussing as a coping strategy. Such findings are in line with the idea that interrelationships between cognitions and behavioural and psychological factors can help to sustain CRF after treatment. Indeed, there was evidence that the relationship between beliefs and outcomes was partly mediated by depression, stress and symptom focussing. The psychosocial mechanisms through which cognitions may impact on outcomes are considered further in the next section.

10.1.1.3 The CSM and CRF in the context of the cognitive-behavioural model. Chapter 5 used the CSM as a theoretical framework for examining the role of cognitive factors in post-cancer fatigue because this framework provides more detailed information about the basis of interactions between specific cognitive and perceptual factors connecting motivation and action than other behavioural models. The CSM thus has the potential to expand our understanding of the development and perpetuation of CRF, in particular the specific types of beliefs that are important and how they relate to outcomes through coping. Constructs with empirical support could then be integrated into the cognitive-behavioural model to capture a comprehensive set of aetiological contributing factors in a single coherent framework.

The results supported the use of the CSM in that participants formed identifiable cognitive representations of their fatigue after cancer, and these representations were related with one another and with fatigue in logical and theoretically predictable ways. Furthermore, in line with the model, cognitions were significant predictors of coping strategies and emotional distress in response to symptoms, and coping strategies partially mediated the relationship between negative representations of fatigue and fatigue outcomes. Nevertheless, although the CSM helped to identify specific beliefs regarding CRF and to guide analysis of the mechanisms underlying the role of beliefs, the use of this conceptual framework did not substantially add to the more general cognitive-behavioural explanatory model of CRF. The results suggested that the link between cognitions and fatigue was driven largely by consequence beliefs and focussing on symptoms. Although other beliefs and coping strategies were correlated with fatigue, consequence perceptions and symptom focussing played a core role in the prediction of fatigue. Such negative thinking patterns are already well established in cognitive-behavioural models of symptom perpetuation, where the key roles of negative

representations, attentional processes and catastrophising are recognised. For example, focussing on symptoms is thought to be one of the central mechanisms through which cognitive processes perpetuate fatigue in CFS and in multiple sclerosis (Knoop et al., 2010; Knoop et al., 2012). Thus, while the CSM can help to elicit more specific beliefs about CRF, the general negative thinking patterns specified in the cognitive-behavioural model seem to sufficiently capture the role of cognitions in CRF.

10.1.2 Is the cognitive-behavioural model a useful conceptual approach to CRF? Chapter 3 outlined the evidence to date for the numerous biological, behavioural, psychological and cognitive factors that have been linked to CRF. The cognitive-behavioural model of illness offers an appealing framework for integrating all of these factors and unravelling the different, but interconnected, roles that they might play. This thesis used this model as a guide for variable selection and examined specific pathways specified by the model in order to explore how various contributing factors might impact on outcomes. The findings supported a role for many of the proposed biological, psychological, behavioural and cognitive factors in the aetiology of fatigue and, furthermore, supported strong interrelationships between these different predictors. Thus, the results suggest that the integrated conceptual framework proposed by the cognitive-behavioural model is a useful approach for understanding CRF; however, not all elements of the model were supported by the data. The findings on the cognitive contributing factors have already been discussed; the broad themes that emerged in relation to the other proposed elements of the model are now considered.

10.1.2.1 Psychological distress and CRF. The findings presented in this thesis support the strong association between CRF and depression that has been identified in previous research; however, by exploring the relationship between depression and other proposed contributing factors to fatigue, and the relationship between depression and fatigue over time, an attempt was made to build on what has been previously reported. Furthermore, findings on depression were compared and contrasted with findings on other psychological factors such as anxiety and stress. The results presented in Chapter 4 indicate that greater levels of depression and stress, but not anxiety, significantly predicted increased fatigue severity in patients prior to the initiation of chemotherapy treatment. Although the cognitive-behavioural model emphasises the role of psychological factors in maintaining persistent fatigue after treatment, the findings indicate that depression and stress, as well as sleep disturbances, can play a role early on, even before systemic cancer treatment. One possibility is that symptoms of

depression and fatigue at this stage are caused by the same underlying factors; for example, they may share a common biological basis. Equally, symptoms of depression before systemic treatment could be induced by physiological factors and mediate the role of such factors in the development of fatigue. The results from Chapter 7 indicated that depression and fatigue had similar relationships with physiological markers of inflammation before chemotherapy; thus, both may be triggered by inflammation. However, of note, depression and concentration of C-reactive protein (CRP), a biomarker for cumulative inflammation, were independently associated with fatigue; thus, the findings do not support the idea that depression accounts for the link between fatigue and inflammation. Rather, the findings suggested that fatigue may explain the association between depression and inflammation at this stage of the treatment trajectory. Nevertheless, although there was no evidence that depression mediated the link between inflammatory activity and fatigue, depression was a strong independent predictor of fatigue, thus supporting the role of psychological contributing factors to pretreatment fatigue.

Findings from Chapter 6 indicated that depression and fatigue had very similar trajectories over time and depression explained a substantial amount of the within-person variance in fatigue severity. While depression did not predict changes in the trajectory of fatigue in the longitudinal study, change scores in fatigue were significantly related to change scores in depression in Chapter 5. It is possible that both symptoms covaried over time as a result of a common physiological basis. Nevertheless, while changes in depression were related to biological markers of inflammation and kynurenine pathway activation in Chapter 7, fatigue was not associated with such factors over time. This supports the idea that physiological factors may help to trigger fatigue, but that psychosocial factors play a greater role in maintaining this symptom post-treatment. The findings are also in line with the self-perpetuating cycle outlined in the cognitive-behavioural model, as strong associations were observed between psychological predictors and other contributing factors. For example, in Chapter 4, depression, stress and anxiety were significantly correlated with one another and with sleep disturbances before chemotherapy, supporting interrelationships between such predictors. In Chapter 5, the psychological predictors stress, anxiety and depression were significantly associated with negative cognitive representations of CRF, symptom focussing, and catastrophising; and depression and stress partially mediated the observed relationships between negative beliefs and fear of

recurrence with fatigue severity. Thus, psychological factors appeared to play a key connective role between various predictors of fatigue.

10.1.2.2 Behavioural factors and CRF. Two behavioural aspects of the cognitive-behavioural model were examined in this thesis: physical activity levels and coping strategies. Although physical activity was not related to fatigue prior to chemotherapy in Chapter 4, the findings from the longitudinal analysis in Chapter 6 suggested that physical activity not only predicted fatigue, but also predicted the rate of change in fatigue over time. Thus, activity levels may play a particularly important role in the trajectory of fatigue. Such findings support reports of the effectiveness of exercise interventions for CRF (Cramp & Daniel, 2008). Nevertheless, in the context of the cognitive-behavioural model, where interrelationships between contributing factors are emphasised, the role of physical activity as a mediator of psychological or cognitive correlates of fatigue was not clear from the findings. Although some significant associations were observed between physical activity and negative cognitions regarding CRF and focussing on symptoms in Chapter 5, physical activity was not consistently associated with the predictors of fatigue either before (Chapter 4) or after cancer treatment (Chapter 5). Furthermore, there was no indication that activity levels mediated, or indeed were even associated with, negative beliefs about activity.

The role of specific coping behaviours in relation to CRF was investigated in Chapter 5. Findings indicated that the coping strategies focussing on symptoms and information seeking partly mediated the relationship between negative beliefs about CRF and fatigue. As previously discussed, this finding is in line with both the cognitive-behavioural framework and the CSM, which support the idea that cognitions can impact on outcomes via coping behaviours. Furthermore, as focussing on symptoms was associated with more negative emotional representations of fatigue, more chronic timeline perceptions and lower perceived personal control, the use of this coping strategy could lead to increased emotional distress and thereby contribute further to fatigue. Although greater use of information seeking was associated with more severe fatigue; there was little evidence in the current study that other active coping strategies played a role in CRF; although greater activity avoidance was significantly associated with greater fatigue, this relationship did not hold up in a multivariate model, and both maintaining activity and accommodating to fatigue were not correlated with fatigue. Together these findings suggest that adopting passive or limiting coping strategies (e.g., symptom focussing) is a better predictor of fatigue severity than the use

of active coping strategies. Seeking information may lead to greater fatigue by contributing to maladaptive limiting coping strategies such as symptom focussing as well as emotional distress.

10.1.2.3 Biological factors and CRF. The fatigue experienced by cancer patients can undoubtedly be related to biological changes brought on by the disease itself and/or by cancer treatments, which can cause a variety of biochemical and physical factors associated with fatigue. However, the role of such factors in maintaining CRF is less clear. This thesis examined two biological mechanisms that have been implicated in CRF: the role of proinflammatory cytokines and subsequent kynurenine pathway (KP) activity, and dysregulation of cortisol rhythms as a symptom of hypothalamic pituitary axis (HPA) dysfunction. Findings from Chapter 7 provided some evidence for the idea that heightened inflammatory activity can play a role in the aetiology of CRF; greater fatigue before chemotherapy was significantly associated with concentrations of CRP, a downstream indicator of inflammation, in a sample of breast cancer patients. As CRP is a reliable marker of cumulative exposure to interleukin-6 (IL-6) activity, this finding supports the hypothesis that increased activation of IL-6 plays a role in the pathogenesis of CRF. Nevertheless, concentrations of IL-6 and concentrations of the other inflammatory markers investigated were not significantly associated with fatigue, and the small sample size and the number of correlations tested means that the findings should be interpreted with caution. However, of note, depression demonstrated the same relationships with the inflammatory biomarkers as fatigue. Thus, inflammation may simultaneously bring on symptoms of both fatigue and depression, or relationships between these symptoms may account for associations with inflammation. The findings indicated that fatigue was independently associated with CRP; however, further research is necessary to explore the causal associations between these factors. The results suggested that changes in depression were associated with inflammatory activity (IL-6 levels) and KP activation (concentrations of kynurenine) over time, while no significant interactions were observed between such physiological factors and changes in fatigue. Thus, while inflammation may play a role in the initial development of fatigue, inflammatory activity may play a greater role in maintaining depressive symptoms, which in turn could contribute to the persistence of fatigue.

There was no evidence that dysregulation of cortisol rhythms played a role in post-treatment fatigue in the current study. Contrary to expectations, lower morning

levels of cortisol were not significantly related to greater fatigue. Furthermore, participants with greater fatigue did not exhibit significantly flatter cortisol slopes than participants with no fatigue, although the trends in the data were in line with expectations. As cortisol levels are known to change rapidly in the time period after wakening and in response to other factors, such as stress and diet, and the correct timing of sample collection relied on participant adherence to collection instructions, the cortisol values obtained may not have accurately captured the actual pattern of cortisol (Clow et al., 2004; Kudielka et al., 2003). It is also possible that HPA dysregulation only plays a role in more severe and/or persistent fatigue, and that therefore the association between cortisol patterns and fatigue is not observed on a continuum as was investigated here. Future research that more adequately ensures sample collection at the specified times and includes participants with a formal diagnosis of persistent post-treatment CRF may reveal stronger relationships between cortisol rhythms and fatigue severity. Nevertheless, it is clear from the current findings and previous research that although biological factors, such as inflammatory activity and HPA-dysfunction, are implicated in CRF, such factors cannot fully account for the occurrence of fatigue either before or after cancer treatment. Furthermore, cancer and treatment-related factors were not significantly associated with fatigue at any of the assessment points. Conversely, psychological, cognitive and behavioural factors were strong predictors of fatigue; targeting such factors thus offers a reasoned approach for treating CRF.

10.2 Theoretical Implications.

Given the multitude of potential contributing factors that have been linked to CRF, and evidence that there is a temporal dimension to the role that they play, the cognitive-behavioural model offers an attractive framework through which to understand CRF. Indeed, the evidence summarised in the preceding section illustrates how many of the pathways proposed by the model were supported by the data presented in this thesis. Specifically, the findings supported the idea that people's beliefs, thinking patterns, and psychological wellbeing can contribute to their level of fatigue, and that interrelations exist between such contributing factors. Nevertheless, other aspects of the model were not supported. For example, there was little evidence that behavioural variables helped to maintain fatigue in the integrated manner suggested by the model. The behavioural variables assessed were not associated with psychological or cognitive predictors (e.g., fear of activity) and the data did not support the idea that factors such as maintaining activity or accommodating to fatigue impacted on fatigue

severity. Instead, more general negative thinking patterns regarding fatigue and a preoccupation with symptoms were predictive of fatigue, supporting the model's focus on the role of cognitive and psychological adjustment but not behavioural responses.

The evidence for the role of the biological/physiological contributing factors proposed by the model was mixed. The role of cancer and treatment-related factors as precipitating factors was not supported; however, there was some evidence that physiological factors were related to fatigue severity. As the cognitive-behavioural model is vague in terms of the specific perpetuating role of biological factors, physiological models on the mechanisms underlying fatigue provided the theoretical basis for the biological factors tested in the thesis; specifically, HPA-axis dysfunction and cytokine dysregulation were investigated. A role for HPA disturbances, and cortisol levels in particular, in post-treatment CRF was not supported; however, the conclusions that can be drawn from this data are limited due to methodological shortcomings in how cortisol was assessed. Nevertheless, the findings did support the idea that mild inflammatory activity is linked to fatigue before chemotherapy. Furthermore, though there was no indication that inflammation was directly related to changes in fatigue, there was tentative evidence that levels of the inflammatory cytokine IL-6 and concentrations of kynurenine play a role in maintaining depressive symptoms over time, and thus may impact on CRF indirectly through such psychological channels. Such findings are in line with the cognitive-behavioural framework, which suggests that biological factors reciprocally influence other contributing factors, including psychological ones, to maintain symptoms. More specific biological pathways of influence, which integrate such physiological models of CRF and draw more explicit links between biological and psychological contributing factors, could thus add to the cognitive-behavioural model, though additional work is necessary to replicate these findings.

The cognitive-behavioural model could also be expanded to incorporate more contextual social influences. The model offers no explanation of how cognitive representations and psychological responses to CRF are formed or what they are based on. In order to consider this, the thesis moved away from the cognitive-behavioural model and explored participants' cognitions regarding fatigue from a social constructivist perspective in Chapter 9. By considering the social discourses of cancer and cancer survivorship, the thesis illustrated the importance of the sociocultural context in shaping people's perceptions of what is "normal" or acceptable after cancer

treatment and how such perceptions are linked with proposed psychological and cognitive predictors of fatigue. Concerns about not fitting into socially prescribed timelines for recovery and embodying the prototypical "cancer survivor" may feed into fears of cancer recurrence, unhealthy preoccupations with symptoms, maladaptive thinking patterns and psychological distress. Indeed, concerns about whether their fatigue was "normal" or an indication of cancer recurrence were raised by several participants in Chapter 9 and fear of recurrence was an indirect predictor of fatigue severity, through catastrophsing, stress, and depression in Chapter 5. Social comparisons and societal expectations may thus influence people's cognitive and psychological responses to symptoms. While contextual factors and previous experiences of symptoms are thought to help shape people's illness representations in the CSM, this process is not formally integrated into this model or into the cognitive-behavioural model. Explicitly incorporating the social context into the cognitive-behavioural model would thus expand the model in a meaningful way.

The current thesis adopted very diverse perspectives and approaches, ranging from physiological measures and theories of CRF to qualitative techniques and a social constructivist perspective, and attempted to integrate these to obtain a better understanding of this complex and multidimensional condition. Given the broad range of potential contributing factors to CRF, this approach was justified. Incorporating a diversity of techniques and theoretical perspectives can enhance understanding as no one perspective on health is entirely adequate. Considering things from another perspective can give rise to new issues or influencing factors that might not have become known otherwise. Nevertheless, it is difficult to integrate diverse and seemingly inconsistent approaches in one uniform theoretical model. Furthermore, applying too broad an approach to a specific problem can make the condition and its treatment more ambiguous rather than more defined, and this could negatively affect how patients are treated in practical terms. It is harder to identify the optimal treatment approach for conditions that are deemed to be caused by many different factors in combination. Given that CRF is already perceived as ambiguous by patients and health care professionals (see Chapter 9), broadening how it is conceptualised in clinical practise may not facilitate understanding and recognition of this condition. However, one of the attractive aspects of integrating different approaches under a cognitive-behavioural framework is that, while the model incorporates many different variables, it does not assume that the same system of influences works for everyone; it is person

specific, whereby one set of contributing factors may apply to one patient but not another. Thus, the framework stresses the importance of an individualised approach to understanding and treating fatigue in any one patient and exploring the role of several, potentially interrelated, contributing factors in a systematic and structured way. Therefore, it can serve as a guide for clinical investigations of CRF, that might otherwise only focus on a select number of commonly perceived contributing factors such as blood counts and depression.

A broad, multidimensional model for understanding CRF makes it more difficult to study, necessitating the inclusion of many different variables and the use of larger samples for research; however, anything less denies the complexity of the condition. If one set of contributing factors is investigated in isolation, a misleading impression of the causes of CRF may emerge since most of the identified contributing factors are interrelated and therefore may mediate or even moderate their relationships with fatigue. Thus while it is challenging to bring together different and often theoretically opposed perspectives and methods of study, failing to at least consider such diverse approaches places unnecessary and unhelpful limits on our understanding.

10.3 Practical Implications

Fatigue can be a distressing symptom that can negatively affect cancer patients' physical and psychological wellbeing and continue to contribute to lower QOL long after the successful completion of treatment. Although the study was unable to determine whether associations with fatigue were causal, the cognitive-behavioural predictors identified nevertheless provide potential targets for interventions to manage the symptoms of CRF. The strong association between negative representations of CRF with both fatigue severity and other psychological and behavioural predictors supports the use of CBT for treating CRF. Furthermore, the consistent relationship between fatigue and depression underscores the importance of addressing the possibility that symptoms of fatigue may be linked to depression. Although no adaptive behavioural coping strategies were identified based on the results, the findings suggest that engaging in passive coping in response to fatigue is harmful. Specifically, focussing on symptoms was associated with poorer outcomes. Furthermore, there was some indication that physical activity predicted the trajectory of fatigue, whereby those with lower activity levels showed less favourable outcomes. Targeting such behavioural factors is also in line with the CBT approach to CRF and supports the use of exercise interventions.

With regards to the timing of interventions, the results from Chapter 4 suggest that patients who experience fatigue before chemotherapy are at increased risk of experiencing fatigue after cancer treatment has been completed. Thus, targeting the correlates of fatigue before or during chemotherapy may have long-term benefits for patients. Screening and management of both fatigue and psychological distress from before the start of cancer treatment should be integrated into routine clinical care; such timely and targeted interventions may help to decrease the burden of fatigue and cancer treatments for patients during and after treatment. Findings from the qualitative analysis in Chapter 9 indicate that the first few months post-treatment can also be a particularly difficult time for patients, as the extent of medical support radically reduces after the acute treatment phase. Uncertainty about the nature of symptoms and the success of treatment during this time may contribute to the development of unhelpful cognitive, psychological and behavioural responses. Thus, interventions that support patients during this transition time may be particularly effective.

The findings from Chapter 9 also illustrate the importance of adequately informing patients about the likelihood of experiencing fatigue during and after treatment. Many participants reported that they were not sufficiently warned about fatigue or prepared for the extent of its impact on their lives. When patients are well informed about side-effects, they are better prepared and less distressed when they occur (Ream et al., 2003). Perceived lack of warning about CRF may reflect differences in how patients and medical staff view cancer treatments; while treatments are a means to a cure, the cost of treatments in terms of their long-term impact on health and functioning are also a key concern for patients. However, the findings suggested that enormity of cancer dwarfs other health concerns and can make it difficult for patients to talk about such issues. A clearer conceptualisation of CRF in clinical practice would facilitate the emergence of a narrative of CRF that acknowledges the potentially enduring effects of cancer. Themes from the qualitative analysis indicated that the distress associated with fatigue can be exacerbated by the lack of recognition this symptom receives both in clinical practice and in the wider social context. Participants reported that their concerns were dismissed when biological indicators of dysfunction were not apparent, when intervention approaches were not offered, or when fatigue was simply attributed to depression. Although the findings from this thesis support the role of psychological factors in the aetiology of CRF, the results highlight

the multitude of factors that are linked with fatigue in cancer patients and thus the importance of adapting an integrated approach to assessment and treatment.

10.4 Limitations

The study sample sizes were small to moderate and a number of analyses (e.g., phase 3 in Chapter 5) were carried out on even smaller subsamples of participants. The participants in all studies were also predominantly female and the breakdown of cancer types did not reflect the incidence of different cancers in Ireland. The use of such samples thus limits the generalisability of the findings to the wider population of cancer patients. In addition, many demographic characteristics and individual differences between participants were not taken into account in the analyses. For example, the impact of socioeconomic factors, additional medication use, specific comorbidities, or details related to surgical or medical treatment were not explored.

Assessment of the various contributing factors examined in this thesis relied heavily on the use of questionnaire measures. The accuracy and reliability of self-report scales for the assessment of behaviours, such as physical activity, was previously discussed in Chapter 4 and is an issue that must be addressed in future studies. Furthermore, although fatigue was assessed using one of the most widely cited and reliable scales of CRF, the FACT-F, the inadequacy of using self-report to assess CRF has previously been noted (Alexander, Minton, & Stone, 2009; Van Belle et al., 2005). Establishing fatigue caseness using the diagnostic criteria for CRF would give a more accurate assessment of CRF and could reveal different relationships with predictors. The use of questionnaires to assess both outcomes and predictors may also mean that the observed associations between constructs were inflated due to a common method bias (Podsakoff et al., 2003). Future studies should guard against this by using a variety of sources to obtain data. Although actigraph data on sleep and activity was also collected in the current study, it was not feasible to do this for all participants and for all assessment occasions.

The accuracy of longitudinal assessment of fatigue severity using questionnaires could also be affected by a 'response shift' in patients' self-reports of this side-effect (Andrykowski et al., 2009). Research suggests that patients may adapt to fatigue over the course of their treatment, and thereby recalibrate their standards for judging fatigue severity. A number of studies on CRF have documented a response shift after cancer treatment whereby patients' retrospective estimates of fatigue pretreatment were lower compared to the actual fatigue severity scores reported before treatment, suggesting that

increased levels of fatigue during active treatment may cause patients to redefine how they evaluate fatigue severity (e.g., Andrykowski et al., 2009; Jansen et al., 2000; Visser et al., 2000). Thus, longitudinal research on the severity and persistence of fatigue after cancer treatment may actually underestimate the extent and impact of CRF. Such issues were not taken into account in the current study.

Finally, the longitudinal analyses reported in Chapters 4, 6 and 7 imposed an oversimplified structure on participants' cancer treatment trajectories. Although all participants were treated with a type of chemotherapy, participants followed different treatment regimens with different chemotherapy drugs and had diverse additional treatments, such as radiation and hormonal therapies. Although every effort was made to assess patients at corresponding stages of their treatment plan, this was not always feasible. As a result, the follow-up occasions varied somewhat between participants and this may have impacted on the relationships between the predictors and fatigue that emerged.

10.5 Future research

Although many factors were significantly related to fatigue and demonstrated very similar patterns to fatigue over time, it was not possible to determine whether the predictors of fatigue that were examined in this thesis contributed to this symptom, occurred as a consequence of this symptom or were caused by similar underlying factors. Although some researchers have used statistical techniques, such as cross-lagged panel analysis, to deduce causal pathways over two timepoints (e.g., Brown et al., 2012), the directionality of such relationships can only be determined through prospective longitudinal studies with sufficient assessment points to establish order of occurrence and intervention studies that address the mediators of treatment-induced changes.

With regards to the CSM and CRF, future research could further examine the relationships between specific cognitions and outcomes and thereby build on the cognitive model of CRF. The findings presented in Chapter 5 suggested that the relationship between negative representations and fatigue was mainly driven by severe consequence perceptions. However, the qualitative findings presented in Chapter 9 indicated that cognitions relating to low coherence perceptions and cancer-related causal attributions could contribute to predictors such as fear of recurrence and catastrophising. Further examination of such indirect relationships between specific cognitions and outcomes may be helpful to develop the cognitive-behavioural model.

However, other ways of quantifying cancer-related causal attributions may be necessary. One option may be to differentiate between the perceived precipitating and perpetuating factors of CRF when assessing causal attributions using the IPQ. Doing so would help to distinguish between patients who attribute the initial development of their fatigue to cancer and/or cancer treatments and those who continue to attribute post-treatment fatigue to disease and treatment-related factors. The absence of this distinction may partly explain why fatigue was not related to cancer-related attributions in the current study. Furthermore, as the cognitive-behavioural model emphasises the dynamic role of cognitions in maintaining post-treatment CRF, prospective studies that assess whether representations of fatigue after treatment can predict the development of persistent CRF are required to test this aspect of the model.

Although some theoretically consistent relationships emerged between physical activity, coping behaviours and fatigue in the current thesis, it is recommended that future studies examine the behavioural aspects of the cognitive-behavioural model of CRF in greater detail, using alternative methods of assessing activity levels and the specific coping strategies used for managing CRF. The use of actigraphs, pedometers, or activity diaries may more reliably assess activity levels than physical activity questionnaires, or could provide a means of triangulating data. With regards to coping behaviours, it is recommended that more specific and tailored scales for assessing coping in CRF are developed. Although the measure used in the current study, showed adequate psychometric properties for most subscales, it did not adequately capture behaviours such as activity avoidance. The internal reliability of the subscale that addressed this construct was consistently low. Furthermore, although the role of the behavioural strategy 'maintaining activity' was explored, which assessed whether individuals coped by pushing past fatigue and carrying on with normal activities, the use of balanced levels of exercise as a management strategy was not captured. In addition, it would be interesting to explore 'all-or-nothing' behaviour, a behavioural pattern characterised by excessive activity followed by enforced rest, in the context of CRF. The tendency to respond to symptoms in an all-or-nothing manner has been linked to chronic pain (Murphy, Lindsay, & De C Williams, 1997), the development of irritable bowel syndrome after gastroenteritis (Spence & Moss-Morris, 2007), fatigue and social impairment in multiple sclerosis (Skerrett & Moss-Morris, 2006), and the onset of CFS (Moss-Morris, 2005). Regaining previous levels of physical functioning after cancer treatment can be a slow process that nevertheless takes place within a

sociocultural context laden with expectations of how recovery should proceed. The findings presented in Chapter 9 illustrate that people often perceive pressure from themselves or from others to be "back to normal" after treatment. Such pressure may lead people to quickly attempt to return to their former levels of activity; however, doing too much too soon can lead to exhaustion and may trigger a maladaptive over-activity/under-activity cycle that could help to prolong fatigue.

10.6 Conclusion

The aim of this thesis was to elucidate the mechanisms underlying the development of CRF using a cognitive-behavioural model of illness as a theoretical framework. A diversity of methods was used to address this aim, enabling the study of a broad range of potential contributing factors and the complexity of interrelationships between them. Although only a selection of the pathways specified by the model could be tested, and causal relationships between predictors and CRF could only be inferred, the results presented in this thesis nevertheless make a significant contribution. The research represents the first comprehensive application of a cognitive-behavioural model to CRF; evidence for biological, psychological, behavioural, and cognitive contributing factors to fatigue both before and after cancer treatment was outlined, and interactions between such factors, based on sound theoretical principles, were demonstrated. Furthermore, a measure for assessing cognitions regarding CRF was presented, and the mechanisms through which cognitions might impact on post-treatment CRF were considered by testing theoretically-informed mediational pathways. The findings suggest that the cognitive-behavioural model offers a useful integrated conceptual approach to understanding CRF. Furthermore, although this research focussed on biological, psychological, behavioural and cognitive predictors, the qualitative findings presented also highlight the importance of considering sociocultural influences on experiences of this side-effect. Social norms and cultural expectations not only shape cognitive representations, but can also play an important role in driving behavioural and psychological responses to CRF.

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Appendix 1: Illness perception questionnaire for cancer-related fatigue (IPQ-CRF)

Section A: Symptoms

Listed below are a number of symptoms that you may or may not have experienced since your Cancer-Related Fatigue (CRF) began. Please indicate by circling ***Yes*** or ***No***, whether you experience any of these symptoms every day or nearly every day, AND whether you believe that these symptoms are specifically related to your CRF, ***Yes*** or ***No.***

Symptom:	I have experienced this symptom		This symptom is related to my cancer-related fatigue	
Diminished energy or increased need to rest	yes	no	yes	no
Diminished concentration or attention	yes	no	yes	no
Pain	yes	no	yes	no
Sleep difficulties or excessive sleepiness	yes	no	yes	no
Problems with short-term memory	yes	no	yes	no
Headaches	yes	no	yes	no
A need to struggle to overcome inactivity	yes	no	yes	no
Difficulty completing daily tasks	yes	no	yes	no
Dizziness	yes	no	yes	no
Unrefreshing or nonrestorative sleep	yes	no	yes	no
Decreased motivation or loss of interest	yes	no	yes	no
Stiff Joints	yes	no	yes	no
Significant distress or impairment in social or occupational functioning	yes	no	yes	no
General weakness or limb heaviness	yes	no	yes	no
Sore Eyes	yes	no	yes	no
Marked emotional response (e.g., sadness, frustration, or irritability)	yes	no	yes	no
Fatigue after physical activity that lasts several hours	yes	no	yes	no
Upset Stomach	yes	no	yes	no

Please list any other symptoms you have experienced that you believe are related to ***YOUR*** CRF:

_____

Section B: Views about your cancer-related fatigue

We are interested in your own personal views of how you see your cancer-related fatigue (CRF). Please indicate how much you agree or disagree with the following statements about your fatigue by ticking the appropriate box below.

Views about your fatigue	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
My fatigue is likely to be permanent rather than temporary.					
My fatigue will last for a long time.					
My fatigue will improve in time.					
The severity of my fatigue changes from day to day.					
My fatigue is unpredictable.					
I go though cycles in which my fatigue gets better and worse.					
My fatigue is a serious condition.					
My fatigue has had major consequences for my life.					
My fatigue causes difficulties for those who are close to me.					
What I do can determine whether my fatigue gets better or worse.					
The course of my fatigue depends on me.					
I have the power to influence my fatigue.					
The negative effects of my fatigue can be prevented by treatment.					
Treatment can control my fatigue.					
There is nothing which can help my fatigue.					
My fatigue is a mystery to me.					
My fatigue doesn't make any sense to me.					
I have a clear picture or understanding of my fatigue.					
I get depressed when I think about my fatigue.					
When I think about my fatigue I get upset.					
Having this fatigue makes me feel anxious.					

Section C: Causes of your fatigue

We are interested in what **you** think is causing your **current level** of fatigue. As people are very different, **there are no correct answers** for this question. We are interested in your own views rather than what others including doctors or family may have suggested to you. Below is a list of factors that may play a role in **causing or contributing** to your fatigue.

Please indicate how much you agree or disagree that they are causes or contributing factors by ticking the appropriate box.

Possible Causes	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The cancer					
My cancer treatment (e.g., chemotherapy, surgery etc.)					
Side-effects from my cancer and/or my treatment					
Other non-cancer related illnesses/conditions					
Problems with my immune system					
Pain					
Poor medical care in the past					
Hereditary - it runs in my family					
My own behaviour					
Decreased activity					
Decreased physical fitness					
My diet / Nutrition					
Sleep disturbances					
Stress					
Overwork					
My personality					
Distress (e.g., anxiety or depression)					
Mental attitude (e.g., thinking about life negatively)					
Family problems or worries					

Please list in rank-order the four most important factors that you now believe are the main causes or contributors to **YOUR** fatigue.

You may use any of the items from the previous section, or you may have additional ideas of your own.

The most important causes or contributing factors to my fatigue are:

1) _____ 2) _____ 3) _____

Appendix 2: Ethical approval letters

University ethical approval letter for studies in Chapters 2 to 9.

School of Psychology
University of Dublin, Trinity College
Dublin 2, Ireland

Tel: +353 1 896 1886
Fax: +353 1 671 2006

12 June 2009

F.A.O. Maria Pertl

School of Psychology Research Ethics Committee

Dear Maria,

Following receipt of specified amendments, I am pleased to inform you that your application entitled "Factors contributing to prolonged cancer-related fatigue" has been approved by the School of Psychology Research Ethics Committee.

Yours sincerely,

Kevin Thomas, PhD
Chair,
School of Psychology Research Ethics Committee

Hospital ethical approval letter for studies in Chapters 2 to 9.

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

Dan Lynch Ph: 4142860 email: Dan.Lynch@amnch.ie
Ursula Ryan Ph: 4142342 email: Ursula.Ryan@amnch.ie
Secretariat Fax 4142371

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
Research Ethics Committee
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Dr. Sonya Collier
Principal Clinical Psychologist
Psychological Medicine Service
Old Admin Building
St. James's Hospital
James Street
Dublin 8

April 30th 2009

Please quote this reference in any follow up to this letter: 2009/04/07 Chairman's Action

Re: A Study Exploring the Factors that Contribute to Cancer Related Fatigue in Disease Free Cancer Patients.

Dear Dr. Collier,

Thank you for your recent submission of the above proposal to the SJH/AMNCH Research Ethics Committee. The Chairman has given ethical approval to this proposal on behalf of the Committee.

Yours sincerely,

Daniel R. Lynch,
Secretary,
SJH/AMNCH Research Ethics Committee.

University ethical approval letter for intervention study in Chapter 5.

COLÁISTE NA TRÍONÓIDE, BAILE ÁTHA CLIATH | TRINITY COLLEGE DUBLIN
Ollscoil Átha Cliath | The University of Dublin

18th March 2011

F.A.O. Maria Pertl

School of Psychology Research Ethics Committee

Dear Maria,

I am pleased to inform you that your application entitled "Evaluation of a cognitive-behavioural intervention for prolonged cancer-related fatigue in cancer survivors" has been approved by the School of Psychology Research Ethics Committee.

Yours sincerely,

Dr. Tim Trimble
Chair
School of Psychology Research Ethics Committee

SCHOOL OF PSYCHOLOGY
Áras an Phiarsaigh
Trinity College
Dublin 2

Scoil na Síceolaíochta,
Dámh na nEolaíochtaí Sóisialta agus Daonna,
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Hospital ethical approval letter for intervention study in Chapter 5.

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

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Principal Clinical Psychologist
Psychological Medicine Service
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Dublin 8

March 3rd. 2011

REC reference: 2011/01/14

(Please quote REC reference and EudraCT number on all correspondence)

RE: Evaluation of cognitive-behavioural intervention for ongoing fatigue after cancer treatment.

Dear Dr. Collier,

The SJH / AMNCH Research Ethics Committee, having reviewed the above application, decided to give ethical approval to this proposed study.

Yours sincerely,

Dr. Ray McDermott,
Chairman, SJH/AMNCH Research Ethics Committee

Appendix 3: Information sheet and consent form for Chapter 2



TRINITY COLLEGE DUBLIN
COLÁISTE NA TRÍONÓIDE, BAILE ÁTHA CLIATH

Fatigue Study Patient Information sheet

1. Title of study:
Cancer-related fatigue: exploring patients' beliefs and coping strategies.

2. Introduction: Many cancer patients report feelings of fatigue after their cancer treatments are finished. Patients use many different strategies to manage such fatigue. Patients' own beliefs about the nature and causes of their fatigue are important. However, at present, there are no adequate ways to assess patients' beliefs about their fatigue or the coping strategies they use. The aim of the current project is to develop questionnaires for this purpose.

Participation in this study involves completing a number of questionnaires.

3. Procedures: Any patient with cancer-related fatigue can participate in this study. Participants must be over the age of 18.

If you choose to participate, you will be asked to complete of a number of questionnaires that ask you about your beliefs regarding your fatigue, the coping methods you are using to manage this symptom, and some medical information about your diagnosis and your treatment. We are interested in what you think about the questions and any thoughts you have about the topics covered.

As we are testing these questionnaires for the first time we are also interested in seeing how reliable they are. Therefore, it would help us if you could complete the questionnaires twice – once today and for the second time in 1 to 2 weeks. If you are happy to complete the questionnaire twice please provide your contact information on the consent form. You will be contacted in one week and another copy of the questionnaire will be sent to you. If you do not want to complete the questionnaire twice you do not have to supply contact information. You can still participate in the first part of the study by completing and returning the questionnaire today.

4. Benefits: The study may have no direct benefit to you but the results may benefit subsequent patients who suffer from cancer-related fatigue.

5. Risks: There are no known physical risks associated with participation in this study.

6. Exclusion from participation: You cannot be in this study if any of the following are true:

- If you have any other severe health problems.
- If you are younger than 18 years of age.
- If you have severe distress.

7. Alternative treatment: You do not have to be a part of this study to be treated.

8. Confidentiality: Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone outside the hospital. A code will be used to anonymise all of the questionnaires you complete. The code will be linked to your identifying information so that follow-up data from each assessment can be linked. However, the linked codes will be kept secure in a password protected file, which can only be accessed by the researchers. None of these measures will interfere with your rights under the Freedom of Information Act 1977 (amended 2003).

9. Compensation: The researchers involved in this study have indemnity cover from Trinity College Dublin or St. James's Hospital. Nothing in this document restricts or curtails your rights.

10. Voluntary Participation: If you volunteer to participate in this study, you may quit at any time. If you decide not to participate, or if you quit, you will not be penalised and will not give up any benefits which you had before entering the study.

11. Stopping the study: You understand that the researchers or the sponsoring company may stop your participation in the study at any time without your consent.

12. Permission: This study has Research Ethics Committee approval from the School of Psychology, Trinity College Dublin. The research is funded by the Irish Cancer Society and the IRCSET 'Embark Initiative'.

13. Further information: You can get more information or answers to your questions about the study, your participation in the study, and your rights from Dr Sonya Collier, Principal Clinical Psychologist, who can be telephoned at 01 410 3457.

You can also contact the researcher Maria Pertl (phone: 01 896 3083, e-mail: pertlm@tcd.ie) or the research supervisor Dr David Hevey (phone: 01 896 2406, e-mail: heveydt@tcd.ie in the School of Psychology, Áras an Phiarsaigh, Trinity College Dublin.

TRINITY COLLEGE DUBLIN
COLÁISTE NA TRÍONÓIDE, BAILE ÁTHA CLIATH

FATIGUE STUDY CONSENT FORM

Title of research study: Cancer-related fatigue: exploring patients' beliefs and coping strategies.

This study and this consent form have been explained to me. The researchers have answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study.

I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights. I have received a copy of this agreement.

PARTICIPANT'S NAME: _____

PARTICIPANT'S SIGNATURE: _____ **Date:** _____
Date on which the participant was first furnished with this form: _____

Please give the following contact information if you are happy to complete the questionnaire twice:

PHONE: _____ **E-MAIL ADDRESS:**_____

ADDRESS:

_____

_____

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Researcher's signature: _____ **Date:** _____

CONTACT DETAILS:

Maria Pertl (researcher)
School of Psychology, TCD
phone: 01 896 3083
e-mail:pertlm@tcd.ie

Dr. David Hevey (supervisor)
School of Psychology, TCD
phone: 01 896 2406
e-mail: heveydt@tcd.ie

Appendix 4: Information sheet and consent form for Chapter 4 - 8

Patient Information and Consent Form

SJH / AMNCH RESEARCH ETHICS COMMITTEE

A STUDY EXPLORING THE FACTORS THAT CONTRIBUTE TO CANCER-RELATED FATIGUE.

1. What is the aim of the study?

Many cancer patients report feelings of fatigue after their cancer treatments are finished. It is not known for certain why some people develop cancer-related fatigue and why some disease-free patients continue to have fatigue for months or even years after their cancer treatment is finished. The purpose of the current project is to investigate the factors that are associated with the development and continuation of fatigue and to evaluate a group intervention for such fatigue.

2. What does participation involve?

Any patient over the age of 18 who is being treated for cancer with either radiation therapy or chemotherapy can participate in this study. Participation involves five assessments over a period of about one year: Time 1 - before radiation and/or chemotherapy treatment, Time 2 – after treatment, Time 3 – three months after treatment, Time 4 - six months after treatment, and Time 5 - nine months after treatment. Each assessment will take place during one of your scheduled clinical visits to the hospital. For each assessment you will be asked to complete a number of written questionnaires. In addition, you may also be asked to give a blood sample and/or saliva samples and to wear a small device called an actigraph, which measures your activity level and how well you are sleeping. If you are currently not experiencing any fatigue then you can still participate in the study. If you are experiencing fatigue, and if you continue to do so for the next few months, you will be randomly assigned to either an intervention group for fatigue or a usual care group.

3. What do I need to do to participate? If you choose to participate, a researcher will meet with you during your scheduled clinical visits to the hospital at each of the 5 assessment points. Each assessment may involve the following:

- Filling in questionnaires: During each assessment you will be asked to complete a number of questionnaires that ask you about your level of fatigue, your level of activity, how well you are sleeping, your coping behaviours, your beliefs about your fatigue, as well as your psychological wellbeing (e.g., your level of anxiety and stress). These questionnaires take approximately 45 minutes to complete. They can be completed while you are receiving treatment or while you are waiting to be seen in the hospital. If you do not have time to complete them during your visit then you will be given a stamped addressed envelope so that you can finish them later and return them to the researchers by post.
- Giving a blood sample: You may also be asked to give blood samples as part of your assessments so that the researchers can test how well your immune system is working. Blood samples will only be taken when you are already getting a blood test as part of your clinical treatment in the hospital. The researchers will arrange for extra blood samples (15ml) to be taken during your scheduled blood testing.
- Giving saliva samples: You may be asked to give saliva samples as part of your assessment so that the researchers can test for biological changes that might have occurred from your cancer treatment. If you are asked to give saliva samples, you will be given more detailed instructions and a simple saliva collection kit that you can post back to the researchers afterwards using stamped addressed envelopes provided.

- Wearing an actigraph: You may be asked to wear a small devise called an actigraph for a few days so that the researchers can measure your level of physical activity and the length and quality of your sleep. The actigraph is worn like a watch on your wrist. If you are asked to wear an actigraph, you will be given more detailed instructions for wearing this device and a stamped addressed envelope for returning it afterwards.

If you still experience severe fatigue at the third assessment (3 months after your treatment has been completed) you may be asked to participate in an intervention for your fatigue. The intervention will involve attending two group-based information sessions provided by a principal clinical psychologist on how to manage and reduce fatigue. Participants will be randomly selected for this intervention.

4. How will this study benefit me?

The study may have no direct benefit to you but the results may benefit subsequent patients who suffer from cancer-related fatigue. The implications of this research could help to improve patients' quality of life by finding an effective intervention to reduce cancer-related fatigue. Attending the group intervention may also be helpful in combating your fatigue. In addition, if you participate you will receive more intensive psychological supervision following your cancer treatment.

5. Are there any risks if I participate?

There are no known physical risks associated with participation in this study.

6. Exclusion from participation.

You cannot be in this study if any of the following are true:

- If you have a cancer recurrence.
- If you have any other severe health problems.
- If you are younger than 18 years of age.
- If you have severe distress.

7. Will my details be kept confidential if I participate?

Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone outside the hospital.

8. What happens if I want to stop participating in the study?

If you volunteer to participate in this study, you may quit at any time. If you decide not to participate, or if you quit, you will not be penalised and will not give up any benefits which you had before entering the study.

10. Compensation:

The researchers involved in this study have indemnity cover from Trinity College Dublin or St. James's Hospital. Nothing in this document restricts or curtails your rights.

11. Permission:

This study has hospital Research Ethics Committee approval.

12. How can I get further information?

You can get more information or answers to your questions about the study, your participation in the study, and your rights from a member of the research team:

Dr Sonya Collier	Principal Clinical Psychologist Department of Psychological Medicine St. James's Hospital	phone : 01 410 3457
Maria Pertl	Researcher School of Psychology Trinity College, Dublin	phone: 087 1315256 e-mail: pertlm@tcd.ie

Patient Consent Form

SJH / AMNCH RESEARCH ETHICS COMMITTEE

A STUDY EXPLORING THE FACTORS THAT CONTRIBUTE TO CANCER-RELATED FATIGUE.

This study and this consent form have been explained to me. The researchers have answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study.

I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights. I have received a copy of this agreement.

PARTICIPANT'S NAME: _____

PARTICIPANT'S SIGNATURE: _____

Date: _____

Date on which the participant was first furnished with this form:_____

PARTICIPANTS' CONTACT NUMBER: _____

PARTICIPANTS' ADDRESS:

_____

_____

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Researcher's signature: _____

Date: _____

Researcher Contact Information: Maria Pertl, phone: 087 1315256

Appendix 5: Sleep diary

Sleep Diary

*Please complete each morning after getting up.

Name: _____ Starting day and date: _____ Actigraph start time: _____

	Example	Day 1	Day 2
Day of the week (start of recording period - end of recording period):	*Monday - Tuesday*		
Location of sleep data collection:	*Home*		
Did another person or pet share your bedroom? *Yes/No*	*Yes, my partner*		
What time did you get into bed last night?	*10pm*		
Lights out time:	*11.30pm*		
Lights on time (wake time):	*7.30*		
Total hours of sleep last night:	*7 ½ hrs*		
How long did it take you to get to sleep?	*25mins*		
Did you wake up during the night? *Yes/No* *If yes,* when and for how long?	*Yes* *3am, 10mins*		
Did you take any naps yesterday? *Yes/No* *If yes,* when and for how long?	*No* *n/a*		
Did you consume any caffeine (coffee, coca-cola, etc.) yesterday? *Yes/No* *If yes*, how much and when?	*Yes* *Coffee 9am, 3pm*		
Did you take any medications yesterday? *Yes / No* *If yes*, what medications (e.g., sleeping tablets)?	*Yes, 1x 50mg* *Clomipramine @10pm*		
How would you rate the quality of your sleep last night on a scale of 0–10 (0= "very bad" and 10= "excellent")?	*3*		
How refreshed do you feel now on a scale of 0–10 (0="not at all refreshed" and 10="extremely refreshed")?	*4*		
How would you rate your fatigue yesterday on a scale of 0–10 (0="no fatigue" and 10="extremely fatigued")?	*6*		
Did you take the actigraph off your wrist at any stage? *If yes,* when and for how long?	*No*		
Current date and time:	*06/01/11, 10am*		

Appendix 6: Details of participants' treatment and comorbidities for Chapter 3

Treatment details and clinical characteristics of participants (n = 100)

Treatment details	No	Comorbidities	No
Surgical procedure		None	51
Breast conservation	46	Hypertension	15
Mastectomy	31	Cholesterolemia	12
Hysterectomy	5	Thyroid problems	12
Anterior resection	3	Asthma	8
Hemicolectomy	4	Osteoarthritis	6
Hartman's procedure	1	Depression	5
No surgery	10	Back pain	3
Chemotherapy drug		Diabetes	3
AC-T	47	Gastro-Oesophageal Reflux Disease	3
TCH	16	Heart disease	3
TC	9	Fibromyology	2
FOLFOX	8	Irritable Bowel Syndrome	2
Cisplatin	7	Anemia	1
Taxol/Carbo	5	B12 deficiency	1
AC	4	Chrone's disease	1
R-CHOP	2	Coeliac disease	1
ABVD	1	Deep vein thrombosis	1
Taxol	1	Hiatus hernia	1
Hormonal therapy (Breast cancer only, n = 77)		Migraine	1
Tamoxifen	50 (65%)	Osteoparosis	1
Letrozole (Femara)	18 (23.4%)	Osteopenia	1
Arimidex	2 (2.6%)	Polycythaemia rubravera	1
None	7 (9%)	Vasculitis	1
Chemotherapy regimen			
Weekly chemotherapy	7		
Two week cycle	58		
Three week cycle	35		

Appendix 7: Information sheet and consent form for Chapter 5

SJH / AMNCH RESEARCH ETHICS COMMITTEE
PATIENT INFORMATION AND CONSENT

EVALUATION OF A COGNITIVE-BEHAVIOURAL INTERVENTION FOR ONGOING FATIGUE AFTER CANCER TREATMENT

1. What is the aim of the study?
Many cancer patients continue to experience fatigue after their cancer treatments are finished. There are many reasons why fatigue might continue after treatment. The purpose of the current project is to evaluate the effectiveness of an intervention for ongoing fatigue, which focuses on all the factors which might be contributing to your fatigue.
The intervention will be evaluated in two different formats: (1) a home-based programme that is delivered through a DVD and an accompanying manual and (2) a group-based programme that is delivered by a clinical psychologist in St. James's Hospital.

2. Who can participate in the study?
Anyone over the age of 18 who has finished their cancer treatment at least 6 months previously and is experiencing significant fatigue can participate in this study.

3. What will happen if I consent to participate?
If you consent to participate in this study you will participate in one of the following intervention groups for fatigue: a home-based or a group-based programme.
What if I participate in the home-based intervention programme?
If you decide on the home-based intervention you will be given a DVD course on cancer-related fatigue and an accompanying manual. The course covers the same 8 topics as the group-based intervention but you will be asked to work your way through the course yourself at home.
What if I participate in group-based intervention programme?
If you decide on the group-based intervention you will attend an 8-week course on cancer-related fatigue that is run in the Psychological Medicine Service in St. James's Hospital. Each session will take 2 hours and focus on a different aspect of cancer-related fatigue.

4. What does participation involve? In addition to completing one of the interventions for fatigue you will be asked to do the following:

- Filling in questionnaires: In order to evaluate how effective the interventions are for fatigue, you will be asked to fill in some questionnaires once before the intervention and twice after the intervention (one month after and 4 months after). These questionnaires will ask you about your level of fatigue, your level of physical activity, how well you are sleeping, your coping behaviours, your beliefs about your fatigue, as well as your psychological wellbeing (e.g., your level of anxiety and stress). These questionnaires take approximately 30 minutes to complete. You will be given a stamped addressed envelope so that you can complete the questionnaires at home and return them to the researchers by post.
- Giving saliva samples: You may be asked to give saliva samples before and after the intervention so that the researchers can test for biological factors that might be contributing to your fatigue. If you are asked to give saliva samples, you will be given more detailed instructions and a simple saliva collection kit that you can post back to the researchers afterwards using stamped addressed envelopes provided.
- Giving a blood sample: You may also be asked to give blood samples before and after the intervention so that the researchers can test for biological factors that might be contributing to your fatigue. Blood samples will only be taken when you

are already attending the hospital. If you do not want to give blood samples you can still participate in the rest of the study.

- Wearing an actigraph: You may be asked to wear a small device called an actigraph for a few days before and after the intervention so that the researchers can measure your level of physical activity and assess the quality of your sleep. The actigraph is worn like a watch on your wrist. If you are asked to wear an actigraph, you will be given more detailed instructions for wearing this device.

5. How will this study benefit me?

Participation in the intervention may be helpful for your fatigue. If the intervention does not have a direct benefit for you the results may benefit subsequent patients who suffer from cancer-related fatigue. The implications of this research could help to improve patients' quality of life by finding an effective intervention to reduce cancer-related fatigue.

6. Are there any risks if I participate?

There are no known physical risks associated with participation in this study.

7. Exclusion from participation.

You cannot be in this study if any of the following are true:

- If you have a cancer recurrence.
- If you have any other severe health problems.
- If you are younger than 18 years of age.

8. Alternative treatment:

You do not have to be a part of this study to be treated. There are other treatments available for treating cancer-related fatigue, which you can discuss with your doctor.

9. Will my details be kept confidential if I participate?

Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone outside the hospital.

10. What happens if I want to stop participating in the study?

If you volunteer to participate in this study, you may quit at any time. If you decide not to participate, or if you quit, you will not be penalised and will not give up any benefits which you had before entering the study.

11. Compensation:

The medical practitioners involved in this study have current medical malpractice insurance cover. The researchers involved in this study have indemnity cover from Trinity College Dublin or St. James's Hospital.

12. Permission:

This study has hospital research ethics committee approval.

13. Funding

This study is funded by the Irish Cancer Society and the IRCSET 'Embark Initiative'.

14. How can I get further information?

You can get more information or answers to your questions about the study, your participation in the study, and your rights from any members of the research team:

Maria Pertl	Researcher School of Psychology, Trinity College, Dublin	0871315256 (pertlm@tcd.ie)
Maeve Murray	Psychologist in Clinical Training School of Psychology, Trinity College, Dublin	4103457 (murram11@tcd.ie)
Dr. Sonya Collier	Principal Clinical Psychologist Department of Psychological Medicine, St. James's Hospital	410 3457
Dr. David Hevey	Research Supervisor School of Psychology, Trinity College, Dublin	8962406 (heveydt@tcd.ie)

SJH / AMNCH RESEARCH ETHICS COMMITTEE

CONSENT FORM

EVALUATION OF A COGNITIVE-BEHAVIOURAL INTERVENTION FOR ONGOING FATIGUE AFTER CANCER TREATMENT.

This study and this consent form have been explained to me. The researchers have answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study. I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights. I have received a copy of this form.

PARTICIPANT'S NAME: _____

PARTICIPANT'S SIGNATURE: _____ **Date:** ___/___/___

Date on which the participant was first furnished with this form: __/___/__

PARTICIPANTS' CONTACT NUMBER: _____

PARTICIPANTS' ADDRESS: _____

_____

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Researcher's signature: _____ **Date:** ___/___/___

Researcher Contact Information:

Maria Pertl	Researcher School of Psychology, Trinity College Dublin	0871315256 (pertlm@tcd.ie)
Maeve Murray	Psychologist in Clinical Training School of Psychology, Trinity College Dublin	4103457 (murram11@tcd.ie)
Dr. Sonya Collier	Principal Clinical Psychologist Department of Psychological Medicine, St. James's Hospital	410 3457
Dr. David Hevey	Research Supervisor School of Psychology, Trinity College Dublin	8962406 (heveydt@tcd.ie)

Appendix 8: Screening protocol of Study 3 in Chapter 5

Fatigue – basic symptoms

1. Have you finished your cancer treatment at least 6 months previously?*

Yes ☐ → ***No*** ☐ ***END***

↓

2. Have you experienced significant fatigue for at least two weeks in the past month?

Yes ☐ → ***No*** ☐ ***END***

↓

3. Have you experienced significant distress or impairment in social, occupational, or other important areas of functioning because of your fatigue and its symptoms?

Yes ☐ ***No*** ☐ → ***END***

↓

Onset of the fatigue

4. When did you first notice the fatigue?

a) **Long before cancer diagnosis** → ☐
END (unless fatigue can be attributed to cancer)

b) Before cancer diagnosis ☐
c) Just before cancer diagnosis ☐
d) During cancer treatment ☐
e) After cancer treatment ☐
f) Long after cancer treatment was finished ☐

↓

Co-morbidities

5. Do you have any other medical conditions that might be contributing to your fatigue?

- e.g., hypothyroidism

No ☐ ***Yes*** ☐ → ***END or carefully consider eligibility***

↓

*can still be on Hormone therapy – ask when they finished primary treatment and for how long they have been on hormones.

6. Do you drink Alcohol?

No ☐ ***Yes*** ☐ → ***How much alcohol do you usually drink per week?_____***

↓

7. Have you experienced any of the following symptoms in the last two weeks?

NO-YES

- Generalized weakness or limb heaviness..... ☐☐
- Diminished concentration or attention..... ☐☐
- Decreased motivation or interest to engage in usual activities..... ☐☐
- Insomnia (difficulty sleeping) or hypersomnia (excessive sleepiness)..... ☐☐
- Experience of sleep as unrefreshing or nonrestorative..... ☐☐
- Perceived need to struggle to overcome inactivity..... ☐☐
- Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued..... ☐☐
- Difficulty completing daily tasks attributed to feeling fatigued..... ☐☐
- Perceived problems with short-term memory..... ☐☐
- Fatigue after physical activity that lasts several hours ..... ☐☐

<5 of these symptoms → ***END***

8. Are you currently experiencing any feelings of depression?

No ☐ *Yes* ☐

a) When did these feelings of depression begin?

- **Long before cancer diagnosis** ☐ → ***consider eligibility***
- Before cancer diagnosis ☐
- During cancer treatment ☐
- After cancer treatment ☐
- Long after cancer treatment ☐

b) Are you receiving any psychological or medical treatment for depression?

i. Please specify:_____

If in structured treatment programme → ***END***

c) Which did you experience first: fatigue or feelings of depression?

Fatigue ☐ **Depression** ☐ → ***consider eligibility carefully***

9. Have you ever had depression?

No ☐ *Yes* ☐

Were you diagnosed with depression?

No ☐ *Yes* ☐

When did you have depression and for how long?_____

a) Did you receive any psychological or medical treatment for depression?

Please specify:_____

10. Have you ever received any form of psychological or psychiatric treatment?

No ☐ *Yes* ☐ Please specify: _____

Appendix 9: Factor structure of the coping with CRF scale.

The factor structure underlying the coping with CRF scale was explored using principal components analysis (PCA) with a Varimax rotation. The number of factors was determined by examining the Eigenvalues and the scree plot; item loadings greater than 0.5 were taken to represent a factor. The analysis produced six factors with Eignevalues over 1, which accounted for 74% of the variance (see table for item loadings). The factors were labelled accommodating to the fatigue, information seeking, focussing on symptoms, activity avoidance, maintaining activity, and emotion focused coping and they accounted for 14%, 14%, 13.5%, 12% 11% and 9.5% of the total rotated variance respectively.

PCA with Varimax rotation of the coping with CRF items

	Component					
	1	2	3	4	5	6
Accommodating to the fatigue						
I manage my time so that I don't have too much to do in one day	**.87**	.04	.02	.10	.03	.05
I try to pace myself so that I don't get too tired.	**.86**	.11	-.06	.15	-.06	.01
I try to schedule activities at times of peak energy.	**.85**	.10	-.07	-.07	.08	.13
Information seeking						
I try to learn as much about cancer-related fatigue as possible.	.06	**.87**	.20	.07	-.07	.18
I follow the advice of others.	.13	**.80**	.07	.07	.10	.27
I look up medical information about cancer-related-fatigue.	.12	**.76**	.34	.06	-.24	.20
Focussing on symptoms						
My life is ruled by my fatigue.	.04	.14	**.89**	.11	-.01	.12
I spend a lot of time thinking about my fatigue.	-.03	.08	**.83**	-.03	-.05	.06
My fatigue is the most significant thing in my life.	-.16	.25	**.83**	.15	-.07	.10
Activity avoidance						
I try to rest at every opportunity.	.29	.27	.09	**.72**	-.05	-.03
I avoid doing anything that may tire me.	.15	.33	.11	**.69**	-.02	-.19
I limit the amount of time I spend napping during the day so as not to interfere with my sleep at night.(R)	-.30	-.20	.09	**.68**	-.21	.22
I try not to rest too much during the day. (R)	.05	-.07	-.01	**.60**	-.25	-.02
Maintaining activity						
I try to ignore my fatigue.	-.06	-.17	.05	.02	**.88**	.02
I try to do everything I did before my fatigue started.	-.06	.13	-.17	-.34	**.73**	.08
I push myself to stay active.	.27	-.07	-.06	-.33	**.67**	.11
Seeking emotional support						
I talk to friends/family/health care professionals about my anxieties.	.05	.28	.23	.03	.08	**.85**
I talk to friends/family/health care professionals about how I feel.	.14	.28	.07	-.09	.09	**.85**

Note. (R) indicates item that were reverse-coded. The factor loadings of the items that loaded on to each component are highlighted in bold font.

Appendix 10: Correlations between fatigue and CSM cognitive representations and coping strategies split by the three study subgroups.

	Subsample 1: Questionnaire study	Subsample 2: Longitudinal study	Subsample 3: Intervention study
1. Identity	-.60**	-.70**	-.63**
2. Timeline chronic	-.34**	-.44**	-.45**
3. Timeline cyclic	-.13	-.13	-.09
4. Consequences	-.54**	-.57**	-.69**
5. Control personal	.22	.41**	.29
6. Control treatment	-.07	-.08	.13
7. Coherence	.39**	.28	.31
8. Emotional representation	-.51**	-.53**	-.52**
9.Negative representation	-.50**	-.52**	-.59**
1. Treatment attribution	-.15	-.21	-.16
11. Medical attribution	-.19	-.52**	.09
12. Behavioural attribution	.13	-.26	.18
13. Psychological attribution	-.15	-.42**	.20
14. Cancer attribution	.01	-.12	.02
15. Sleep attribution	-.24*	.12	.12
16.Activity avoidance	-.32**	-.27	-.25
17. Maintaining activity	.01	-.08	.01
18. Accommodating to fatigue	-.02	.23	-.09
19. Focussing on symptoms	-.47**	-.69**	-.66**
20. Information seeking	-.39**	.01	-.52**
21. Emotional support seeking	-.15	-.17	-.26

Note. Lower fatigue scores indicate greater on the FACT-F scale used to measure fatigue; therefore; negative correlation coefficients with fatigue indicate a positive relationship between that variable and fatigue severity. *$p < .05$, **$p < .01$, ***$p < .001$.

Appendix 11: Significant correlations between the predictors and fatigue severity and intercorrelations among the significant predictors split by study subsample.

	1	2	3	4	5	6	7	8	9	10	11
1. Fatigue[1]	-	-.52**	-.65**	-.73**	.44**	.26	-.55**	-.52**	-.69**	.01	-.17
2. Anxiety	-.38*	-	.66**	.52**	-.13	-.28	.70**	.48**	.49**	.01	.43**
3. Depression[2]	-.48**	.59**	-	.69**	-.24	-.27	.62**	.43**	.56**	-.07	.05
4. Stress	-.46**	.42*	.48**	-	-.16	-.27	.48**	.43**	.50**	-.05	.01
5. Physical activity	-.03	.05	.16	-.07	-	.10	-.24	-.43**	-.37*	-.04	-.08
6. Social Support	.24	-.26	-.15	-.32	-.16	-	-.35*	-.45**	-.32	-.16	.07
7. Catastrophising	-.58**	.68**	.44*	.32	.05	-.39*	-	.56**	.74**	.32*	.08
8. Neg. cognitive representation	-.59**	.25	.19	.25	.18	-.12	.31	-	.50**	.13	.04
9. Symptom focussing	-.66**	.35*	.24	.23	-.08	-.02	.52**	.44**	-	.26	.23
10. Information seeking	-.52**	.05	.19	.17	-.02	.10	.05	.13	.40*	-	.19
11. Emotional support	-.26	.01	-.19	-.04	.03	-.01	0	.02	.20	.62**	-

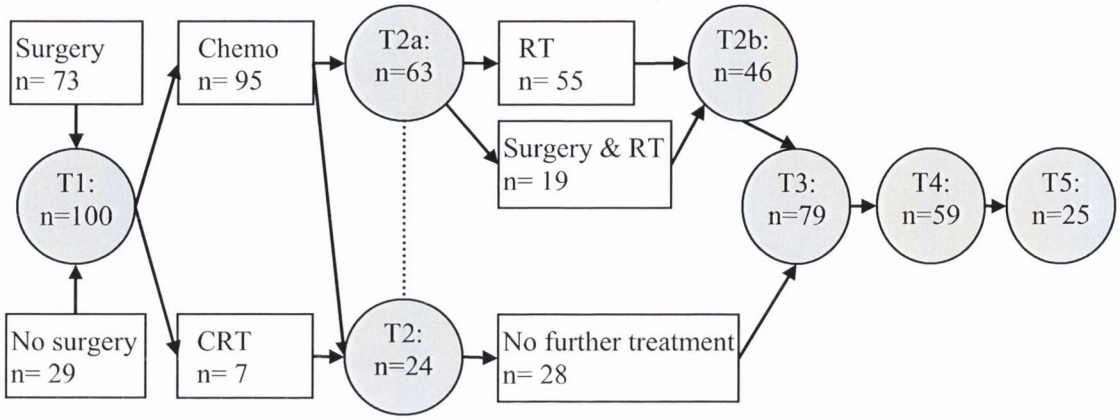
Note. Correlation coefficients for the longitudinal study subgroup are displayed above the diagonal while the correlation coefficients for the participants from the intervention study are displayed below the diagonal. [1]Lower fatigue scores indicate greater fatigue. [2]HADS depression excluding item 8 ("I feel as if I am slowed down"). Neg. cognitive representation = negative cognitive representation. $*p < .05$, $**p < .01$, $***p < .001$.

Appendix 12: Descriptive statistics for subscale change scores and correlations between change scores on each subscale and changes in fatigue severity between Time 1 and Time 2 and between Time 2 and Time 3

	Time 1 – Time 2 (n = 20)				Time 2 – Time 3 (n = 38)			
	M change (*SD*)	Min – Max	*r*	n	*M* change (*SD*)	Min – Max	*r*	n
Anxiety	1.25 (3.14)	-400 – 8.00	-.37	20	0.12 (3.76)	-6.00 – 14.00	-.27	38
Depression	-1.00 (4.14)	-9.00 – 8.00	-.63**	20	1.42 (3.36)	-5.00 - 10	-.34*	38
Physical activity	2424.29 (5107.81)	-3714 - 13398	.03	16	-2031.34 (3105.57)	-9893.7 – 3882	.38*	33
Stress	0.04 (0.86)	-1.25 - 2.25	-.68**	20	0.17 (0.90)	-2.00 - 2.50	-.45**	38
Social support	0.48 (1.42)	-2.33 – 3.00	-.23	14	-0.02 (1.81)	-5.00 – 5.00	.37*	31
Sleep disturbance	0.19 (2.03)	-4.67 - 4.67	-.64**	18	0.25 (1.62)	-5.00 – 4.00	.18	38
Kinesiophobia	0.19 (0.58)	-0.83 - 1.50	-.06	19	-0.08 (1.86)	-10.83 - 1.33	-.19	38
Catastrophising	-0.07 (0.75)	-1.30 - 1.50	-.29	10	0.06 (0.66)	-1.80 - 1.20	-.23	38
Fear of recurrence (FOR)	-	-	-	-	-0.05 (0.57)	-1.20 - 1.20	-.16	37
Timeline - chronic	0.17 (0.83)	-1.00 - 1.67	-.03	16	0.05 (0.89)	-1.67 - 2.67	.03	34
Timeline - cyclical	-0.53 (1.01)	-2.00 - 1.33	.01	16	0.22 (0.90)	-1.33 - 2.00	-.18	34
Consequences	-0.35 (0.75)	-1.33 - 1.67	-.47	16	0.20 (1.05)	-2.33 - 3.33	-.11	34
Control – personal	0.03 (1.06)	-2.00 - 1.67	.03	16	-0.24 (0.67)	-2.00- 2.00	-.25	34
Control - treatment	0.04 (1.05)	-1.50 - 2.50	.14	14	-	-	-	-
Coherence	0.05 (139)	-4.00 – 2.00	.34	16	-0.16 (1.20)	-3.00 – 3.00	.26	34
Emotional representations	0.04 (1.18)	-1.50 - 3.67	-.27	14	0.42 (1.20)	-4.00 - 3.00	-.16	33
Psychological attributions	0.25 (0.97)	-2.00 - 1.75	-.18	17	-0.08 (1.05)	-2.50 - 3.00	-.30	34
Behavioural attributions	0.40 (0.80)	-1.40 - 1.60	-.11	14	-0.05 (0.55)	-1.40 - 1.00	-.31	29
Medical/somatic attributions	0.07 (1.03)	-1.60 – 2.00	.04	17	0.08 (0.78)	-1.80 - 1.80	-.33	31
Cancer attributions	0.33 (1.50)	-2.00 - 4.00	-.04	15	-0.09 (1.24)	-3.00 - 2.00	.11	34
Sleep-related attributions	0.24 (1.30)	-2.00 - 2.00	-.31	17	-1.53 (6.72)	-39.00 - 2.00	.05	34
Maintaining activity coping	0.14 (1.22)	-1.67 - 3.00	.32	15	-0.38 (1.42)	-4.00 - 2.67	.08	31
Accommodating coping	-0.37 (1.44)	-2.83 - 2.50	.16	15	0.13 (1.48)	-2.00 - 4.00	-.31	31
Focus on symptoms coping	-	-	-	-	0.46 (1.24)	-2.00 - 3.67	-.19	33
Seeking information coping	0.57 (1.35)	-2.33 - 2.67	-.21	17	-0.16 (1.35)	-5.00 - 2.67	-.14	33
Emotional support coping	0.01 (1.37)	-2.50 - 1.50	-.29	9	-0.23 (1.69)	-3.00 - 3.00	.43	13

Note. FOR not assessed at T1. Change scores and correlations were not calculated for the focussing on symptoms (T1-T2) or the treatment control (T2-T3) subscales because of poor internal reliability on at least one of the timepoints ($\alpha < .60$). *p<.05, **p<.01, ***p<.001.

Appendix 13: Details of the timing of the study assessment points and they related to participants' treatment trajectories in Chapter 6.



Timing of study assessment points in relation to participants' treatment pathways.

Note. Total n = 102, n within each timepoint represents the number of questionnaires analysed for that timepoint.

The baseline assessment (T1) was completed after diagnosis and prior to commencing chemotherapy for all participants; however, some participants had already had surgery at this point. The first post-treatment assessment (T2) was completed within six weeks of completing chemotherapy for all participants. At this point some participants were finished with their treatment while others still had surgery and/or radiation to come (labelled as T2a in the figure above). Participants who went on to have such additional treatments after chemotherapy completed the next questionnaire (T2b) within six weeks of finishing the last of these treatments. Thus, these participants had two immediate post-treatment assessment points. T3 for all participants was between three and five months after finishing all cancer treatment; time since treatment was based on time since the last treatment (i.e., time since chemotherapy for those who received no additional treatments after chemotherapy or time since RT for those who completed the T2b assessment). T4 was carried out at between five and seven months after completing all cancer treatments; this was the fifth and final timepoint for most participants (i.e., those who completed T2b). The remaining participants completed their fifth assessment (T5) three months later (approximately nine months after treatment).

Appendix 14: Details of participants' treatment and comorbidities

Treatment details and clinical characteristics of participants (n = 102)

Treatment details	No	%	RT and Comorbidity Details	No
Surgical procedure			RT (n = 78)	
Breast conservation	48	47.10%	Breast: 50Gy in 25 fractions ±16 Gy boost in 8 fractions	69
Mastectomy	31	30.40%	Cervical: 50.4 Gy + Brachytherapy	7
Hysterectomy	5	4.90%	Lymphoma: 40Gy in 25 fractions	1
Anterior resection	3	2.90%	Endometrial 45 Gy in 25 fractions	1
Hemicolectomy	4	3.90%	Comorbidities	
Hartman's procedure	1	1.00%	None	51
No surgery	10	9.80%	Hypertension	15
Chemotherapy drug			Cholesterolemia	12
AC-T	48	47.10%	Thyroid problems	12
TCH	16	15.70%	Asthma	8
TC	10	9.80%	Osteoarthritis	6
FOLFOX	8	7.80%	Depression	6
Cisplatin	7	6.90%	Back pain	3
Taxol/Carbo	5	4.90%	Diabetes	3
AC	4	3.90%	Gastro-Oesophageal Reflux Disease	3
R-CHOP	2	2.00%	Heart disease	3
ABVD	1	1%	Fibromyology	2
Taxol	1	1%	Irritable Bowel Syndrome	2
Hormonal therapy (breast cancer only, n = 79)			Anemia	1
Tamoxifen	50	63.30%	B12 deficiency	1
Letrozole (Femara)	18	22.80%	Chrone's disease	1
Arimidex	2	2.50%	Coeliac disease	1
None	9	11.40%	Deep vein thrombosis	1
Chemotherapy regimen			Hiatus hernia	1
Weekly chemotherapy	7	6.90%	Migraine	1
Two week cycle	59	57.80%	Osteoparosis	1
Three week cycle	36	35.30%	Osteopenia	1
			Polycythaemia rubravera	1
			Vasculitis	1

Appendix 15: Detailed output on the unconditional growth models of fatigue in Chapter 6.

Comparison of fitting alternative polynomial change trajectories and Level 1 covariance structures to the fatigue data (n = 102)

		Model A No change	Model B Linear change	Model C Quadratic change	Model D Cubic change	Model D-Diag. Cubic with diagonal covariance structure at Level 1	Model D-AR1 Cubic with autoregressive covariance structure at Level 1
Fixed effects							
Composite model	Intercept (T1)	-0.36	-1.64	-0.50	1.09	1.26	1.09
	Time (linear)	-	0.69*	-1.74	-11.15***	-11.54***	-11.15***
	$Time^2$ (quadratic)	-	-	0.57**	6.11***	6.22***	6.11***
	$Time^3$ (cubic)	-	-	-	-0.79***	-0.80***	-0.79***
Variance components							
Level 1	Within person (residual)	88.28***	80.88***	79.33***	67.75***	T1: 49.90** T2: 74.27*** T2b: 106.29*** T3: 56.24*** T4: 49.75*** T5: 61.91*	AR1: 67.56*** (diagonal: var. at each occasion) AR1 rho: -.01 (correlation between successive occasions)
Level 2	In T1 (intercept)	53.86***	78.07***	79.06***	86.54***	94.34***	87.83***
	In linear term (slope)		2.00	1.95	3.08	4.21*	3.11
	Covariance between linear term & intercept		-8.15	-8.38	-10.55*	-12.79*	-10.62*
No of parameters		3	6	7	8	13	9
Goodness of fit	-2LL (deviance statistic)	2973.42	2964.54	2957.79	2927.49	2920.82	2927.48
	AIC	2979.42	2976.54	2971.79	2943.49	2946.82	2945.48
	BIC	2991.32	3000.34	2999.55	2975.21	2998.38	2981.18

*$p < .05$, **$p < .01$, ***$p < .001$.

Model A.

Model A represents the unconditional model and is interpreted in the main text.

Model B.

Model B introduced a linear growth parameter into the unconditional model. The nonsignificant value for the intercept suggests that the average participants' fatigue at baseline is not different from the overall grand mean fatigue score across the different measurement points. However, the random error term associated with the intercept was significant, suggesting that participants differed substantially in their level of fatigue at T1 and that this variability could be explained by between-individual predictors. The linear slope parameter indicated that there was a significant linear increase in fatigue score over time (indicating a decrease in fatigue across measurement occasions as a higher fatigue score represents lower fatigue). The random error term associated with the linear slope parameter was not significant, suggesting that there was no significant variation in the linear rate of change across participants. There was a decline of 7.40 in the within-individual variation in initial status between model A and model B, which suggest that about 8% of the variation within individuals was associated with a linear rate of change. The goodness of fit indices of Model B indicated that this model is a better fit for the data than Model A.

Model C.

Model C examined whether the rate of growth accelerated or decelerated over time by adding a quadratic parameter to the previous model (i.e., to test if the trajectory of fatigue had one stationary point or peak/trough). The deviance statistic declined by 6.75, which exceeds the .01 critical value of the χ^2 distribution on 1 *d.f.* and therefore indicated that this model was a better fit for the data. The linear slope parameter was no longer significant, indicating that the mean instantaneous rate of change was not significantly different from 0. However, the quadratic slope parameter was significant indicating that there was a significant change in the rate of change (i.e., curvature in the trajectory of fatigue). There was no evidence of significant variability in individual change parameters for quadratic rate of growth between participants ($p > .05$); thus, this parameter was treated as fixed in the analyses. The occasion at which the change in trajectory occurred was after T2 [-(-1.74)/2(0.57) = 1.53] (Singer & Willett, 2003). This indicates that after initial (nonsignificant) decreases in fatigue scores, fatigue scores began to increase (i.e., fatigue improved) after chemotherapy.

Model D.

Model D tested a third-order polynomial model with two stationary points by adding a cubic parameter to the previous model. The deviance statistic declined by 30.30, which exceeds the .001 critical value of X^2 distribution on 1 *d.f.* and therefore indicates that this model was a significantly better fit for the data. In addition, the AIC and the BIC decreased, which also supports a better fit. The estimates of the cubic change model are interpreted in main text.

Model D-Diag.

Model D-Diag. specified a diagonal covariance structure covariance structure that allowed heterogeneous variances for difference measurement occasions. There were differences in the size of the within-individual residual variation for the different timepoint; specifically, the variability at T2b appeared to be greater than at the other timepoints. However, changing the covariance structure did not improve model; there was a small nonsignificant decrease in -2LL ($p > .05$) but the AIC and BIC increased, reflecting the greater number of model parameters to be estimated.

Model D-AR1

Model D-AR1specified an autoregressive covariance structure, which assumes a constant within-individual variance across measurement occasions and correlated residuals from one occasion to the next. The within-individual variance was estimated at 67.56 and was significantly different from 0 ($p < .001$). There was no evidence of covariance among measurement occasions (AR1 rho = -.01). Changing the covariance structure to an autoregressive structure had no impact on the fixed effects or on the -2LL; however, both the AIC and the BIC increased.

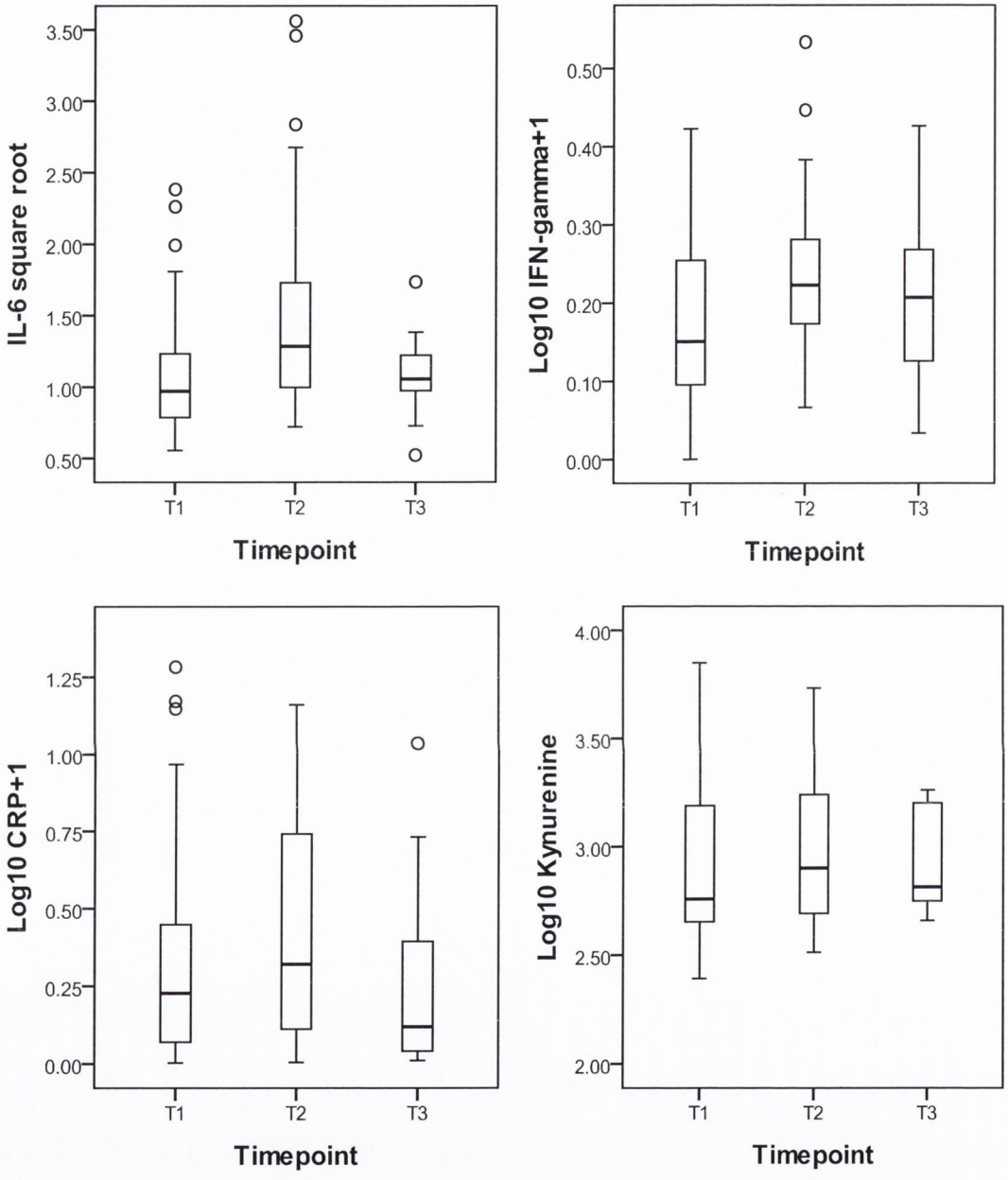
Appendix 16: Unconditional growth models for quality of life in Chapter 6.

Comparison of fitting alternative polynomial change trajectories to the QOL data (n = 102)

		No change	Linear	Quadratic	Cubic change
Fixed effects					
Composite model	Intercept (T1)	6.70***	6.57***	6.65***	6.82***
	Time (linear)	-	0.07	0.11	-1.05**
	$Time^2$ (quadratic)	-	-	0.04	0.60***
	$Time^3$ (cubic)	-	-	-	-0.08*
	Fatigue	-	-	-	-
Variance components					
Level 1	Within person (residual)	2.42***	2.29***	2.29***	2.14***
Level 2	In T1 (intercept)	2.14***	2.09***	2.11***	2.22***
	In linear term (slope)	-	0.04	0.04	0.06
	Covariance between linear term & intercept	-	-0.02	-0.03	-0.06
No of parameters		3	6	7	8
Goodness of fit	-2LL (deviance statistic)	1589.58	1586.34	1585.12	1574.96
	AIC	1595.58	1598.34	1599.12	1590.96
	BIC	1607.46	1622.11	1626.85	1622.65

*$p < .05$, **$p < .01$, ***$p < .001$.

Appendix 17: Boxplots demonstrating the distribution of the transformed values for biomarkers in Chapter 7.



Distribution of IL-6, IFN-γ, CRP and KYN at each timepoint after transformation.

Note. Boxes represent data ranging from the 25th to the 75th percentile of the observed distribution of values; horizontal lines represent the median levels of biomarkers; whiskers range from the minimum and maximum observed data values; and outliers are identified by open circles or, in the case of extreme outliers, asterisks.

Appendix 18: Instructions of collecting saliva samples.

Instructions for collecting saliva samples

If you are unsure of any of the instructions below or if you have any questions please contact me: Maria Ph 087 1315256

What is included in my saliva collection pack?

4 x Saliva collection tubes with cotton swabs in a clear grip seal bag

1 x Saliva collection log to be completed when giving the samples

1 x Clear plastic grip seal bag with a spare tube

1 x Stamped addressed polythene bubble mail bag for returning the samples (a list of contents is included in the return envelope)

How many saliva samples do I need to collect?

We would like you to give 4 saliva samples:

These must be provided at very specific time during the day:

Sample 1 – immediately after you wake up in the morning

Sample 2 – 15 minutes after you have woken up in the morning

Sample 3 – 45 minutes after you have woken up in the morning

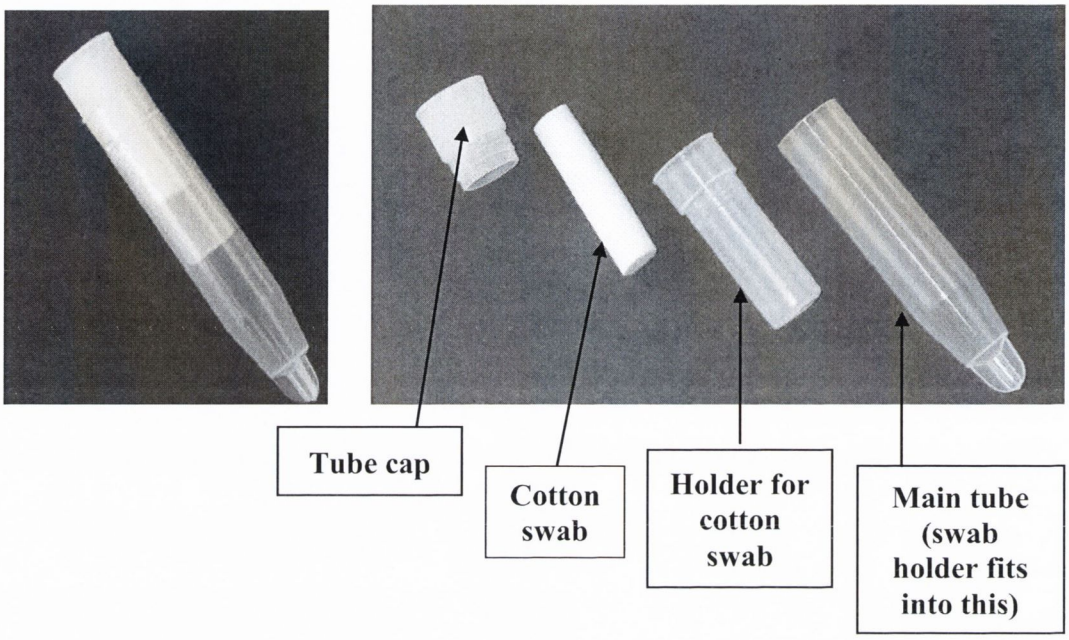
Sample 4 – at 5pm in the evening

Why do I need to collect my saliva at exactly these times?

Saliva samples are being collected for this study to measure levels of the hormone cortisol. Cortisol levels follow a very specific pattern: in the morning, just before you wake up, they are at their highest and then they gradually decrease over the course of the day. Some research suggests that this pattern is different in patients who are fatigued after their cancer treatment and this may help to explain the causes of cancer-related fatigue. We would like to test whether this is the case. It is therefore very important that you give your saliva samples at exactly the times specified above.

How do I collect my saliva?

The tubes provided for collecting saliva samples have four basic parts:

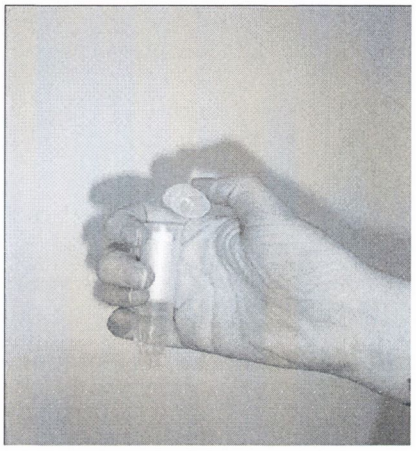


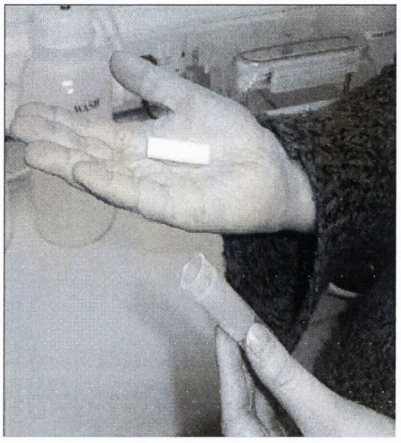
Each of the tubes has been labelled with a sample number and they have been arranged in order to make collection easier for you (see picture below). Please use the appropriate tube for each collection time e.g., the tube labelled 'sample 1' for your first saliva collection.



To collect a saliva sample follow the 6 steps below.

1. Take the appropriate tube from the holder in the bag, remove the cap from the tube and take out the cotton swab. There is no need to remove anything else from the tube (leave the holder for the swab inside).





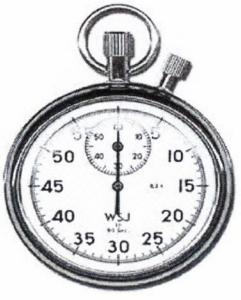
2. Place the cotton swab in your mouth. Do not chew on the swab – just roll it around in your mouth. Do this for about **90 seconds (1 and ½ minutes)** until the swab has collected plenty of saliva.



3. Remove the cotton swab from your mouth and place it carefully back in the tube.

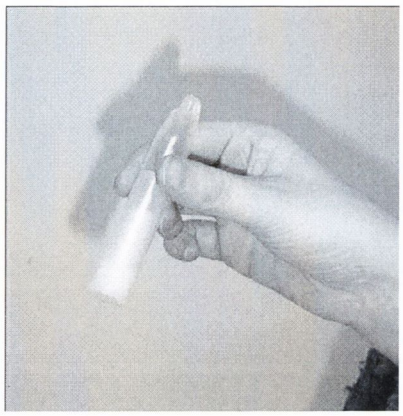
*Remember not to eat or drink anything or brush your teeth within 1 hour before giving each sample.
*Do not drink any water in the 15mins before giving a sample.



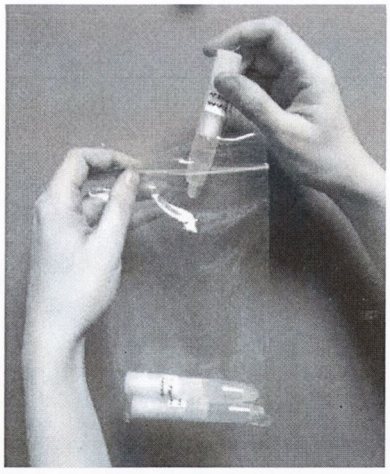


4. Put the cap back on the tube – make sure the cap is tightly sealed so that saliva doesn't leak out (you might need to push it down hard to do so). **TIP** – when the cap is in place turn the tube upside down over some tissue paper to make sure it doesn't leak.





5. Once you have made sure the tube is capped tightly and securely, place it back in one of the small clear plastic bags provided and store it in the fridge until you have collected all of your saliva samples (Please **DO NOT** store the samples in the freezer).



6. Complete the saliva collection log for the sample you have just collected. It is important that you note the date and time at which you give each sample in the log.

How do I send my saliva samples back to the research team?

It is very important that you follow the steps below for posting your samples safely back to the research team.

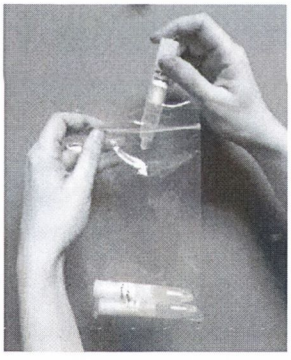
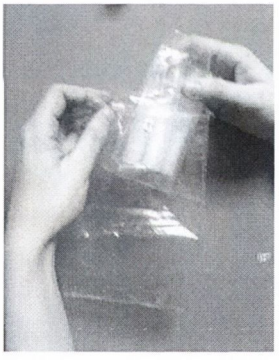
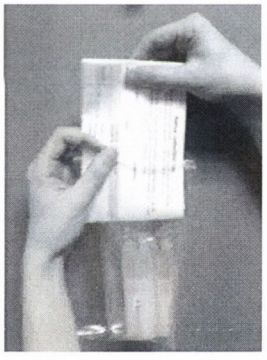
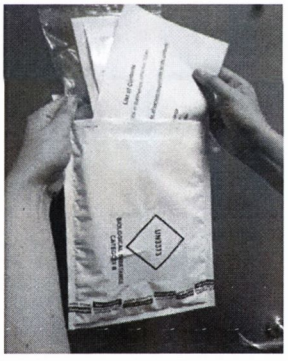
1. Make sure your saliva tubes are sealed tightly and securely so that saliva doesn't leak out.

2. Place all of the tubes back in the **small clear plastic bag** provided (and seal it securely at the top.

3. Place the bag and **the saliva log** into the spare clear plastic bag and seal it securely.

4. Place the clear plastic bag into the polythene bubble mail bag with the list of contents. Seal the mail bag securely.

5. Post the mail bag as soon as you can.

Important things to note when giving saliva samples:

1. GIVE THE SALIVA SAMPLES AT THE SPECFIED TIMES

- Sample 1 – immediately after you wake up in the morning
  Sample 2 – 15 minutes after you have woken up in the morning
  Sample 3 – 45 minutes after you have woken up in the morning
  Sample 4 – at 5pm in the evening
- It may be helpful to set an alarm to remind you when to collect each saliva sample after waking.

2. MAKE SURE YOU USE THE CORRECT TUBE FOR EACH SAMPLE YOU COLLECT

- The tubes provided are labelled with specific collection times. Please check the labels on each tube *very carefully* before giving each sample. They have been placed in the order they should be used.
- An extra Saliva tube has been provided in case a cotton swab is dropped or the sample is damaged in some other way. If the extra Saliva tube is used to give a sample, please record the number **on the tube itself.** This is important, because the extra Saliva tube is not labelled with this information.

3. CONSUMING FOOD AND DRINK AFFECTS THE SALIVA SAMPLES, SO:

- **Do not eat, drink anything or brush your teeth within 1 hour before giving each saliva sample.**
- If you do accidentally eat or drink **in the hour** before your scheduled sampling time, please rinse your mouth with clean water as soon as you remember. Then, delay your sample until 1 hour after you rinsed your mouth. If this occurs, please record this on the sampling log (see below).
- Smoking can also affect the saliva sample. Please do not smoke during **the hour** before giving each sample.
- **Do not drink any water in the 15mins** before giving a saliva sample.

4. DRY MOUTH

- If you have trouble giving a saliva sample because of dry mouth you could try the following:
  - Pressing the tip of your tongue against your teeth or chewing the cotton swab gently for a few seconds before rolling it around in your mouth.
  - Smelling (not eating) a lemon or other food can also start saliva flow.
  - Rinsing your mouth with water 15 minutes before collecting a sample can also help.
- Drink plenty of water the night before giving a saliva sample to help saliva production.

The Sampling Log

Please record the exact time each saliva sample is given on the sampling log. Please do this *at the end* of each sampling time. Please also use your sampling log to record if/when you eat or drink anything other than water during the sampling period.

Appendix 19: Saliva collection log

Saliva collection log

You must keep a record of each saliva sample in this log.
Please provide the samples at each of the specified times.
If you eat or drink by mistake (see saliva sampling guidelines) before giving a sample, or if you do not give a sample at the appointed time, please make a note of this in the 'NOTES' section below.

Participant ID#:_____

Date: ___/___/_____

	I collected this sample at:	**Notes:**
Sample 1: Immediately after waking up	**Time:**_____ **Minutes since waking:**_____	
Sample 2: 15 minutes after waking up	**Time:**_____ **Minutes since waking:**_____	
Sample 3: 45 minutes after waking up	**Time:**_____ **Minutes since waking:**_____	
Sample 4: 5pm	**Time:**_____	