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A Systematic Review of the Association between Immunogenomic Markers and Cancer-Related Fatigue

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Abstract

Fatigue, which is one of the most commonly reported symptoms in cancer, can negatively impact the functional status and the health-related quality of life of individuals. This paper systematically reviews 34 studies to determine patterns of associations between immunogenomic markers and levels of cancer-related fatigue (CRF). Findings from the longitudinal studies revealed that elevated fatigue symptoms especially of women with early stages of breast cancer were associated with high levels of neutrophil/monocyte, IL-1ra, and IL-6 during radiation therapy; high levels of CD4+, IL-1β, and IL-6 with stressing stimuli; high levels of IL-1β during chemotherapy; low NK cell levels after chemotherapy; and presence of homozygous IL-6 and TNF alleles. In the cross-sectional studies, associations between levels of fatigue and immune/inflammatory markers were not consistently found, especially when covariates such as BMI, ethnicity, menopausal status, and educational level were controlled in the statistical analyses. However, a number of genomic markers were observed to be elevated mostly in fatigued breast cancer survivors in the cross-sectional studies. Gaps in knowledge and recommendations for future research are discussed.

Advances in cancer treatment have led to high survival rates and prolonged the natural history of the disease. However, improved survival rates are mitigated by symptoms associated with treatments that lower the health-related quality of life (HRQOL) for survivors. Fatigue is one of the most commonly reported symptoms in cancer with a prevalence rate of 59% to 100% depending on the clinical status of the disease (Weis, 2011).

Cancer-related fatigue (CRF) is defined as a “distressing, persistent subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that interferes with usual functioning” (Berger et al., 2010, p. 906). CRF considerably impacts the functional status and HRQOL of individuals by imposing physical limitations and psychological impairments (Curt et al., 2000). Although studies have been conducted to identify associations between immune and inflammatory markers with the severity and intensity of CRF, no causation between a specific biomarker and CRF has been established, contributing to its inadequate clinical management.

The diversity of factors that predispose to CRF suggests that it is a multidimensional symptom that has common related molecular pathways with multiple contributory

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Conflict of interest

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mechanisms (Miaskowski, 2002). The current understanding about the etiology of CRF is based on limited evidence that environmental, genetic, psychological, and physiological factors play important roles in the impairment of oxygen supply, neuromuscular signaling, and the hypothalamus-pituitary-adrenal axis functioning. The goal of this literature review was to systematically review studies that evaluated immunogenomic markers and CRF in order to identify patterns of associations between these variables.

Methods

An initial generic search in PubMed (any date) using the following key words, “Fatigue AND cancer”[title] yielded 867 articles. A basic search query based on the terms from the 867 articles was developed. These key words/phrases include: (“Neoplasms”[Medical Subject Heading (Mesh)]) AND (“Fatigue/blood”[Mesh] OR “Fatigue/cerebrospinal fluid” [Mesh] OR “Fatigue/enzymology”[Mesh] OR “Fatigue/etiology”[Mesh] OR “Fatigue/genetics”[Mesh] OR “Fatigue/immunology”[Mesh] OR “Fatigue/pathology”[Mesh] OR “Fatigue/physiology”[Mesh] OR “Fatigue/physiopathology”[Mesh] OR “Fatigue/urine” [Mesh]. This basic search query yielded 1992 articles. The search was further refined, limiting the search using specific terms to include, (“Cytokines”[Mesh] OR “Receptors, Cytokine”[Mesh]) OR (“Antigens, Surface”[Mesh] OR “Receptors, Immunologic”[Mesh] OR “Immunologic Factors”[Mesh])) OR “Antigens”[Mesh]) OR “Lymphocytes”[Mesh]) OR “Inflammation”[Mesh]) OR “Interleukins”[Mesh]) OR “Leukocytes”[Mesh]) OR “Biological Markers”[Mesh]) OR (“Gene Expression/genetics”[Mesh] OR “Gene Expression/immunology”[Mesh] OR “Gene Expression/physiology”[Mesh])) OR “Genotype”[Mesh]) OR (“Immunity, Cellular/genetics”[Mesh] OR “Immunity, Cellular/immunology”[Mesh] OR “Immunity, Cellular/physiology”[Mesh]). This refined search yielded 348 articles. Review, editorial, case studies, and meta-analysis articles were excluded from the list, which reduced the number of indexed articles to 63. To retrieve recent, unindexed articles in PubMed, the following key words were used, Fatigue AND (Cancer OR neoplasms) AND protein* OR biomarker* OR receptor* OR genes OR gene OR genet* OR immunolog* (*truncated words). The search for unindexed articles was limited to articles published in the last 90 days. This search yielded 35 articles. The abstracts of these 98 articles (indexed=63, unindexed=35) were visually reviewed to determine if they met the following inclusion criteria: (a) tested a relationship between specific immune agents and CRF or (b) mentioned the function, concentration, and/or activity of an immune marker and its association with the increasing level, duration, or worsening in intensity of CRF.

Results

The 34 articles that met the eligibility criteria were reviewed. The earliest article appeared in 2001 and 73.5% (n = 25) of the articles were published from 2006 to the present. Eleven (32%) of the studies used longitudinal designs, while 23 (68%) were cross-sectional. Eighteen (53%) studies enrolled only women subjects, most with breast cancer (94%). Of these, 24% studied women in early stages of breast cancer and 65% studied breast cancer survivors (BCS). About 39% of studies (N = 7/18) investigating BCS were written by one research team who screened participants from the same subject data pool. Sixteen (47%) studies enrolled both men and women participants, with eight (50%) investigating participants with various types of cancer and seven (44%) focusing on terminal cases. One study enrolled pediatric patients (Vallance et al., 2010) and one study enrolled only male participants (Orre et al., 2009). Findings on the relationships between immunogenomic markers and fatigue are presented for the longitudinal and cross-sectional studies separately, according to five categories: systemic inflammatory markers, signals of immune response, concentrations of cytokines, markers of cytokine activity, and genomic markers.

Longitudinal studies

There were 10 studies that serially collected biologic samples from study subjects and explored the associations between levels of immunogenomic markers and fatigue at different time points. Seven of these studies showed significant associations between fatigue and an immunogenomic marker. Eleven different fatigue measures were used in the 10 longitudinal studies, with one study using multiple fatigue scales (Panju et al., 2009) and another using an interview to measure fatigue (Olson et al., 2002). Three of these fatigue questionnaires were administered and validated in non-English languages (Ahlberg et al., 2004; Geinitz et al., 2001; Reinertsen et al., 2011). No other questionnaire, except for the Functional Assessment of Cancer Therapy – Fatigue (FACT-F) was used twice, by two longitudinal studies (Panju et al., 2009; Wratten et al., 2004). The FACT-F is the most preferred instrument to measure CRF because it has been used extensively in large studies, has been shown to be sensitive to clinically significant changes in fatigue, and has robust psychometric properties (Minton et al., 2009). No other fatigue measure was used by more than one study.

In four of the ten longitudinal studies, subjects were followed during their radiation therapy (Ahlberg et al., 2004; Bower et al., 2009; Geinitz et al., 2001; Wratten et al., 2004), three studies followed subjects during chemotherapy (Mills et al., 2005; Panju et al., 2009; Vallance et al., 2010), and in one study, subjects were followed while they were receiving chemotherapy with or without radiation as adjuvant treatment (Olson et al., 2002). One study followed BCS pre and post stress testing (Bower et al., 2007), and another followed patients after completing their adjuvant therapy and 2–3 years after that initial assessment (Reinertsen et al., 2011). A number of studies controlled for covariates in data analyses. Body mass index (BMI) was the most commonly controlled covariate in the longitudinal studies, followed by depressed mood and age.

Systematic Inflammatory Markers—Four longitudinal studies evaluated associations of systemic inflammatory markers with levels of fatigue (Bower et al., 2007; Olson et al., 2002; Reinertsen et al., 2011; Wratten et al., 2004) and all used whole blood samples. Two of the longitudinal studies followed patients with early breast cancer stages during their radiation therapy (RT). Of these, one demonstrated a significant association between high levels of C-reactive protein (CRP) and increased fatigue duration (Bower et al., 2009) and the other study showed a significant association between high levels of CRP and fatigue at baseline but not during RT (Wratten et al., 2004). Significant association was also noted between higher fatigue levels and elevated neutrophil count prior to cancer treatment in patients with terminal cases (Olson et al., 2002) and during RT in women with early breast cancer (Wratten et al., 2004). An elevated monocyte count also was significantly correlated with higher fatigue levels at baseline and during RT after controlling for BMI (Wratten et al., 2004). Lymphocyte count did not show an association with fatigue levels (Wratten et al., 2004).

Signal of Immune Response—$CD4^+$ lymphocyte was the only signal of immune response measured using a longitudinal design in patients with early stage breast cancer, and it showed a significant association with fatigue level (Bower et al., 2007). These systemic inflammatory markers and the signal of immune response are measures of cumulative activity of pro-inflammatory cytokines such as IL-6 (Bower et al., 2009). The positive associations between these systemic inflammatory markers, signal of immune response, and fatigue may reflect subclinical inflammatory changes related to the disease and/or treatment. Another possible explanation for these associations may be related to chance effect from the multiple analyses brought about by the use of several covariates.

Concentrations of Cytokines—Eleven cytokines were measured in eight longitudinal studies, with IL-6, TNF-α, and IL-1β being the most measured cytokines. These three pro-inflammatory cytokines showed inconsistent associations with fatigue levels; however, IL-6 levels from serum and blood cell supernatant samples of breast cancer patients with early disease showed positive significant associations with fatigue levels during RT (Wratten et al., 2004) and with induction of stress (Bower et al., 2007). However, plasma levels of IL-6 and fatigue symptoms were negatively associated in women with early stages of uterine cancer before and during their RT (Ahlberg et al., 2004). This significant association with fatigue levels was not observed when serum IL-6 levels were measured from cancer patients with terminal disease (Olson et al., 2002) nor in older individuals (>50 years) with acute myeloid leukemia (Panju et al., 2009), suggesting that the association of IL-6 and fatigue in these longitudinal studies is influenced by the stage and type of cancer and not the specific type of sample used. TNF-α was not associated with fatigue in three longitudinal studies that followed patients during cancer treatment (Ahlberg et al., 2004; Olson et al., 2002; Panju et al., 2009). Higher levels of IL-1β were associated with higher levels of fatigue in women with early stage breast cancer when stress was induced (Bower et al., 2007). However, a significant association between IL-1β and fatigue was not observed in a German study of women with breast cancer receiving RT (Geinitz et al., 2001), which might be related to the inability to find a change in fatigue score during RT using the German-version of the Fatigue Assessment Questionnaire (Geinitz et al., 2001). The negative associations found in the above mentioned studies may be related to the variability in laboratory methodologies used, limited biological half-life of cytokines, or insufficient diffusion of cytokines from peripheral sites into the blood stream (Fuchs et al., 1988).

Marker of Cytokine Activity—IL-1ra was the only marker of cytokine activity measured in the study by Bower and colleagues (2009), where it showed a positive significant association with fatigue levels. Pro-inflammatory cytokines such as IL-6 and IL-1β are known as key mediators of neuroimmune interactions, and are thought to play a role in the development of fatigue (Bower et al., 2009). These pro-inflammatory cytokines, especially the IL-1 family of cytokines (IL-1α, IL-1β) have also been suggested to play an important role in breast cancer progression (Miller et al., 2000; Pantschenko et al, 2003). Animal data strongly suggest that IL-1 is the crucial factor in determining the balance between immunity and inflammation in tumor progression (Voronov et al., 2010). The elevation of IL-1ra in the reviewed articles may be related to its role as a natural inhibitor of IL-1 and is necessary to counter the pro-metastatic activities of IL-1 and IL-6 (Apte et al., 2006).

Genomic Markers—Although there were two longitudinal studies that measured genomic markers, neither found a significant association between a genomic marker and fatigue (Reinertsen et al., 2011; Vallance et al., 2010). DNA extracted from peripheral blood cells of children with acute lymphoblastic leukemia treated with dexamethasone explored polymorphisms from 3 genes (*AHSG, IL6, POLDIP3*), which were found to be related to sleep disturbance but not to fatigue (Vallance et al., 2010). Single nucleotide polymorphisms (SNPs) of inflammation-related genes including, IL1β (rs16944), IL6 (rs1800795), IL6 receptor (rs4129267, rs4845617, rs2228145), and CRP (rs2794521) did not show significant correlations with persistent fatigue in BCS; however, the CRP gene SNP rs3091244 was associated with serum hsCRP level among persistent fatigued BCS (Reinertsen et al., 2011). The study by Vallance and colleagues (2010) study was the first to explore associations between genomic markers and fatigue in pediatric cancer population, therefore more investigation is necessary to validate the results. Reinertsen and colleagues (2011) grouped subjects into persistent fatigued, defined as having fatigue for more than 6 months in duration, much different than the proposed definition CRF (Cella et al., 2001). This study

also collected samples at 2 time points that were two to three years apart, which should be considered in interpreting their results.

Summary—Findings from the longitudinal studies reveal that elevated fatigue symptoms especially of women with early stages of breast cancer were associated with high levels of neutrophil/monocyte, IL-1ra, and IL-6 during RT; as well as high levels of $CD4^+$, IL-1β, and IL-6 with stressing stimuli. There were too few longitudinal studies that focused on terminal (Olson et al., 2002) and pediatric cases (Vallance et al., 2010) to identify a trend in association between CRF and immunogenomic markers. In addition, no associations were found between fatigue levels and most genomic markers (Reinertsen et al., 2011; Vallance et al., 2010). Findings from these longitudinal studies suggest that the relationship between fatigue levels and inflammation is complex and not easily discernible.

Cross-sectional studies

Twenty four studies collected biologic samples from subjects at one study time point and explored associations between the levels of immunogenomic markers and fatigue. Twenty two studies showed significant associations between fatigue and an immunogenomic marker. Of these 24 studies, 13 enrolled women with breast cancer and 46% of these 13 studies were conducted by one research team using participants from the same data pool of BCS (Bower et al., 2002; Bower et al., 2003; Bower et al., 2011a; Bower et al., 2011b; Collado-Hidalgo et al., 2006; Collado-Hidalgo et al., 2008). Five studies enrolled patients with terminal disease (Kwak et al., 2012; Inagaki et al., 2008; Minton et al., 2012; Rausch et al., 2010; Scheede-Bergdahl et al., 2012).

Fourteen different fatigue questionnaires were used in the cross-sectional studies and six of these were administered and validated in languages other than English. One non-English fatigue measure was author-developed (Inagaki et al., 2008) and reliability and validity had been established for it in a previous study (Okuyama et al., 2000). The vitality scale of the Medical Outcomes Study Short Form (SF)-36 was the most frequently used to categorize fatigued from non-fatigued subjects (Bower et al., 2002; Bower et al., 2003; Bower et al., 2011a; Collado-Hidalgo et al., 2006; Rausch et al., 2010). Although the SF-36 vitality scale has been found to have good internal consistency (0.85 – 0.87) using large samples, and a high test-retest reliability (0.80) over a two-week period, one concern is that this four-item scale with two items asking about energy and two asking about fatigue might be an inadequate representation of fatigue (O'Connor, 2004). Age was the most commonly controlled covariate in these cross-sectional studies. Other covariates controlled during statistical analyses included gender, body mass index (BMI), type of cancer treatment received, time since completion of cancer treatment, depression, and behavioral status such as smoking, caffeine, and alcohol uses.

Systemic Inflammatory Markers—Of the 24 cross-sectional studies, 13 evaluated associations of systemic inflammatory markers with levels of fatigue. White blood cells (Alexander et al., 2009; Bower et al., 2003; Kwak et al., 2012; Landmark-Høyvik et al., 2009; Orre et al., 2011; Paddison et al., 2009), CRP (Alexander et al., 2009; Booker et al., 2009; Bower et al., 2011b; Kwak et al., 2012; Minton et al., 2012; Orre et al., 2009; Orre et al., 2011; Schroecksnadel, 2007; Scott et al., 2002), and lymphocytes (Alexander et al., 2009; Bower et al., 2003; Collado-Hidalgo et al., 2006; Landmark-Høyvik et al., 2009; Paddison et al., 2009) were the most commonly measured. Results were inconsistent in regard to significant associations between levels of these systemic inflammatory markers and fatigue regardless of type and stage of cancer. WBC levels were significantly elevated in fatigued BCS (Alexander et al., 2009; Landmark-Høyvik et al., 2009; Orre et al., 2011) and in lung cancer patients with stage IIIb-IV disease (Paddison et al., 2009). However, this

significant association was not observed in other studies that enrolled BCS (Bower et al., 2003) nor in a study of patients with various types of terminal cancers (Kwak et al., 2012). Although CRP levels were significantly elevated in patients with high fatigue symptoms in five studies (Alexander et al., 2009; Booker et al., 2009; Kwak et al., 2012; Orre et al., 2009; Schroecksnadel, 2007), two other studies did not find empirical support for this association (Bower et al., 2011b; Minton et al., 2012). Three studies also showed an association between high levels of lymphocytes and fatigue in BCS (Bower et al., 2003; Collado-Hidalgo et al., 2006; Landmark-Høyvik et al., 2009), but two other studies did not show similar significant associations between the two variables (Alexander et al., 2009; Paddison et al., 2009).

A common observation that may explain these inconsistent associations between levels of fatigue and systemic inflammatory markers was the type of covariates used in the analyses. Positive, significant associations between levels of fatigue and the systemic inflammatory markers (WBC, CRP, and lymphocytes) were generally found after controlling for covariates such age, gender, and time since completion of cancer treatment. However, significant associations, especially of fatigue with WBC and CRP, were not observed when BMI was added as a covariate to the statistical analyses (Bower et al., 2003, Bower et al., 2011; Kwak et al., 2012; Minton et al., 2012). Low tryptophan concentrations and high kynurenine/tryptophan ratio showed significant associations with high fatigue levels in patients with malignant disease (Schroecksnadel et al., 2007). Further investigation is necessary to determine the role of tryptophan, a precursor of serotonin in CRF, which can be valuable information for CRF management.

Signals of Immune Response—Four cross-sectional studies explored associations between levels of fatigue and signals of immune response, all in breast cancer survivors (Bower et al., 2002; Bower et al., 2003; Collado-Hidalgo et al., 2006; Von Ah et al., 2008). All these studies showed significant associations between levels of fatigue and signals of immune response. Although NK cell activities were noted to be lower in fatigued BCS (Bower et al., 2002; Von Ah et al., 2008), CD3+ and CD4+ T lymphocytes were higher in the same population in one study (Bower et al., 2003).

Concentrations of Cytokines—Seven cross-sectional studies explored the relationship between levels of fatigue and cytokines (Collado-Hidalgo et al., 2006; Kwak et al., 2012; Inagaki et al., 2008; Orre et al., 2009; Orre et al., 2011; Scheede-Bergdahl et al., 2012; Von Ah et al., 2008). The pro-inflammatory cytokine, IL-6, was the most common cytokine investigated. Higher plasma levels of IL-6 were significantly associated with fatigue symptoms in cancer patients with terminal disease (Inagaki et al., 2008). IL-6 production was also elevated in an *ex-vivo* experiment of stimulated monocytes from fatigued BCS; however, plasma IL-6 levels from the same subjects were not significantly different from non-fatigued BCS samples (Collado-Hidalgo et al., 2006). Four other cross-sectional studies did not find significant associations between levels of fatigue and IL-6 (Kwak et al., 2012; Orre et al., 2009; Orre et al., 2011; Scheede-Bergdahl et al., 2012).

The inconsistency in association between the levels of IL-6 in the blood and fatigue might be related to the fatigue measure used. Although an author-developed questionnaire showed significant association between these two variables, the rest of the cross-sectional studies using more psychometrically sound scales failed to document an association. TNF-α was the other cytokine that was most measured among the cross-sectional studies and its blood level did not show an association with fatigue in three studies (Kwak et al., 2012; Scheede-Bergdahl et al., 2012; Von Ah et al., 2008).

Markers of Cytokine Activity—Four cross-sectional studies investigated the association between levels of fatigue and markers of cytokine activity. Three were written by one

research team who screened participants from the same data pool of BCS (Bower et al., 2002; Bower et al., 2011; Collado-Hidalgo et al., 2006). IL-1ra and sTNF-RII were the two signals of immune response that were most measured in these eight cross-sectional studies. Inconsistent results in the association between levels of fatigue and these two signals of immune response might be related to confounders adjusted during analysis. The positive, significant association between levels of fatigue and IL-1ra persisted even after controlling for age, BMI, depressive symptom scores, time since completion of cancer treatment (Collado-Hidalgo et al., 2006) and behavioral factors such as smoking, caffeine, and alcohol use (Bower et al., 2002). However, these positive, significant associations between fatigue scores with IL-1ra and sTNF-RII were not observed when ethnicity, menopausal status (Collado-Hidalgo et al., 2008), and educational level (Orre et al., 2011) were added as covariates. One study showed a positive association between level of fatigue and sTNF-RII in breast cancer survivors who received chemotherapy as their primary cancer treatment or initial therapy to treat their cancer, but not in those who received other cancer treatments as primary therapy (Bower et al., 2011b).

Genomic Markers—Seven cross-sectional studies exploring associations between levels of fatigue and genomic markers showed positive, significant associations between these markers and fatigue (Aouizerat et al., 2009; Bower et al., 2011a; Collado-Hidalgo et al., 2008; Fernandez-de-las-Penas et al., 2011; Landmark-Høyvik H et al., 2009; Miaskowki et al., 2010; Rausch et al., 2010). TNF and IL-6 alleles extracted from DNA of archived buffy coat samples were significantly associated with fatigue levels. Both studies used the same sample population. Common, homozygous (AA) alleles of IL-6 were associated with higher levels of evening and morning fatigue symptoms among oncology patients and their family caregivers (Miaskowski et al., 2010). Higher morning fatigue, but not evening fatigue was also noted with homozygous (GG) alleles of the TNF-α gene in the same subjects (Aouizerat et al., 2009). SNPs of several cytokines including IL-1β (rs1143633, rs2853550), IL-1RN (rs397211, rs4252041), and IL-10 (rs1878672, rs3021094) showed significant associations with fatigue levels in lung cancer survivors (Rausch et al., 2010). PLOD1 (procollagen-lysine 1, 2-oxoglutarate 5-dioxygenase 1), a gene involved in glycoprotein metabolism, and the NPCDR1 gene (nasopharyngeal carcinoma, downregulated 1) were differentially expressed in fatigued BCS (Landmark-Høyvik H et al., 2009). Overrepresentation of CC alleles in the IL1B-511 (C/T) polymorphism and elevated occurrence of homozygosity for both the variant C allele and the wild type G allele of the IL6 – 174 (G/C) polymorphism were found to be independent predictors of CRF among breast cancer survivors (Collado-Hidalgo et al., 2008). Genes associated with activation of inflammatory cytokines, chemokine signaling, activation of transcriptions and vascular growth factor, as well as NF-κB response were differentially expressed in fatigued BCS (Bower et al., 2011a). Furthermore, genotypic characterization of BCS showed that specific catechol-O-methyltransferase (COMT) genotypes (Valine (Val)/Methionine (Met) and Met/Met) were significantly correlated with higher fatigue scores compared to survivors with Val/Val genotype (Fernandez-de-las-Penas et al., 2011).

Summary—Findings from the cross-sectional studies demonstrate that elevated fatigue symptoms had positive, significant associations with systemic inflammatory markers such as WBC, CRP, and lymphocytes, however, these significant associations failed to persist after including BMI as a covariate in the analyses (Bower et al., 2003, Bower et al., 2011; Kwak et al., 2012; Minton et al., 2012). Moreover, associations between levels of fatigue and signals for immune response (IL-1ra, sTNF-RII) also failed to persist when ethnicity, menopausal status, and educational level were added as covariates to the statistical analyses (Collado-Hidalgo et al., 2008, Orre et al., 2011), and when these signals were measured in BCS who received primary cancer treatments other than chemotherapy (Bower et al.,

2011b). A number of studies did not find significant associations between levels of fatigue and the pro-inflammatory cytokine, IL-6 (Kwak et al., 2012; Orre et al., 2009; Orre et al., 2011; Scheede-Bergdahl et al., 2012). A marker of IL-6 activity (IL-6R) was found to be elevated in stimulated cells from fatigued BCS (Bower et al., 2002).

All genomic markers explored by the seven cross-sectional studies showed positive, significant associations with fatigue (Aouizerat et al., 2009; Bower et al., 2011a; Collado-Hidalgo et al., 2008; Fernandez-de-las-Penas et al., 2011; Landmark-Høyvik H et al., 2009; Miaskowki et al., 2010; Rausch et al., 2010). Results from cross-sectional immunogenomic studies provide a pattern that subclinical inflammation and immune dysregulation are observed in patients who had a tendency to get fatigued. However, because of the research design used, these findings fell short in identifying whether the experience of fatigue was related to cancer and/or its treatment. Table 1 summarizes the studies demonstrating significant associations between CRF and immunogenomic markers and Table 2 reports on the studies that did not find empirical support for such an association.

Discussion

The goal of this review was to determine patterns of associations between immunogenomic markers and CRF. In the longitudinal studies, there were trends of associations between levels of CRF and markers of inflammation and immune response, especially in women with early stage of breast cancer. It is premature to specify potential biomarkers for CRF based on the findings because all results were based on associations and therefore do not prove causation. However, this review provides empirical support for the association between high levels of CRF and elevated systemic inflammatory markers (CRP, neutrophils, monocytes, lymphocytes); increased signal of immune response ($CD4^+$); high cytokine (IL-6, IL-1β) concentrations; and increased markers of cytokine activities (IL-1ra, sTNF-RII).

Elevation of inflammatory/immune markers has been observed with cancer progression and cancer treatment. Inflammation is considered a direct cause of certain types of malignancies (Ruffell et al., 2010) and some tumors attract inflammatory cells to promote its growth and progression (Whiteside, 2006). Tumor cells are infiltrated by immune cells, predominantly by CD4+ T cells, which are recruited by chemokines and cytokines (Whiteside, 2008). These tumor cells have been shown to induce immune cell dysfunction by interfering with signal transduction, cytokine production and proliferation, and cell migration (Whiteside, 2010). On the other hand, cancer treatment has been shown to cause long-lasting imbalance of the immune system, resulting in a chronic inflammatory state (Ma et al., 2010), as seen by the elevated levels of pro-inflammatory cytokines even during survivorship (Bower et al., 2007; Reinertsen et al., 2011). These pro-inflammatory cytokines are produced in large amounts by monocytes (Fieren, 2012), which were found to be elevated in the studies included in this review (Paddison et al., 2009; Wratten et al., 2004). These pro-inflammatory cytokines are known to act on brain structures to alter behavior; and variations in their concentrations, especially IL-6, IL-1β, and TNF-α can lead to sickness behavior including the symptom of fatigue (Fung et al., 2012). Cytokines cross the blood-brain barrier (BBB) using specific transport systems as demonstrated in previous radio-imaging studies (Banks et al., 1995; Konsman et al., 2004). Prostaglandins released in response to cytokine activation can alter BBB permeability (Schenk et al., 2008) leading to increased cytokine movement and leukocyte migration across the BBB (Strey et al., 2002). The pathway involved in the interaction of cytokines and brain structures may help explain pathways behind CRF as displayed in Figure 1.

Gaps in knowledge were also found that limit the ability to draw conclusions related to the associations of immunogenomic markers and CRF. In this section results of the review are

discussed in relation to: (a) gaps in knowledge, (b) genomic findings, (c) study limitations, and (d) recommendations for future research.

Gaps in Knowledge

The first gap identified is the lack of longitudinal studies exploring the associations of immunogenomic markers and fatigue. Only 29% of the studies used a longitudinal design. More longitudinal studies are necessary to prospectively explore the important roles of cancer progression and treatment in the experience of fatigue in this population. Another gap is the lack of a case-definition for CRF. Only 12 of the 34 studies conceptually defined fatigue. In three studies, CRF was defined as a multidimensional concept where increased levels of CRF were associated with elevated levels of cytokines (IL-6, IL-1β) (Inagaki et al., 2008; Panju et al., 2009; Von Ah et al., 2008). A similar association was observed in one study that used the ICD-10 criteria to define CRF as the presence of significant fatigue nearly every day for two weeks in the past month (Alexander et al., 2009). Three studies did not observe a similar association between CRF and cytokine levels, but higher levels of CRF were associated with higher concentrations of systemic inflammatory markers (CRP, neutrophils) when CRF was conceptualized as having both physical and attentional/mental components (Booker et al., 2009; Olson et al., 2002: Scott et al., 2002) or when it was defined as a sense of tiredness that lasted more than 6 months (Orre et al., 2009; Reinertsen et al., 2011). A non-significant or inverse relationship was observed between CRF and levels of cytokine (IL-6) or systemic inflammatory marker (CRP) when CRF was defined as persistent tiredness (Ahlberg et al., 2004; Kwak et al., 2012) or as part of a symptom cluster (Minton et al., 2012). Variations in the associations between CRF and inflammatory/ immune markers are related to the differences in scope of the concept of fatigue being measured and the duration of symptom experience.

A third gap identified is the lack of standard CRF measures that can predict clinical significance. Only 2 of the 11 questionnaires used in the ten longitudinal studies namely, the Fatigue Symptom Inventory (FSI) and the Multidimensional Fatigue Symptom Inventory (MFSI), were reported to be sensitive to changes of disease progression or treatment (Whitehead, 2009). Thus, the other CRF measures used in the longitudinal studies had not been validated for longitudinal designs to be sensitive to cancer progression or effect of cancer therapy. Another important gap that emerged from this review relates to identifying whether fatigue symptoms experienced by cancer patients were related to disease progression, cancer treatments, or other covariates. Inconsistent or non-significant associations were found in studies that enrolled subjects with terminal cases or older individuals or when BMI, ethnicity, and menopausal status were included as covariates in the analyses. A final gap of knowledge is the lack of consistent associations between concentrations of pro-inflammatory cytokines (IL-6 and TNF-α) and levels of fatigue. These latter associations require further investigation using more sophisticated approaches.

After addressing the aforementioned knowledge gaps, the use of genomic and proteomic technologies in identifying the roles of genes, proteins, and environment in CRF may best describe pathways that might play a crucial role in the development of fatigue in cancer populations. These approaches have been proven successful in identifying mechanisms in other symptoms such as depression (Keers R, Uher R, 2011) and pain (Kaszas et al., 2012).

Genomic Findings

Genomic technology is a novel approach for providing information about possible pathways that may explain development of CRF and a closer attention to the findings reported by the reviewed articles is warranted. The findings related to the genetic association studies conducted by Collado-Hidalgo et al. (2008) and Bower et al. (2011a) must be considered

with caution because of two critical limitations: both used small samples and both further stratified their samples during analysis. For example, the genetic association study investigated 33 fatigue patients and 14 non-fatigue patients and further subdivided the sample into two ethnic groups (whites and non-whites) to control for ethnicity. However, a closer investigation of the non-white subjects especially those who were fatigued, revealed that 40% were Asians. Furthermore, there were no Asian subjects in the non-fatigued group (Collado-Hidalgo et al., 2008), which made it more difficult to interpret the results.

Aouizerat et al. (2009) and Miaskowski et al. (2010) reported a genetic association between certain SNPs and fatigue. Both used the same population of cancer patients and caregivers. Even though these studies found significant associations, there were some limitations in their similar study design. The authors combined cancer patients and their family members for the analysis, which could have led to different types of fatigue being analyzed: cancer-related fatigue and fatigue not related to cancer. The population stratification is another limitation of these studies considering that categorizing different races into a single, non-white, ethnic category would provide additional complexity to genomic analysis.

The Norwegian research team reported significant associations between genomic markers and fatigue in breast cancer survivors (Landmark-Høyvik H et al., 2009; Reinertsen et al., 2011). Among the eight articles reporting on genomic marker association with fatigue, the study conducted by Landmark-Høyvik, H. et al. (2009) deserves a closer inspection because of its large sample size. An initial sample of 403 subjects was reduced to a subset of 137 with chronic fatigue assessed at two different time points. These 137 subjects were further stratified into fatigue and non-fatigue groups to control for differences in anxiety and depression levels. This study showed an association between a single gene expression using blood and fatigue levels using linear analysis. However, more sophisticated gene set enrichment analyses (GSEA) using pathways from the Molecular Signature Database (MSigDB) revealed a difference of gene expression in inflammatory process and immune system. The study conducted by Reinertsen et al. (2011) showed a weak association between a C-reactive protein encoding gene SNP (rs3091244) and fatigue. Because the uncorrected p-value of the reported association was only 0.02, it may be considered as a false positive result.

Findings from a study by Fernandez et al. (2011) also warrant further consideration. This study reported a positive association between high fatigue levels in breast cancer survivors with a Met/Met COMT 158 when these subjects also complained of more pain in the neck and shoulder areas. Considering high minor allele frequency of COMT 158, the sample size of this study (N = 128) seems to be appropriate. This COMT SNP has been studied extensively including its role in experimental and clinical symptoms such as opioid responses in cancer patients, but some inconsistencies have been reported (Kambur et al., 2010; Laugsand et al., 2011). The role of COMT SNP in CRF needs to be investigated further.

Recommendations for future research

More longitudinal studies that address the identified gaps are needed to fully advance the investigation of mechanisms related to CRF and to capture the dynamic changes that occur in these immunogenomic markers during cancer progression and treatment. Careful sample and study design selection, utilization of valid and reliable CRF measures that are sensitive to changes in fatigue overtime, and inclusion of relevant covariates in statistical analyses are important considerations in designing future studies. Establishing causation between biomarkers and CRF will not be fully realized without CRF being case defined, clearly measured, and clinically translated. Identifying a biomarker of CRF will be immensely

beneficial not only in the clinical management of CRF but also in improving treatment outcomes of individuals with cancer.

Conclusion

This review identified some patterns of associations between specific immunogenomic markers and fatigue in survivors with early stages of cancer. Inconsistent associations between fatigue and immunogenomic markers were found in subjects with terminal cases of cancer and when other covariates where considered in the analysis. The most important findings of this review are the identification of the gaps of knowledge that must be addressed in order to advance the science of CRF research. Future efforts should focus on defining CRF, reassessing clinical significance of CRF measures especially using longitudinal approaches, and using biomarkers in predicting changes in CRF. Methodologically improved designs can pave the way in understanding etiologic mechanisms and therapeutic targets of CRF.

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Highlights

This review identified patterns of associations between immunogenomic markers and CRF, and gaps in knowledge needed to advance the science of CRF research.

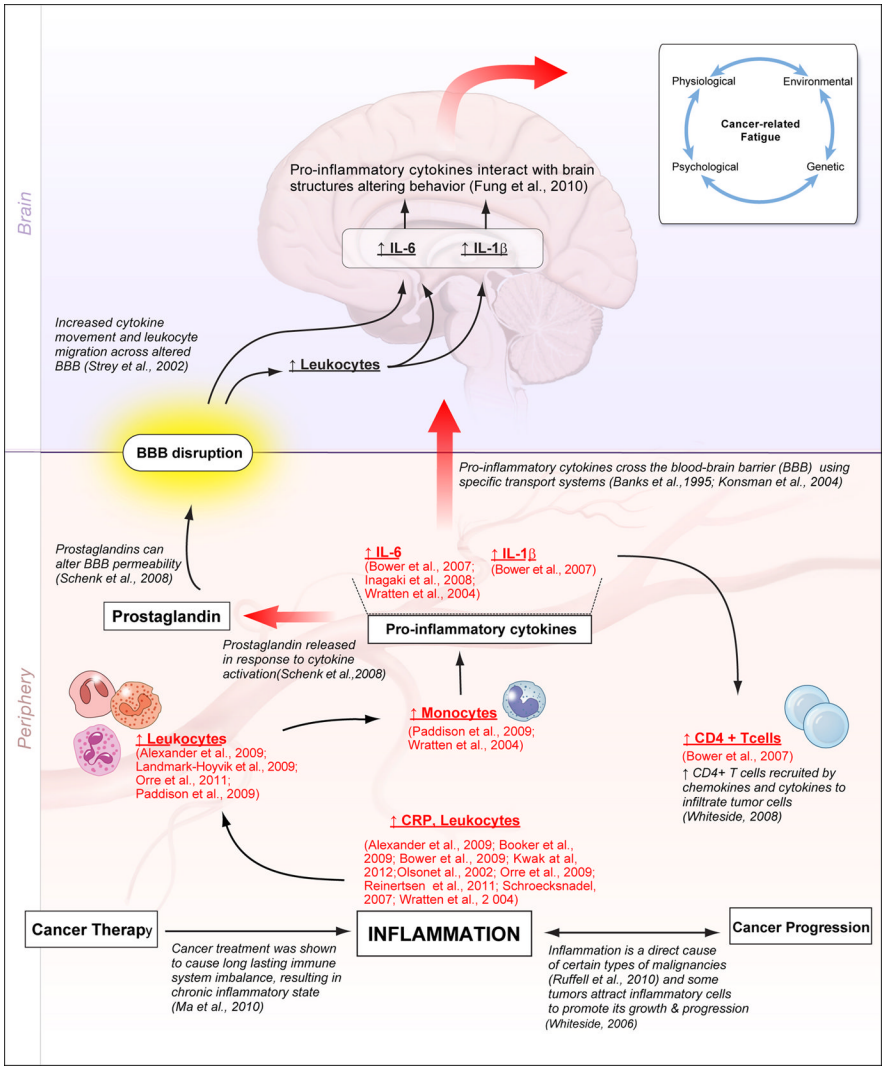

Figure 1. Association of Inflammatory Markers and Cancer-Related Fatigue

The link between inflammatory markers and cancer-related fatigue may be related to the inflammatory state generated by cancer progression and/or cancer therapy. Both conditions trigger an increase in pro-inflammatory cytokine production by white blood cells (especially monocytes). The systemic experience of CRF may be related to the interactions of pro-inflammatory cytokines and immune cells with brain structures that migrate through a disrupted blood-brain barrier altered by pro-inflammatory cytokine-related activities. CRF intensity is dependent on physiological, psychological, genetic, and environmental factors.

Table 1

gnificant Associations Between Immunogenomic Markers And CRF

Longitudinal Studies											
ncer	**Sample**	**Exclusion**	**Control**	**Intervention**	**Measure**	**Data Collection**	**Marker**	***p* value**	**Association**	**Covariates**	**Direction of Association**
erine, 86% stage I, st hysterectomy	*n* = 15	Dementia, history of psychiatric disorder	None mentioned	Radiation Therapy (RT)	Multidimensional Fatigue Inventory (MFI) (Swedish)	Plasma, pre RT, post 30 Gy (+3 wks), post RT (46 Gy, or +5–6 wks), 1 week post RT	Interleukin (IL)-6	0.006	$r = -0.65$		Positive, significant correlation between IL-6 and fatigue from baseline to 3 weeks into RT
								0.04	$r = -0.54$		Positive, significant correlation between IL-6 and fatigue from baseline to end of RT
east, stages 0, I, or II	*n* = 10 (fatigued)	Cancer recurrence, diagnosis with other cancer, history of immunologic or hormonal disease, current medical illness, heavy alcohol use	n = 15 (non-fatigued)	Survivors	Short Form (SF)36– vitality scale	Lymphocytes extracted at baseline, post stress, after 30 minutes of recovery.	CD4+	0.024	$F(2,46) = 4.0$	Time between blood draw, age, marital status, cancer treatment, body mass index (BMI), and depressed mood score	Higher level and greater increase in number during stress test in fatigued group
						Blood supernatant at baseline, post stress, after 30 minutes of recovery.	IL-6	0.006	$F(1,20) = 9.3$		Increase in lipopolysaccharide (LPS)-stimulated production during stress test in fatigued group
							IL-1β	0.02	$F(1,20) = 6.1$		Increased from baseline to recovery from stress test in fatigued group.
east (stage 0, I, II); state (T1-Tumor 3, de 0, Mets 0)	*n* = 28 (breast); n = 20 (prostate)	Tobacco use, recurrent cancer, previous/planned chemo, immunosuppressant use, active illness/ infection	Baseline values for each patient	RT	Fatigue Symptom Inventory (FSI)	Serum drawn at baseline, 4 time points during RT, 2 time points post RT	C-reactive protein (CRP)	0.022	$\beta = 0.32$, SE = 0.14	Sleep disturbance, depressive symptoms, age, body mass index, hormone therapy	Higher with increased fatigue duration
							IL-1ra	0.016	$\beta = 0.63$, SE = 0.26		Higher with increased fatigue severity
east, stages 1–IIIA	*n* = 29 (Same subjects used by Aouizerat et al., 2009)	Undergoing bone marrow transplants, metastatic breast cancer, confounding illness (e.g. renal failure, pre-existing anemia)	none	Chemo (adjuvant or neoadjuvant)	Multidimensional FSI (MFSI)	Plasma before chemo cycles 1 and 4; 2.5 months between plasma collection	Vascular Growth factor (VEGF)	< 0.03	beta = 0.468	Depression, stage of disease	Higher levels predicted high fatigue in the 4th cycle of chemo, but no association with fatigue when depression was added.
lon, rectal, Small l lung cancer CLC), NSCLC ages IIIb–IV)	*n* = 18	None mentioned	none	Chemo and/or RT (for rectal and SCLC patients)	Interview	Serum before treatment, midtreatment, 3 and 6 months post treatment	Absolute neutrophil	0.01	$r = 0.737$	None mentioned	Higher levels associated with high fatigue pre-chemo in colon cancer patients

Longitudinal Studies

ncer	Sample	Exclusion	Control	Intervention	Measure	Data Collection	Marker	*p* value	Association	Covariates	Direction of Association
east, stages II and III	Timepoint 1 (T1)=302, Timepoint 2 (T2)=236 (175 eliminated for reporting fatigue only in 1 time point). Fatigued, n=55	Breast cancer recurrence, other cancer (except melanoma, ovarian cancer in situ), depression in T1	None fatigue d, n =120,	None	Fatigue Question naire (FQ - Norwegian)	Deoxyribonucleic acid (DNA) from peripheral blood, blood drawn 2–3 years apart for 2 timepoints	hsCRP	0.03	OR = 1.11, 95% CI (1.01 – 1.21)	Treatment strategies; subset of subjects: BMI, treatment-area related fibrosis	Higher level in patients with non-depressed, chronic fatigue at T1 and subset analysis (higher with persistent fatigue after controlling for covariates)
east, early stage	*n* = 52	Severe current illness, history of major breast surgery, history of breast irradiation treatment, metastatic disease	None mentioned	Adjuvant RT post surgery	Functional Assessment of Cancer Therapy –Fatigue (FACT-F)	Blood before RT, weekly during RT, then 2 & 6 weeks post RT	Neutrophil	Baseline (p=0.03,), week 5 (p=0.01)	Baseline (r=− 0.315), week 5 (r=−0.381)	BMI	Fatigue correlated with higher neutrophil level at baseline & week 5 of RT
							Monocyte	baseline (p=0.05), week 5 (p=0.01)	baseline (r= −0.289), wk5 (r=−0.394)		Fatigue correlated with higher monocyte level at baseline & week 5 of RT
							CRP	p<0.01	r=−0.456		Fatigue correlated with higher CRP at baseline
						Serum before RT, weekly during RT, then 2 & 6 weeks post RT	Fibroblast growth factor *β*	0.04	Not given		Decreased in non-fatigued subjects at week 5 of RT
							IL6	baseline (p=0.05), wk5(p=0.03)	baseline (r= −0.322), wk5(r= −0.367)		Fatigue correlated with higher IL6 at baseline and week 5 of RT
							Intercellular adhesion molecule -1 (ICAM-1)	p=0.04	r= −0.311		Fatigue correlated with higher ICAM-1 at baseline

Cross-sectional Studies

ncer	Sample	Exclusion	Control	Intervention	Measure	Design	Marker	*p* value	Association	Covariates	Direction of Association
rious, non-metastatic	*n* = 185	Metastatic disease, more than one cancer diagnosed, diagnosed sleep disorder	n = 103 (family caregivers)	RT	Lee Fatigue Scale (LFS)	Archived buffy coat DNA	Homozygous allele of *TNFA* genotype (i.e., GG)	0.02	*t* = −2.22	age, *TNFA* genotype	Higher in patients with morning fatigue
east, stages 1–IIb	*n* = 60 (fatigue)	Pregnancy, other cancer, recurrent disease, confusion, dementia	n = 104 (non-fatigued)	Survivors, 3 months -2 year post primary therapy	Brief Fatigue Scale	Peripheral Blood	White blood cell (WBC)	0.021	Not given	None mentioned	Higher in fatigued group
							CRP	0.015	Not given		Higher in fatigued group
							Basophil	0.04	Not given		Higher in fatigued group

Longitudinal Studies

ncer	Sample	Exclusion	Control	Intervention	Measure	Data Collection	Marker	*p* value	Association	Covariates	Direction of Association
ultiple myeloma, ges I, II, III	*n* = 56	Other plasma cell dyscrasia	None	None	FACT-F	Peripheral blood	CRP	0.034	β = −0.350	None mentioned	Significant predictor of fatigue using FACT-F
					Quality of Life Questionnaire (QLQ)-C30			0.003	β = 0.514		Significant predictor of fatigue using QLQ-C30
east, recruited from a ol of 332 survivors o met eligibility teria used by Bower al., 2006	*n* = 20 (fatigued)	Change in energy level between 2 assessments, cancer recurrence, other cancer, comorbid medical problem, immune disease, on immunosuppressant, psychiatric hospitalization in past 6 months, heavy alcohol use	*n* = 20 (non-fatigued)	Survivors recruited from 1994–1997; 5 years from diagnosis	RAND36, FSI	Serum taken between 8–10 am, fasting/no alcohol/caffeine/ smoking 12 hours before draw	IL-1ra	0.006	95% CI = 2% to 89%	caffeine, alcohol use, smoking	46% more in fatigued group
							Soluble tumor necrosis factor (TNF)-RII	0.005	95% CI = 6% to 59%		18% more in fatigued group
							Neopterin	0.018	95% CI = 1% to 34%		33% more in fatigued group
							Natural killer (NK) cells	< 0.05	$F(1,33) = 4.33$	Smoking	Lower percentage in fatigued group
							CD45RO:CD45DA	0.05	$F(1,33) = 4.01$		Higher ratio in fatigued group
east, recruited from a ol of 332 survivors o met eligibility teria used by Bower al., 2002	*n* = 19 (fatigued)	Recurrence of breast cancer, history of immune disease	*n* = 18 (non-fatigued)	Survivors recruited from 1994–1997	RAND SF36 fatigue scale grouped subjects to fatigued and non-fatigued during 2 assessments	Lymphocytes from fasting blood	Lymphocytes	0.011	95% CI = 7% to 49%,	age, income, ethnicity, BMI, depressed mood, cancer treatment	28% more in fatigued group
							CD3+	0.015	95% CI = 6% to 56%		31% more in fatigued group
							CD4+	0.003	95% CI = 15% to 68%		41% more in fatigued group
							CD3+/CD56+	0.027	95% CI = 4% to 99%		52% more in fatigued group
east (stage 0,I, II); ected from same ol of subjects ntified by Collado-dalgo et al., 2006.	*n* = 11 (fatigue d), ≥ 40 score with SF-36 fatigue scale for 2–3 assessments	Cancer recurrence, immune disease, immunosuppressant use	n = 10 (non-fatigued), >70 in SF-36 fatigue scale for 2–3 assessments	Survivors, 1–5 years post diagnosis, 21– 65 years of age	SF-36 vitality scale	Peripheral blood mononuclear cells	*IL1A, IL1B, IL6, OSM, GZMH*	<0.001	Not given	Age, time since diagnosis and cancer treatment prior to gene analyses	Upregulated in fatigued group (>30% difference)
							CXCL2, CXCR5, CCL20, CMKLR1	<0.001	Not given		Upregulated in fatigued group (>30% difference)
							IER3, ZNF331, NR4A2, NR4A3	<0.001	Not given		Upregulated in fatigued group (>30% difference)
							VEGFA, TRGC2, TIGIT, CX3CR1	<0.001	Not given		Upregulated in fatigued group (>30% difference)
							NLRC4, HP, CROP, MGAM	<0.001	Not given		Upregulated in fatigued group (>30% difference)
							NF-κB response elements in promoters of upregulated genes	<0.0001	2.28-fold difference ±0.09		Promoter upregulated in fatigued group (across nine combinations of promoter length)

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Longitudinal Studies

ncer	Sample	Exclusion	Control	Intervention	Measure	Data Collection	Marker	*p* value	Association	Covariates	Direction of Association
							Glucocorticoid response elements in promoters of upregulated genes	<0.007	0.45-fold difference ±0.07		Promoter under represented in fatigued group (across nine combinations of promoter length)
							Proinflammatory transcription factor-binding motifs in the promoters of upregulated genes	0.041	2.72 fold increase		Upregulated in fatigued group
east, stages 0–IIIA, ected from same hort as Bower et al., Bower et al., 2003; wer et al., 2011a; llado-Hidalgo et al., 06	*n* = 103	Neurologic or immune disease, smokers	None mentioned	Completed primary treatment within 3 months and not started on endocrine treatmen	FSI	Plasma	sTNF-RII	0.036	Not given	Exposure to RT, age, time since treatment completion, BMI	Higher levels associated with higher fatigue scores with subjects treated with chemotherapy only.
east (stages 0,I, II); ruited from same ol of subjects used Bower et al., 2002 d Bower et al., 2003	*n* = 32 (fatigued), < 50 score with SF-36 fatigue scale	Cancer recurrence, immune disease, immunosuppressant use, psychiatric disease, smokers, alcohol use, SF-36 fatigue score 50–70, advanced cancer stage, >5 years post treatment	n = 18 (non-fatigued), score >70 in SF-36 fatigue scale	Survivors, 1–5 years post diagnosis	SF36–vitality scale grouped subjects to fatigued and non-fatigued during 2–3 assessments	Plasma	IL-1ra	0.05	$t(48)= -1.53$	Age, BMI, time since treatment, treatment mode, depressive symptom scores	Higher level in fatigued group
							sIL-6R	< 0.001	$t(44) = -4.07$		Higher level in fatigued group
						Monocytes	IL-6 (*ex vivo*)	0.049	t (45) = −1.813 t = −1.983 $t(29) = 2.195$		Increased ex-vivo monocyte production in fatigued group after LPS exposure
							TNF-α (*ex vivo*)	0.03			Increased ex-vivo monocyte production in fatigued group after LPS exposure
							IL-6R (*in vivo*)	0.03			Lower levels on CD14+ cells in fatigued group after exposure of monocyte to toll-like receptor (TLR) 4 ligand LPS
						Peripheral blood mononuclear cells (PBMCs)	Lymphocytes	Not given			Increased % as fraction of total leukocyte in fatigued group with selective increase in frequency of CD4 T lymphocytes.
							Myeloid dendritic cells (HLA-DR+/CD11c+/ CD14 dim)	0.04	$t(29) = 2.047$		Decreased frequency in circulating dendritic cells from fatigued group

Longitudinal Studies

ncer	Sample	Exclusion	Control	Intervention	Measure	Data Collection	Marker	*p* value	Association	Covariates	Direction of Association
							Activated T lymphocytes (CD3+/ CD69+)	0.04	$t(29) = 1.077$		Decreased frequency in circulating activated T lymphocytes from fatigued group
			Healthy blood				IL-6R (*in vitro*)	<0.01 for IL6 and IL1β; 0.23 for TNFα; 0.0006 for IL6, IL1β, TNFα	$t(4) = 4.12$ for IL6; $t(4) = 4.51$ for IL1β; $t(4) = 1.36$ for TNFα; $t(4) = 5.18$ for all 3 cytokines		Lower IL6R from cell surface of PBMCs of fatigued group after exposure to 3 cytokines
east (stage 0,I, II); ne pool of subjects ed by Bower et al., 02; Bower et al., 09; subset used by llado-Hidalgo et al., 06	*n* = 33 (fatigue d), SF36 fatigue score <55	Cancer recurrence, immune disease, on immunosuppressant	n = 14 (non-fatigued), SF36 fatigue score >70	Survivors, 1–5 years post diagnosis	MFSI	Leukocytes from peripheral blood	*IL1B*-511– CC alleles	0.008	None given	Age, ethnicity, menopausal status, BMI, depressive symptoms, cancer treatment	Overrepresentation in fatigued group.
							IL1B-511 – TT alleles	0.008	None given		Underrepresentation in fatigued group.
							IL1B-511 – cytosine	0.052	95% CI = 0.91 to 16.6		Higher prevalence in fatigue group
							IL6 – 174 (G/C)	0.024	95% CI = 1.12 to 17.9		Elevated homozygosity in variant C and wildtype G alleles noted in fatigued group except when covariants were controlled.
						Plasma	sIL-6R	0.028	None given		Higher levels in fatigued group
east, stage I–IIIA	*n* = 128 (34 Val/Val, 64 Val/Met, 30 Met/Met)	Active cancer, receiving chemo/ RT, breast surgery for cosmetic purpose, inflammatory disease, recurrent cancer, fibromyalgia	Val/Val versus Val/Met versus Met/Met genotypes	Survivors treated with RT and chemo (from 6/2009 to 3/2011), 36–65 years old	Piper Fatigue Scale (PFS-Spanish	Genomic DNA extracted from saliva cell sediments	*COMT* genotypes Val/ Met and Met/Met:	< 0.01	Not given	Pain intensity	Significantly correlated with higher fatigue scores than those with Val/Val genotype.
rious, terminal cases ruited from /1997–11/1999	*n* = 27 (fatigued)	Receiving curative cancer treatment, too ill to answer, cognitive impairment, non-Japanese speakers, only included those that died 6 months after 1st assessment, taking NSAIDS and steroids	*n* = 19 (non-fatigued)	None	Cancer Fatigue Scale (CFS - Japanese – author developed)	Plasma	IL-6	0.01	β = 0.38	Gender, weight, survival time	Higher levels in fatigued group (correlated w/ physical subscale score, but not with total, affective & cognitive scores).
rious, terminal cases ruited from 6/2009–2010; survival time is s than 6 months	*n* = 90 (mild= 23, modera te =	Cognitive impairment, chemo/ RT to treat active cancer, hematologic	Mild versus moderate versus severe	None	Brief Fatigue Inventory (BFI -Korean)	Peripheral blood collected within 24 hours from	CRP	0.005	*r* = 0.29	Age, gender, BMI, cancer site, previous cancer treatment, comorbid disease,	Higher levels in more severe categories of fatigue

Longitudinal Studies

ncer	Sample	Exclusion	Control	Intervention	Measure	Data Collection	Marker	*p* value	Association	Covariates	Direction of Association
	30, severe =37)	malignancies, use of psychostimulant, h/o psychiatric disease, fever, use of antibiotics and antiepileptics, high TSH	categories of fatigue			enrolment between 9–11 am				pain score, sleep disorder, dyspnea	
east (stage II, III, classifiable)	*n* = 403	Cancer recurrence, >75 years old, other cancer except basal cell cancer or cancer in situ, prior surgery for contralateral breast cancer stage I with no adjuvant therapy	Low fatigue	Survivors, treated from 1998–2002 with adjuvant RT	FQ (Norwegian), responses categorized into high and low fatigue	Peripheral blood drawn in 2004	Leukocytes	0.0016	Not given	None mentioned	Higher in fatigued, non-depressed group
							Neutrophils	0.0059	Not given		Higher in fatigued, non-depressed group
							Lymphocytes	0.0046	Not given		Higher in fatigued, non-depressed group
						Ribonucleic acid (RNA) from blood collected using PAX tube	*PLOD1*	False Discovery Rate (FDR) < 0.20	Not given		Downregulated in fatigued group, regardless of depression status
							NPCDR1	FDR < 0.20	Not given		Upregulated in fatigued, non-depressed group
ute myelogenous kemia or myelodys stic syndrome	*n* = 54 (baseline), n= 26 (1 month of treatment)	None mentioned	Normal control (no N given)	Chemo	BFI	Serum drawn at baseline, fatigue measure at baseline and 1 month of treatment	IL-6	Not given	*r* = 0.62	None given	Higher levels associated with higher fatigue scores
							IL-IRA	Not given	*r* = 0.52		Higher levels associated with higher fatigue scores
							TNF-α	Not given	*r* = 0.41		Higher levels associated with higher fatigue scores
rious, non-metastatic	*n* = 185	Metastatic disease, more than one cancer diagnosed, diagnosed sleep disorder	n = 103 (family caregivers)	RT	LFS	Archived buffy coat DNA	IL-6 AA genotype	0.001	3.8%	Age, gender, IL-6 genotype	Associated with higher mean evening fatigue scores
sticular	*n* = 92 (chronic fatigue)	Mental retardation, extragonadal germ cell malignancy (except skin), removal of non-affected testicle related to benign condition, concurrent infection or inflammation	n = 191 (without chronic fatigue)	Survivors, recruited from 1980–1998 database, 18–75 years old	FQ (Norwegian)	Plasma drawn from 0800-12 noon; subjects allowed light breakfast	IL-1ra	< 0.01	*r* = 0.18	Age, BMI, smoking, anxiety, depression, neuroticism	Higher in fatigued group, but lost significance when adjusted for BMI
							CRP	< 0.05	r = 0.16		Higher in fatigued group but lost significance when adjusted for behavior (smoking)

Longitudinal Studies

ncer	Sample	Exclusion	Control	Intervention	Measure	Data Collection	Marker	*p* value	Association	Covariates	Direction of Association
east (stage II, III, classifiable).	*n* = 299	Cancer recurrence, >75 years old, other cancer except basal cell cancer or cancer in situ, prior surgery for contralateral breast cancer stage I with no adjuvant therapy	None	Survivors, treated from 1998–2002 with adjuvant RT; subsample of Reinersten et al., 2011 & Landmark-Høyvik H et al., 2009	FQ (Norwegian)	Blood drawn from 0900-12 noon; subjects allowed light breakfast	Leukocytes	<0.018	*Beta* = 0.014	Age, educational level	Higher levels associated with higher fatigue scores but lost significance when adjusted for covariates (*p* = 0.78)
						Serum	High sensitivity CRP	< 0.001	*Beta* = 0.26		Associated with total fatigue even after controlling for age and education (p = 0.02)
CLC, Stages IIIb d IV	*n* = 44	None mentioned	None	None	Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) – 2 items, 1 item from Hamilton Depression scale	Retrospective extraction of clinical results (peripheral blood)	WBC	0.01	R^2 = 0.27, β = 0.41	Age, gender, time since treatment completion, hemoglobin	Increased with higher fatigue
							Neutrophil	0.01	R^2 = 0.28, β = 0.43		Increased with higher fatigue
							Monocyte	0.05	R^2 = 0.20, β = 0.31,		Increased with higher fatigue
ng, stages I–IV	*n* = 1149	None mentioned	None mentioned	None	Lung Cancer Symptom Scale, (LCSS)	DNA from peripheral blood	IL-1B rs1143633	Not given	OR estimate = 1.00 – 1.02	Age at diagnosis, sex, smoking status, disease stage, treatment modality	Increased with higher fatigue
							IL-1B rs2853550	Not given	OR estimate = 1.01 – 1.06		Increased with higher fatigue
							IL-1RN rs397211	Not given	OR estimate = 0.97 – 1.00		Increased with higher fatigue
					SF-8		IL-10 rs3021094	Not given	OR estimate = 1.02 – 1.18		Increased with higher fatigue
							IL-10 rs1878672	Not given	OR estimate = 0.91 – 0.94		Increased with higher fatigue
							IL-1RN rs4252041	Not given	OR estimate = 0.80 – 0.97		Increased with higher fatigue
rious	*n* = 146 (stable/ remitting = 60;	None mentioned	None mentioned	None	Fatigue scale	Serum	Neopterin	<0.01	r_s = 0.274		Increased with high fatigue
							Tryptophan	<0.05	r_s = −0.179		Lower concentration associated with increase fatigue
							kyn/trp	<0.01	r_s = 0.276		High ratio with high fatigue
							CRP	<0.001	r_s = 0.375		Increased with high fatigue
							Erythrocyte sedimentation rate (ESR)-1	<0.01	r_s = 0.234		Increased with high fatigue

Longitudinal Studies											
ncer	**Sample**	**Exclusion**	**Control**	**Intervention**	**Measure**	**Data Collection**	**Marker**	***p* value**	**Association**	**Covariates**	**Direction of Association**
	progressing = 86)						ESR-2	<0.01	r_s = 0.241		Increased with high fatigue
perable NSCLC, ges III and IV	*n* = 106	Infection	None	None	QLQ-C30	Peripheral blood collected from 1/1995–11/1998	CRP	0.011	Not given	None mentioned	High levels associated with high fatigue scores
east, stage 0–IIIa	*n* = 44	Psychiatric disorder, dementia, history or current substance abuse, thyroid issues, immune disorders, immunosuppression, other cancer except noninvasive type	None mentioned	Adjuvant chemo + RT	Revised Piper Fatigue Scale (rPFS)	Blood collected 9–33 days post surgery (lumpectomy or mastectomy) before adjuvant therapy	IL-1β	≤ 0.01	r = 0.32	Type of adjuvant therapy, mood, network support, satisfaction, cortisol, perceived stress, optimism	Higher levels associated with high fatigue scores
						Mononuclear cells collected 9-33 days post surgery (lumpectomy or mastectomy) before adjuvant therapy	NK cell activity	≤ 0.01	r ≥ 0.20		Lower levels associated with high fatigue scores

trp = kynurenine to tryptophan ratio

Table 2

Studies With Non-Significant Associations Between Immunogenomic Markers And CRF

Longitudinal Studies											
Authors	**Cancer**	**Sample**	**Exclusion**	**Control**	**Intervention**	**Measure**	**Data Collection**	**Marker**	***p* value**	**Association**	**Covariates**
Ahlberg et al., 2004	Uterine, 86% stage I, post hysterectomy	*n* = 15	Dementia, history of psychiatric disorder	None mentioned	Radiation Therapy (RT)	Multidimensional Fatigue Inventory (MFI) (Swedish)	Plasma, pre RT, post 30 Gy (+3 wks), post RT (46 Gy, or +5–6 wks), 1 week post RT	Tumor necrosis factor (TNF)-α	0.51 (baseline - 30 Gray), 0.50, (baseline to 46 Gray)	*r*= 0.20 (baseline - 30 Gy), *r* = −0.19 (baseline to 46 Gy)	None mentioned
								Interleukin (IL)-1	Not given	Low concentration, cannot estimate	
Geinitz et al., 2001	Breast, no stage specified	*n* = 41	Metastatic disease, chemo with RT, 2nd cancer, inflammatory disease, thyroid disease, history of depression, use of tranquilizers, streroids, non-steroidal	None	Adjuvant RT (27–120 days post surgery)	Fatigue Assessment Questionnaires (FAQ), German version	Serum pre RT, end of weeks 1–5 during RT, 2 months post RT	IL-1β	Not given	No association with fatigue	None mentioned
								IL-6			
								TNF-α			
Olson et al., 2002	Colon, rectal, Small cell lung cancer (SCLC), NSCLC (stages IIIb–IV)	*n* = 18	None mentioned	None	Chemo and/or RT (for rectal and SCLC patients)	Interview	Serum before treatment, midtreatment, 3 and 6 months post treatment	IL-6	0.12–0.62	*r* = 0.19–0.61	None mentioned
								TNF-α	Not given	Not given	
Panjute et al., 2009	Acute myeloid leukemia, within 1 year of diagnosis	Timepoint (T)1=34 (23 Male, 11 Female), T2=28	Other cancer, hematopoietic stem-cell transplantation, taking growth factors	None	Chemo or supportive care	Functional Assessment of Cancer Therapy –Fatigue (FACT-F) and Edmonton Symptom Assessment System (ESAS) fatigue severity	Serum T1 (pre treatment, between treatment, upon completion of full treatment); T2 (4–6 weeks post T1)	Interferon (IFN)-γ	Not given	No association with fatigue level and severity	None mentioned
								IL-2	Not given		
								IL-8	Not given		
								TNF-α	Not given		
								Monocyte chemotactic protein-1	Not given		
						FACT-F and Quality of Life Questionnaire (QLQ)-C30 and ESAS		IL-5	0.08 (FACT-F), 0.07 (QLQ-C30)	r=0.33 (FACT-F), r=0.34(QLQ-C30)	
								IL-6	0.059	r=0.332	
								IL-10	0.09	r=0.33	
						ESAS fatigue severity		Monokine induced by IFN-γ	Not given	Strongest trends of change across changes in fatigue severity	
								IL-4	Not given		
Reinertsen et al., 2011	Breast, stages II and III	Timepoint 1 (T1)=302, Timepoint 2	Breast cancer recurrence, other cancer (except melanoma, ovarian	None fatigue d, n =120,	None	Fatigue Questionnaire (FQ - Norwegian)	Deoxyribonucleic acid (DNA) from peripheral blood, blood drawn 2–3 years apart for 2 timepoints	IL6R mRNA	0.59–0.92, subset = 0.57–0.7, T2= 0.6–0.64	No association with fatigue	Treatment strategies; subset of subjects: BMI, treatment-area related fibrosis

Longitudinal Studies											
Authors	**Cancer**	**Sample**	**Exclusion**	**Control**	**Intervention**	**Measure**	**Data Collection**	**Marker**	***p* value**	**Association**	**Covariates**
		(T2)=236 (175 eliminated for reporting fatigue only in 1 time point). Fatigued, n=55	cancer in situ), depression in T1					IL1β mRNA	0.59–0.92, subset = 0.57–0.8		
								IL1Brs1694 4 (A/G)	Not given		
								IL6Rrs4129 267 (C/T)			
								IL6Rrs4845 617 (A/G)			
								IL6Rrs2228 145 (A/C)			
								IL6Rrs1800 795 (G/C)			
								CRPrs2794 521 (C/T)			
								CRPrs3091 244 (A/G/T)			
Vallance et al., 2010	Acute Lymphoblastic Leukemia (ALL), low or standard risk using St Jude & Children's Oncology Group (COG)	*n* = 72	Do not meet COG/ St Jude low and standard risk criteria	None	Chemo + dexamethasone	Fatigue Symptom Inventory (FSI), pediatric and parent versions	DNA from blood pre dexamethasone, 1, 2, 4, 8 hours post oral dexamethasone dose	*AHSG*	None given	Expression not associated with fatigue	Ethnicity
								IL6 G17AC			
								IL6 C634G			
								POLDIP3			
Wratten et al., 2004	Breast, early stage	*n* = 52	Severe current illness, history of major breast surgery, history of breast irradiation treatment, no metastatic disease	None mentioned	Adjuvant RT post surgery	FACT-F	Blood before RT, weekly during RT, then 2 & 6 weeks post RT	Lymphocyte	Baseline and week 5 ($p<0.01$)	Decreased in both fatigued and nonfatigued groups from baseline to week 5	Body mass index (BMI)
Cross-sectional Studies											
Authors	Cancer	Sample	Exclusion	Control	Intervention	Measure	Data Collection	Marker	p value	Association	Covariates
Alexander et al., 2009	Breast, stages 1–IIb	*n* = 60 (fatigue)	Pregnancy, other cancer, recurrent disease, confusion, dementia	n = 104 (non-fatigue d)	Survivors, 3 months - 2 year post primary therapy	Brief Fatigue Scale (BFS)	Peripheral Blood	Neutrophils	0.51	No association with fatigue	None mentioned
								Lymphocyte	0.25		
								Monocyte	0.052	Trended towards significant association with fatigue	
								Eosinophil	0.051		
Bower et al., 2003	Breast	n = 19 (fatigued)	Recurrence of breast cancer,	n = 18 (non-fatigued)	Survivors recruited from 1994–1997	RAND SF36 fatigue scale grouped subjects to fatigued	Peripheral blood, fasting	White blood cells (WBC)	Not given	No association with fatigue	Age, income, ethnicity, BMI,
								Granulocyte			
								Monocyte			
							Lymphocytes extracted from fasting blood	CD8+T lymphocyte	0.124	31% more in fatigued group	
								CD38 T lymphocyte	Not given	No association with fatigue	

Longitudinal Studies											
Authors	**Cancer**	**Sample**	**Exclusion**	**Control**	**Intervention**	**Measure**	**Data Collection**	**Marker**	***p* value**	**Association**	**Covariates**
			history of immune disease			and non-fatigued during 2 assessments		HLA-DR T lymphocyte			depressed mood, cancer treatment
							Serum from fasting blood	IL-1ra	0.253		
Bower et al., 2011b	Breast, stages 0–IIIA	*n* = 103	Neurologic or immune disease, smokers	None mentioned	Completed primary treatment within 3 months and not started on endocrine treatment	FSI	Plasma	IL1ra	>0.70	No association with fatigue	Exposure to RT, age, time since treatment completion, BMI
								C-reactive Protein (CRP)			
								Soluble TNF-RII		Especially with patients receiving therapy other than chemo	
Collado-Hidalgo et al., 2006	Breast (stages 0,I, II)	n = 32 (fatigued), < 50 score with SF-36 fatigue scale	Cancer recurrence, immune disease, immunosuppressant use, psychiatric disease, smokers, alcohol use, SF-36 fatigue score 50–70, advanced cancer stage, >5 years post treatment	n = 18 (non-fatigue d), score >70 in SF-36 fatigue scale	Survivors, 1–5 years post diagnosis	SF36 – vitality scale grouped subjects to fatigued and non-fatigued during 2–3 assessments	Lymphocytes taken in the morning	CD8+T lymphocyte	>0.10	No difference between fatigued and non-fatigued groups	Age, BMI, time since treatment, treatment mode, depressive symptom scores
								CD18 B cells			
								CD3−/CD16+/C D56+ natural killer (NK) cells			
							Plasma taken in the morning	IL-6	Not given	Plasma levels did not reach significance	
								TNF-rII			
Collado-Hidalgo et al., 2008	Breast (stage 0,I, II)	*n* = 33 (fatigued), SF36 fatigue score <55	Cancer recurrence, immune disease, on immunosuppressant	n = 14 (non-fatigue d), SF36 fatigue score >70	Survivors, 1–5 years post diagnosis	Multidimensional FSI	DNA from leukocytes extracted from peripheral blood	IL1B511cytosine	0.052	Not significantly associated with fatigue after controlling for depression	Age, ethnicity, menopausal status, BMI, depressive symptoms, cancer treatment
							Plasma	IL1ra	0.074	Marginally higher in fatigued group	
Minton et al., 2011	Various, incurable metastatic or locally advanced cancer (multicenter, international study, 16 centers)	*n* = 741 (324 with severe fatigue)	Physical/cognitive impairment, language problems	*n* = 417 with no severe fatigue	May be undergoing palliative anticancer treatment	QLQ-C30 (multi-language version): 3-item fatigue subscale	Whole blood drawn within 72 hours after obtaining questionnaire responses.	CRP	Not given	No association with fatigue	Age, BMI, disease stage
Orre et al., 2009	Testicular	n = 92 (chronic fatigue)	Mental retardation, extragonadal germ cell malignancy (except skin), removal of non-affected testicle related to benign condition, concurrent infection or inflammation	n = 191 (without chronic fatigue)	Survivors, recruited from 1980–1998 database, 18–75 years old	FQ (Norwegian)	Plasma drawn from 0800-12 noon; subjects allowed light breakfast	IL-6	0.835	No association with fatigue	Age
								sTNF-RI	0.321		
								Neopterin	0.390		
Orre et al., 2011	Breast (stage II, III, unclassifiable).	n = 299	Cancer recurrence, >75 years old, other cancer except basal cell cancer or cancer in situ, prior	None	Survivors, treated from 1998–2002 with adjuvant RT; subsample of Reinersten et al., 2011	FQ (Norwegian)	Blood drawn from 0900-12 noon; subjects allowed light breakfast	IL-6	0.76	*Beta* = −0.015	Age, educational level
								sTNF-RI	0.713,	*Beta* = 0.019	
								Neopterin	0.85	*Beta* = 0.009	

Longitudinal Studies											
Authors	**Cancer**	**Sample**	**Exclusion**	**Control**	**Intervention**	**Measure**	**Data Collection**	**Marker**	***p* value**	**Association**	**Covariates**
			surgery for contralateral breast cancer stage I with no adjuvant therapy		& Landmark-Høyvik H et al., 2009			IL-1ra	0.183	*Beta* = 0.71	
Paddison et al., 2009	NSCLC, Stages IIIb and IV	n = 44	None mentioned	None	None	Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) – 2 items, 1 item from Hamilton Depression scale	Retrospective extraction of clinical results (peripheral blood)	Lymphocytes	0.78	R^2 = 0.11, β = 0.04	Age, gender, time since treatment completion, hemoglobin
Schedde-Bergendahl et al., 2011	Inoperable III & IV GI or NSCLC, from 3–11/2007	*n* = 83	Less than 18 years of age	None mentioned	None	Brief Fatigue Inventory (BFI)	Plasma processed within 4 hours of collection	IL1β	>0.05	β = 8.8	Sex, age, diagnosis, cancer treatment, Charlson comorbidity index, and concurrent pharmcological treatment
								IL-6		β = 10.78	
								IL-8		β = 5.37	
								TNF-α		β = 4.6	
Von Ah et al., 2008	Breast, stage 0–IIIa	n = 44	Psychiatric disorder, dementia, history or current substance abuse, thyroid issues, immune disorders, immunosuppr ession, other cancer except noninvasive type	None mentioned	Adjuvant chemo + RT	Revised Piper Fatigue Scale (rPFS)	Blood collected 9–33 days post surgery (lumpectomy or mastectomy) before adjuvant therapy	TNF-α	Not significant	*r* = 0.07– 0.14	Type of adjuvant therapy, mood, network support, satisfaction, cortisol, perceived stress, optimism
Kwak et al., 2011	Various, terminal cases recruited from 6/2009–7/2010; survival time is less than 6 months	n = 90 (mild=23, moderate = 30, severe =37)	Cognitive impairment, chemo/RT to treat active cancer, hematologic malignancies, use of psychostimula nt, h/o psychiatric disease, fever, use of antibiotics and antiepileptics, high TSH	Mild versus moderate versus severe categories of fatigue	None	BFI – Korean version	Peripheral blood collected within 24 hours from enrolment between 9–11 am	IL-6	0.29	*r* = 0.12	Age, gender, BMI, cancer site, previous cancer treatment, comorbid disease, pain score, sleep disorder, dyspnea
								TNF-α	0.67	*r* = 0.05	
								WBC	0.75	Not given	