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Cancer-Related Fatigue and Its Associations with Depression and Anxiety: A Systematic Review

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Abstract

Background—Fatigue is an important symptom in cancer and has been shown to be associated with psychological distress.

Objectives—This review assesses evidence regarding associations of CRF with depression and anxiety.

Methods—Database searches yielded 59 studies reporting correlation coefficients or odds ratios.

Results—Combined sample size was 12,103. Average correlation of fatigue with depression, weighted by sample size, was 0.56 and for anxiety, 0.46. Thirty-one instruments were used to assess fatigue, suggesting a lack of consensus on measurement.

Conclusion—This review confirms the association of fatigue with depression and anxiety. Directionality needs to be better delineated in longitudinal studies.

Keywords

cancer; fatigue; depression; anxiety

Fatigue is a pervasive and vexing problem in individuals with cancer. It adds considerably to suffering and exists across all types and stages of the disease. It has been found to be a problem before, during, and after treatment, sometimes continuing long after treatment has ended, even in those believed to be disease-free (1). Cancer-related fatigue (CRF) has been reported by up to 40% of patients at diagnosis, 90% of patients treated with radiation and 80% of those under chemotherapy treatment (1). In research in patients with advanced cancer, fatigue is one of the most common and disabling symptoms (2–5). In view of its prevalence and detrimental impact on quality of life, fatigue is an important symptom to target in the treatment of cancer survivors.

New Focus on Understanding CRF

The mechanisms of CRF are not well understood, but it is known to occur both as a consequence of the cancer itself and as a side effect of treatment (1). Until recently, CRF was infrequently discussed or treated, partly because of focus on other symptoms such as pain, nausea, and vomiting, and partly because fatigue was considered an unavoidable symptom to be endured rather than treated (2). Fortunately, fatigue has recently caught the attention of cancer researchers who are seeking to better understand its nature in order to develop efficacious

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interventions. A recent state-of-the-science statement from the National Institute of Health (NIH) called for more efforts toward symptom management in cancer, with fatigue named specifically along with pain and depression as the symptoms needing attention (6). Based on a panel's evaluation of available evidence, the report called for prospective research focused on the definition, occurrence, assessment, and treatment of these three cancer symptoms and their interrelationships.

Two of the three symptoms in the NIH call to action—fatigue and depression—are a focus of this review, along with anxiety. Their interrelationships in cancer patients are of special interest. Psychological symptoms—especially depression and to a lesser degree anxiety—have been found to have relatively high correlations with CRF. In fact, depression's relationship to fatigue has been shown to be of greater magnitude than that of disease activity as measured by such markers as nutritional status and tumor-specific tests (7). Understanding the nature of these relationships, however, has proven elusive. Does a cancer patient become depressed and/or anxious because of the effects of being fatigued or might it be the reverse? Alternatively, is there a bidirectional relationship between the two symptoms, with each having an influence on the other? Are there external factors that independently cause *both* fatigue and depression and/or anxiety? Also, does the relationship of CRF with depression and anxiety differ by type and stage of cancer, by type of cancer treatment, or by differences within the individual person?

Measurement Issues

Measurement is an important issue, particularly the ability to distinguish fatigue from depression. Both fatigue and depression are heterogeneous constructs with physical, cognitive, and emotional dimensions and a high degree of overlap across the dimensions. For example, "fatigue or loss of energy nearly every day" is one of the core symptoms used in establishing a clinical diagnosis of depression (8, p. 356). Both constructs can be assessed as a single symptom, a cluster of symptoms, or as a clinical syndrome (9). Both are measured primarily by self report. Cancer patients often endorse items that could be interpreted as suggesting high levels of fatigue, high levels of depression, or both. A recent review found 26 different scales that had been used to assess CRF, some of which were developed specifically for cancer fatigue and some of which were non-specific to cancer (10).

The discriminant validity of the existing measures has been called into question by the generally high positive correlations found on continuous measures of fatigue and depression administered together (11). However, some studies have found that the correlation of fatigue and depression remains high even after removing the fatigue items from depression measures (12-14). Furthermore, fatigue measures correlate rather strongly with measures that assess just the mood aspects of depression (15). Some have suggested that the overlap problem may be addressed by use of a single-item measure in which patients are asked to rate fatigue experience on a 1-to-10 scale, such as "to what degree have you experienced fatigue during the past week?" (10). Others have proposed that CRF is best measured as a syndrome, using a set of diagnostic criteria. Such a set has been proposed for future inclusion in the *International Classification of Diseases Tenth Edition.* To meet criteria, a cancer survivor must experience at least 6 of 11 symptoms and meet three other requirements, one of which is that the symptoms are not related to a comorbid condition such as major depression (16). Because measurement issues may confound attempts to understand the relationship between CRF and psychological variables, we include it as a secondary topic in this review.

Purposes of the Present Review

In undertaking this review, we expected to find a recent increase in the number of studies examining associations between CRF and depression and anxiety, and we expected to find consistently significant correlations. Although the association between CRF and depression

has been previously reviewed (15,17–19), our current paper provides several important contributions to the literature. First, the inclusion of new studies substantially expands the number of studies evaluated. Second, it is the first systematic review of studies reporting associations between CRF and anxiety. Third, special attention is directed to methods of measurement in the effort to distinguish CRF from depression. Fourth, longitudinal studies are highlighted in order to explore potential causal relationships between CRF, depression, and anxiety.

METHOD

Literature Search and Study Selection

Medline and PsychInfo databases were searched using keywords or descriptors FATIGUE and CANCER or NEOPLASMS and ANXIETY or DEPRESSION. The search was limited to English language journal articles or chapters. No date limits were imposed; the Medline database included articles from 1950 to 2007 and PsychInfo covered from 1806 to 2007. These searches yielded 160hits in Medline and 113 in PyschInfo. Each abstract was reviewed and articles were considered for inclusion if the cancer sample size was at least 25, provided that fatigue was mentioned as a primary outcome in either the title or the abstract. The selected articles were further reviewed to identify those that provided correlation or odds ratio statistics for fatigue and its association with depression, anxiety, or both. All original research articles that met these criteria were included. Articles were added that did not emerge from the database search but were located by reviewing reference lists of retrieved articles.

Data were abstracted on the following key variables: sample size; type and stage of cancer; control group if there was one; treatment status; and specific measures of fatigue, depression, and anxiety used. The correlation of fatigue with depression and/or anxiety was the primary outcome extracted from each paper.

Data Analysis

Average untransformed correlation coefficients weighted by sample size have been suggested as the preferred summary statistic in reviews of correlational studies (20). Weighted average correlations of fatigue with depression and with anxiety were computed by multiplying the sample size by the appropriate correlation coefficient for each study and dividing the sum of the products of all studies by the total sample size across all studies. For longitudinal studies reporting correlations at multiple time points, the average of the reported correlation coefficients was entered into the analysis. Confidence intervals (95%) were calculated using Fisher's *z* transformation. Coefficients of determination were calculated for the summary statistics. A calculation of r^2 provides the coefficient of determination, which suggests the proportion of variance in a construct that is accounted for by its associated variable. Average odds ratios weighted by sample size were calculated separately.

RESULTS

Fifty-nine articles were ultimately included, the earliest of which was published in 1989 (4,5, 12,13,21–66)(14,67–74). The majority of studies (n = 52) have been published in the last decade (1998 to 2007), indicating a marked increase in research interest in fatigue and its association with psychological variables. Fifteen of the studies had scale validation as a primary objective. The individual studies and key findings are presented in Table 1.

Study Characteristics

The total number of subjects from all studies was 12,103. Twenty-three (39%) of the studies were longitudinal, and 12 included a control or comparison group, which in most cases were

individuals with no cancer history. Most studies reported correlation coefficients; five reported odds ratios. Twenty-one studies focused on a breast cancer sample, 4 on lung cancer patients, 4 on hematological disease, 2 on prostate cancer, 1 on testicular cancer, and 4 on a mix of specific cancers. The remaining 23 studies included patients with any cancer type. Studies in which treatment status was specified most commonly focused on the post-treatment period (13 studies). Ten studies included only participants who were disease-free after treatment, and 3 looked at patients characterized as "long-term survivors," ranging from at least 1-year post-diagnosis to 10-years and beyond. Six studies focused on advanced cancer patients; three on persons in palliative care. Study attributes are presented in Table 2.

Fatigue and Depression

Depression was significantly associated with fatigue in every study in which the correlation was reported except one, and in some cases the magnitude was strong. The range of correlation coefficients was 0.16 to 0.84. The average correlation between fatigue and depression, weighted by sample size, was 0.56 (95% CI, 0.54 to 0.58) across the 51 studies reporting this statistic (see Table 3). The unweighted average was 0.57. A calculation of the coefficient of determination (r^2) suggests that fatigue shared approximately 31% of its variance with depression. It should be noted that 31 different scales were used to measure fatigue, potentially contributing to some of the variation across studies. For the three studies reporting odds ratios, the weighted average association of fatigue with depression was 1.16.

Fatigue and Anxiety

Anxiety was significantly correlated to fatigue in 33 of the 35 studies reporting the association, although the magnitude was not as great as for depression. The range of correlation coefficients was 0.16 to 0.73. The weighted average was 0.46 (95% CI, 0.44 to 0.49), and the unweighted average was 0.49. The coefficient of determination weighted by sample size indicated that fatigue shared about 23% of its variance with anxiety across all the studies. The weighted mean for the two studies reporting odds ratios was 1.19.

Measurement Issues

A lack of consensus about the best way to measure fatigue in cancer research is evident by the fact that 31 different instruments were used to assess fatigue in the 59 studies. No single scale emerged as a clear favorite. The instrument used most frequently, the Multidimensional Fatigue Inventory, was used in only 9 studies. In contrast, two scales predominated for measuring depression—a subscale of the Hospital Anxiety and Depression Scale (HADS)(75) was used in 24 studies, and the Center for Epidemiological Studies Depression Scale (CES-D)(76) was used in 14. Altogether, 12 depression scales were used across all studies. The HADS was also the favored instrument to measure anxiety, serving that purpose in 21 studies. Six different scales for anxiety were used across all studies. Table 4 provides details about the measures used in the 59 reviewed studies. Further information about most CRF scales, including reliability and validity data, can be found in a review by Wu and McSweeney (77).

A few investigators took steps to reduce potential measurement overlap in order to enhance discrimination between fatigue and depression. For example, two groups of researchers who chose the CES-D described its advantage of focusing on cognitive and affective symptoms of depression rather than physical symptoms, minimizing overlap with fatigue items (28,53). Visser and Smets (72) dropped 6 items of the CES-D that measured somatic symptoms to avoid construct overlap in their analysis and nevertheless found significant correlations between fatigue and depression (range of 0.35 to 0.48 across 3 timepoints).

Some felt that an advantage of the HADS is that its depression subscale does not include any physical symptoms such as lack of energy or sleep disturbance, thereby reducing potential

contamination of the relationship with a measure of fatigue (12,38,40). Yet item 8 of the HADS-D, "I feel as if I am slowed down," can be deemed as similar to fatigue and was therefore dropped from the analyses of correlation with fatigue in 5 studies (12–14,66,70). Four of these 5 studies still found significant correlations between fatigue and depression ranging from 0.46 to 0.70, with only 1 study showing a nonsignficant relationship.(70)

The Zung self-rating depression scale (SDS) is another instrument that was modified to minimize overlap with fatigue measures. Passik and colleagues (31) used an abbreviated version in which 9 of 20 items were dropped because the somatic nature of the items could lead to confounding of cancer and its treatment. In another study, 3 of the 20 items were excluded because of concern the items reflected somatic symptoms of fatigue (34). Relatively high correlations of fatigue with depression were nevertheless found. Kirsh and colleagues (56) singled out an item of the SDS, "I get tired for no reason" and tested its utility as a single-item measure of CRF. They found the item to have a relatively high correlation with both the SDS (r = 0.63) and their fatigue measure (r= −.070).

Longitudinal studies

The average weighted correlation coefficients of fatigue with depression and anxiety in longitudinal studies were not significantly different compared to those statistics across all 59 studies. Of the 23 studies that were longitudinal, 15 investigated associations between fatigue and depression or anxiety at multiple time points. Of these 15 studies, 5 examined patients undergoing radiation therapy; 4 had a sample of patients receiving chemotherapy, 2 were during stem cell transplant, 1 during hormone therapy, 1 during treatment in leukemia patients, and 2 sampled cancer patients post-treatment. We examined these studies to see if patterns could be detected relative to the directional relationships between fatigue, depression and anxiety. Overall, no such pattern emerged, partly due to heterogeneity of the samples between studies and partly due to inconclusive or contradictory findings. In only 2 studies did the authors clearly assert that their findings suggest that changes in fatigue were associated with changes in depression and anxiety (13,25). Authors of at least 4 studies concluded that no evidence of relationships in longitudinal changes had been found—2 referring to depression only (68,72), and 2 assessing both depression and anxiety (14,50). Authors of the remaining studies reported findings that were relatively ambiguous on this matter.

DISCUSSION

Depression is consistently moderately associated with CRF. Anxiety is also an important correlate, though at a somewhat lower magnitude than depression. Taking into account the complex and multifactorial nature of fatigue, even moderate associations are impressive. These findings support the conclusions of previous reviews of psychological correlates of CRF(15, 17–19). Moreover, our systematic review included 59 studies which is nearly double that of the largest previous review of 30 studies (18). The heterogeneity of the 59 studies, however, precludes specific conclusions about the directionality or mechanisms underlying the relationships among fatigue, depression, and anxiety. Furthermore, data on these constructs are inherently subjective and subject to recall bias, further limiting the potential for conclusive findings.

The consistent correlation between depression and CRF has raised questions about a common etiology. Jacobsen and Weitzner (15) discuss three possible causal relationships: that fatigue causes the cancer patient to become depressed; that cancer patients may become fatigued because they are depressed; or a third factor may cause both depression and fatigue. Although the authors cited some supporting evidence for each of these possibilities, their findings were inconclusive. Depression is a predisposing factor for the development of chronic fatigue syndrome (78,79), but CRF may have different mechanisms. Some studies suggest that fatigue

and depression are independent conditions in cancer patients with patterns that differ over the disease course (72,78). The subset of longitudinal studies in this review assessing fatigue, depression and/or anxiety at several time points provides additional support for an interdependence among these symptoms, though the mixed findings still do not provide definitive evidence for whether fatigue is a consequence of these psychological factors, a cause, or the product of a common pathway. The development of CRF may involve several physiological, biochemical, and psychological systems (79) which in turn may vary by type of cancer, stage of disease, and type of treatment.

Further research with robust measures administered at multiple time points and more sophisticated statistical analyses such as times series or structural equation modeling might be informative. Also, translational research examining biological or physiological measures (e.g., cytokines, neuroimaging, etc.) might disclose both shared as well as disparate mechanisms underlying fatigue, depression, and anxiety. Control groups of noncancer populations (including healthy individuals), of individuals with fatigue or depression/anxiety only, or of patients with comorbid medical illnesses might further enrich our understanding of the fatigue-depression-anxiety relationship.

Intervention studies aimed at improving outcome variables that are correlated with CRF may also be helpful in teasing apart the interrelationships (7). For example, an intervention that improves cancer-related depression could be evaluated in terms of its concomitant effect on fatigue. Conversely, interventions targeting fatigue could be analyzed for effects on depression and anxiety. Along those lines, Tchekmedyian and colleagues (2003) found that improvements in fatigue in 250 lung cancer patients receiving darbepoetin alfa for treatment of anemia were associated with parallel reductions in depression and anxiety. In this type of research, it is critical to include elevated fatigue levels as an inclusion criterion.

Fewer studies have explored the relationship between anxiety and CRF and have often done so as an adjunct to investigating depression's associations with CRF. In many studies that included both variables, depression and anxiety scores were reported as if operating as a cluster. A few studies found CRF associations that were specific to anxiety, however, such as the correlation of trait anxiety with CRF and the effects of baseline anxiety on later fatigue, depression or anxiety (38,39,44,49,51,55). Moreover, our pooled results suggest anxiety is consistently associated with CRF. Thus, anxiety warrants inclusion as an important psychological variable in future CRF research.

The measurement challenges already described demand careful attention in future studies. The wide variety of measures that have been used to measure fatigue has been problematic. Research in this domain will benefit if the field of fatigue instruments is narrowed to a few that have been well-validated to accurately assess CRF and distinguish it from depression. Latent variable path analysis may be particularly useful in future research. In longitudinal studies, this structural equation modeling technique can support or disconfirm *a priori* hypotheses about directionality of causal effects The procedure may reduce effects of measurement error by assessing multiple indicators of study constructs within a single analysis (80).

In conclusion, cancer-related fatigue is an important and highly prevalent symptom that negatively affects cancer patient's quality of life and therefore should be a high priority for treatment. Depression and anxiety are prominent among the correlates of CRF; however, the nature and direction of causality among these variables remains uncertain, despite a recent increase in research interest in this area. More longitudinal and/or intervention studies would be desirable, as well as a more uniform use of measures across multiple studies. Meanwhile, clinicians should screen for and treat the comorbid depression and anxiety that commonly accompany cancer-related fatigue.

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Table 1

Summary of Studies Examining the Relationship of Cancer-Related Fatigue with Depression and Anxiety

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Andrykowski (1998) Longitudinal	N = 88 BC pts. Control = 88 age-matched women without BC	Post-treatment; mean is 28 mos. Initial assessment & 4-mo followup.	Chalder Fatigue Scale; PFS	CES-D		0.68 p < 0.01		BC pts report more fatigue (but not depression) than controls. Fatigue may be chronic & unrelated to severity of treatment or time since completion.
Blesch (1991) Cross-sectional	N = 77 BC (44), or Lung cancer (33).	Receiving chemotherapy or RT.	VAS-fatigue	POMS-D	POMS-A	0.46 p = 0.0001	0.40 p = 0.0005	Fatigue correlated with pain but not with psychological or biochemical variables. Depression and anxiety correlated with one another..
Bower (2006) Longitudinal	N = 763 Long-term BC survivors	Assessment at 1–5, and 5–10 yrs after diagnosis	SF-36 vitality subscale	CES-D		OR = 1.17 P < 0.0001		Longitudinal predictors of fatigue included depression, cardiovascular problems, and type of treatment. 34% reported significant fatigue 5–10 yrs after diagnosis; 21% at both assessment points, indicating persistence
Bower (2000) Cross-sectional	N = 1,957 Disease-free BC survivors	1-to-5 yrs post-treatment	SF-36 energy/fatigue subscale	CES-D		OR = 1.13 p = .0001		The strongest predictor of fatigue was depression, followed by pain. Majority of participants did not experience more fatigue than general population, though a subgroup reported severe, persistent fatigue.
Bruera (1989) Cross-sectional	N = 64 Advanced BC	Receiving chemotherapy or hormonal therapy	Customized 4- test asthenia assessment	SCL-90 depression subscale	SCL-90 anxiety subscale	0.62 < 0.001	0.42 < 0.05	Asthenia correlated with depression & psychological distress, but not with nutritional status, lean

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								body mass, tumor mass, anemia, or type of treatment.
Byar (2006) Longitudinal.	N = 25 Stage I or II BC	Chemotherapy post-surgery. Assessed at base- line, treatment 4, & 60-days and 1 yr after treatment.	PFS, Daily fatigue intensity item, SES fatigue items	HADS-D	HADS-A	NS-- T1 0.618 --T2 p = 0.002 0.789 --T3 p < 0.001 0.510--T4 p = 0.031	NS-- T1 NS--T2 0.620 --3 p = 0.004 0.480—T4 p = 0.044	Fatigue levels were moderately intense during treatments & decreased over time. Anxiety was highest at baseline, & depression was highest during the 4th chemotherapy treatment. Higher fatigue compromises QoL.
Chan (2005) Longitudinal	N = 27 Advanced lung cancer	Receiving palliative RT. Assessed at baseline & 2 times during RT.	VAS		VAS		0.36-Base NS 0.49 T2 p < 0.05 0.53 T3 p < 0.01	Prevalence of breathlessness, fatigue, & anxiety ranged from 59% to 96%, with intensity becoming worse at Time 2 and 3. This symptom cluster had high internal consistency across 3 time points.
Dimeo (2004) Cross-sectional	N = 71 Hematological malignancies without relapse	At least 3 mo after treatment	FACT-F	CES-D		0.84 p < 0.0001		Fatigue was related to depression & reduced performance status. No correlation between fatigue & impairment of thyroid function, anemia, or persistent activation of immune system.
Dimeo (1997) Cross-sectional	N = 78 Solid tumors or hematological malignancies		POMS-F	POMS-D SCL-90 Depression	SCL-90 Anxiety	0.61 POMS-D 0.68 SCL-90 p < 0.001	0.63 p < 0.001	Fatigue was weakly associated with physical performance but more highly correlated with depression, somatization, & anxiety.
Fernandes (2006) Cross-sectional.	N = 25 Female inpatients. Control N = 25 Healthy volunteers	Varied	EORTC QLQ-C30 fatigue subscale, BFS	HADS-D	HADS-A	0.63 p = 0.002	0.37 ns	Fatigue severity was correlated with low QoL, depression, constipation, & decreased physical

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
								function. Fatigue severity was not related to impairment in sleep & circadian rhythm.
Fillion (2003) Cross-sectional.	N = 604 BC Prostate cancer	RT or other therapy underway or recently completed	MFI-15	HADS-D	HADS-A	0.58 significant but no p-value	0.37 significant, no p-value	This was validation study: the MFI-5 showed good psychometric qualities for assessment of CRF
Fleer (2005) Longitudinal	N = 52 Stage 1 or disseminated non-seminomatous testicular tumor	Within 1 mo. orchidectormy & 3 & 12 mo later	MFI-20		STAI		0.51 p < 0.001	Older age, trait anxiety & early fatigue predicts fatigue. 1 yr after orchidectomy. Trait anxiety had causal effect on all fatigue subscales. Fatigue is not enduring problem in testicular cancer, with treatment only having an impact on fatigue levels shortly after treatment.
Fossa (2003) Cross-sectional. Mail survey comparing 3 groups	N = 1038 survivors 791 testicular cancer & 247 Hodgkin's disease Control N = 1112 general population	Testicular cancer survivors (TCS) treated at least 4 yrs earlier.	FQ	HADS-D	HADS-A	OR = 1.1.83 P < 0.001	OR = 1.190 P < 0.001	16% of long-term survivors of testicular cancer had chronic fatigue, with age, anxiety, depression, & comorbidity as predictors. The highest & lowest mean scores of anxiety & depression were in the youngest TCS. Anxiety is a larger problem among TCS than depression, especially among the youngest.
Fox (2006) Cross-sectional.	N = 51 Lung cancer recruited via web	Varied; 94% had undergone some treatment pre-study	SF-36	SF-36		0.44 p = 0.01		Depression, fatigue, & pain found in majority of survivors, with pain being the least common. Fatigue was the most intense & correlated with depression.

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Gaston-Johansson (2000) Cross-sectional analysis of RCT	N = 110 Stage II, III or IV BC	Scheduled for autologous bone marrow transplantation	VAS	BDI	STAI	0.32 p < 0.01	0.43 p < 0.001	Bundled intervention (education, cognitive restructuring, & relaxation with imagery) reduced fatigue & nausea. Both groups had mild depression after treatment. The treatment group experienced mild anxiety compared to moderate anxiety in controls.
Geinitz (2004) Longitudinal	N = 38 Localized BC after radiotherapy	Assessment at 8 days before RT & 2 mo and 2.5 yrs post-treatment	FAQ VAS for fatigue	HADS-D	HADS-A	0.56 & 0.62 p < 0.001	0.62 & 0.47 p < 0.001 & p = 0.003	Chronic fatigue correlated closely with psychological distress. Pretreatment fatigue, anxiety and depression were risks for chronic fatigue. Fatigue 2.5 yrs after RT did not increase above baseline levels
Geinitz (2001) Longitudinal	N = 41 BC	Post-operative RT after surgery. Assessed before, weekly during, & 2 mo. after end of RT	FAQ VAS, intensity	HADS-D	HADS-A	0.56 p < 0.001	0.67 p < 0.001	Fatigue increased during RT. Neither anxiety nor depression increased during RT. VAS correlated with HADS-D only for wks 2 & 5 (0.48 & 0.44) & .with HADS-A only for wks 2 & 5 (0.43 & 0.41)
Geiser (2007) Longitudinal	N = 54 Cancer pts with anemia Control N = 25 Non-anemic pts	Treatment group assessed before start of epoetin alfa treatment & at 4, 8, 12, & 26 wks	FACT-F	HADS-D	HADS-A	0.67 – 0.73 mean = 0.70 p not reported	Not reported	Depression & QoL before treatment correlated with reduction of fatigue during treatment. Anxiety did not correlate.
Glaus (1998) Cross-sectional	N = 77 Cancer pts. Controls 77 healthy hospital workers	Currently receiving treatment	FAQ	HADS-D	HADS-A	0.54 no p-value	0.48 no p-value	This is a scale development study. FAQ was found to be reliable & valid.
Haghighat (2003) Cross-sectional	N = 112 BC	During treatment or at follow-up exam	CFS	HADS-D	HADS-A	OR = 1.3 P = 0.003	OR = 1.2 P = 0.04	Prevalence of fatigue, anxiety, & depression

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
								was 49%, 16% & 32% respectively. Fatigue predicted by anxiety depression, pain, tamoxifen use, having mastectomy.
Hann (2000) Cross-sectional	N = 342 Cancer pts	Varied.	FSI	CES-D		0.55 p < 0.01		FSI was found to be a reliable & valid measure of fatigue in a heterogenous sample of cancer pts.
Hann (1999) Longitudinal	N = 31 BC Control N = 49 women with no cancer history	Undergoing Autologous Stem Cell Transplantation (ASCR).	POMS-F FSI	CES-D	STAI	0.77 p < 0.001	0.52 p < 0.01	BC pts reported worse depression than controls & pts' depression worsened over course of treatment. Pts' anxiety was not significantly higher than controls & did not change during ASCR. Worse fatigue during ASCR was associated with worse depression & anxiety.
Hann (1998) Longitudinal	N = 220 Disease-free BC pts	Varied	FSI	CES-D	STAI	0.46 p < 0.001	0.48 p < 0.001	FSI found to be a reliable & valid measure of fatigue. Women with BC had more fatigue during & after treatment than other women of similar age.
Hann (1997) Cross-sectional	N = 43 BC Control N = 43 women with no cancer history	Disease free, 3 mo. after bone marrow transplant (BMT). Mean time since treatment = 20 mo.	POMS-F FSI	CES-D	STAI	0.80 p < 0.001	0.65 p < 0.001	Fatigue was more frequent & severe for BMT recipients & had greater impact on functioning & QoL. Fatigue was more severe for those in whom more time had passed since BMT.
Hwang (2003) Cross-sectional.	N = 180 Male cancer pts	Varied	BFI FACT-F MSAS-SF lack-of-energy item	Zung SDS (dropped 3 somatic items)		−0.70 (BFI global) P < 0.0001 −0.68 FACT-F 0.61 MSAS		All three fatigue measures showed strong correlations with depression. The lack-of-energy single item yielded similar

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
								information as multi-item scales & may provide a simple way to assess fatigue.
Kim (2006) Longitudinal. Secondary analysis of trial	N = 525 Cancer patients	Chemotherapy underway	FSCL	CES-D	POMS-SF Anxiety Scale	0.67 T1 0.72 T2 0.73 T3 0.71 T4 p not reported		2 dimensions of psychological factors —arousal & valence —predicted changes in fatigue & depression. Fatigue changes depended more on valence; depression changes on both valence & arousal.
Kirsh (2001) Cross-sectional.	N = 52 Cancer pts in urban & rural centers	Varied.	Zung item, “I get tired for no reason.” Also, FACT-An	Zung SDS		0.63 $p < 0.0001$ (Zung item)		The single fatigue item from the Zung SDS was highly correlated with the Zung SDS and the FACT-An. Use of the single Zung fatigue item as a brief measure for fatigue was supported.
Loge (2000) Cross-sectional	N = 421 Hodgkin’s disease survivors	Varied.	FQ	HADS-D	HADS-A	0.49 $p < 0.001$	0.44 $p < 0.001$	26% of Hodgkin’s disease survivors had substantial fatigue for ≥ 6 mo. These pts had higher anxiety & depression, but not more past psychiatric problems.
Meek (2000) Longitudinal	N = 212 Cancer patients	Pts receiving treatment for cure or local control. treatment	POMS-F MAF LFS MFI	POMS-D	POMS-T	0.53 POMS-F 0.53 MAF 0.41 LFS-F −0.37 MFI $p < 0.05$	0.57 POMSF 0.52 MAF 0.47 LFS-F −0.40 MFI $p < 0.05$	Results supported validity of three of four fatigue scales tested; MFI required further testing.
Mock (1997) Longitudinal.	N = 46 Breast cancer pts	Post surgery & at start, midpoint and end of 6-wk RT	PFS	VAS	VAS	0.61 $p < 0.001$	0.60 $p < 0.001$	Exercise group had significant improvements in physical functioning & symptom intensity, particularly fatigue, anxiety, & sleep problems.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Morant (1996) Cross-sectional	N = 225 Cancer pts	Varied.	LASA	LASA		0.48 p < 0.0001		Fatigue correlated with mood, weakness, lack of concentration, lack of appetite, insomnia, & pain.
Munch (2006) Cross-sectional	N = 130 Advanced cancer pts	Palliative care	MFI-20 Subscales Physical	HADS-D	HADS-A	0.52 p < 0.0001	0.23 p = 0.011	Fatigue levels were high. Depressed pts had higher levels on 4 fatigue subscales (general, mental, reduced activity, reduced motivation) but not on physical fatigue
Okuyama (2001) Cross-sectional	N = 157 Advanced lung cancer pts	No active cancer in preceding 4 wks	CFS FNS	HADS-D	HADS-A	OR = 1.24 p = 0.001		Half the sample had clinical fatigue. Dyspnea on walking, appetite loss, & depression were correlated.
Okuyama ((2000) Cross-sectional	N = 307 Cancer pts	Varied	CFS	HADS-D	HADS-A	0.69 p < 0.001	0.69 p < 0.001	Results suggest the CFS is a brief, valid, and feasible measure of CRF.
Okuyama (2000) Cross-sectional	N = 134 Disease-free BC	Post-surgery & not in active treatment	CFS	HADS-D		0.63 p < 0.001	0.52 p < 0.001	Depression, dyspnea, & insufficient sleep accounted for 46% of fatigue variance. Disease & treatment variables (e.g., disease stage, time since surgery) were not correlated with fatigue.
Passik (2002) Cross-sectional	N = 200 100 pts from urban, 100 from rural sites	Receiving chemotherapy	FACT-F	Zung-SDS (dropped 9 somatic items)		−0.66 p < 0.001		Depressed pts more likely to have heard about fatigue interventions, and wanted medications for fatigue Few urban-rural differences were noted.
Prieto (2006) Longitudinal	N = 220 Hematologic cancer	Hospitalized for stem cell transplant. Assessment at admission, day of transplant, & 7-& 14-day post-surgery	Validated 1- item energy scale	HADS-D	HADS-A	−0.45** T1 −0.25** T2 −0.27** T3 −0.22* T4	−0.26** T1 −0.20* T2 −0.21* T3 −0.16 T4	Depression was variable most consistently associated with

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						* p < 0.01 ** p < 0.001	* p < 0.01 ** p< 0.001	fatigue, measured using an energy level scale validated to capture the most physical dimension of fatigue. Baseline depression showed significance or a trend toward significance in predicting subsequent fatigue scores during hospitalization.
Redeker (2000) Cross-sectional	N = 263 Cancer pts	Undergoing chemotherapy	SDS	POMS-D	POMS-T	0.43 p < 0.001	0.44 p < 0.001	Symptoms & psychological variables explained 47% of variance in QoL, with the largest proportion explained by depression. Fatigue & insomnia explained only 4%
Respini (2003) Cross-sectional	N = 77 Cancer outpatients age 60 and older	During treatment with chemotherapy or pamidronate	FSI	GDS		0.29 p < 0.01		Fatigue was almost universal. Fatigue disruptiveness higher for women (p < 0.007). Depression was signifycantly related to fatigue severity & disruptiveness.
Reuter (2006) Cross-sectional	N = 353 BC recently diagnosed	Post-surgery & within 12-mo. of diagnosis	POMS-F	HADS-D		0.59 P < 0.001		Fatigue was positively associated with depression & pain but inversely related to age. The association between coping & fatigue was weak.
Roscoe (2002) Longitudinal.	N = 78 BC pts	At 2nd & 4th on-study chemotherapy cycles. Assessment 7 days after each treatment. Circadian rhythm monitored over 72-h period.	MAF FSCL	CES-D HDI		FSCL&CESD 0.63 FSCL&HDI 0.66 MAF&CES-D 0.66 MAF&HDI 0.68 (All p < 0.01)		Changes in the fatigue and depression measures from the 2nd treatment to the 4 th correlated with changes in circadian rhythm. Suggests circadian rhythm disruption may contribute to fatigue

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
								& depression in cancer
Schneider (1998) Cross-sectional	N = 54 Cancer pts	Receiving RT or chemotherapy	MFI-20	BDI		0.56 p < 0.001		In this construct validation study, MFI-20 was found to be a potentially useful measure of fatigue.
Schumacher (2002) Longitudinal	N = 101 Pts newly diagnosed with acute myeloid leukemia	Undergoing treatment. Assessment at 12 sequential time points over 3 years.	EORTC QLQ-C30 fatigue subscale,	POMS-D		0.38** T2 0.38** T3 0.37* T4 0.34* T5 0.52** T7 0.47** T8 0.39* T9 n.s. T1,T6,T10,T11,T12 *p < 0.05 **p < 0.01		Depression was significantly inversely correlated with emotional functioning subscale of the QLQ-C30 throughout the study but its correlation with the fatigue subscale was nonsignificant at 5 of 12 time points.
Servaes (2007) Longitudinal.	N = 150 Disease-free BC survivors diagnosed before age 50.	≥ 6-mo post-treatment. and then monthly for 2 yrs	POMS-F	BDI-primary care	STAI	N/A	0.612 P < 0.001	Fatigue persisted in a quarter of disease-free cancer pts during 2-yr follow-up. High anxiety, impairment in role functioning, & low sense of control over fatigue at baseline predicted persistent fatigue.
Servaes (2000) Cross-sectional.	N = 85 Disease-free cancer pts Comparison N = 16 CFS pts	≥ 6-mo post-treatment	CIS	BDI	STAI	0.73 p not reported	0.60 p not reported	Severity of fatigue in cancer pts was comparable to that of pts with CFS. Severe fatigue is associated with problems of concentration and motivation, reduced physical activity, emotional health, and pain. Highest frequence of severe fatigue was in pts treated with RT.
Smets (1998A) Longitudinal. Same sample as Visser 1998	N = 250 Cancer pts receiving RT.	Assessment before RT, every 2 wks during treatment, & 2 wks post-RT..	MFI-20	CES-D		0.43 p < 0.001		Fatigue increased over the course of RT, followed by a decrease after RT ended, suggesting an

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
								acute radiation effect. Pre-treatment fatigue was greatest predictor of post-treatment fatigue; fatigue after RT only slightly but significantly higher than before RT
Smets (1998B) Cross-sectional	N = 154 Disease-free cancer patients after RT. Control N = 139 General population	9 mo after RT.	MFI-20	CES-D		0.49 p < 0.001		Fatigue in disease-free cancer pts did not differ from general population, although 39% listed fatigue as one of their 3 most distressing symptoms, & 34% reported fatigue following treatment was worse than expected. Overall QoL negatively related to fatigue (r = −0.46).
Smets (1996) Cross-sectional	N = 116 Cancer pts	During RT	MFI-20	HADS-D w/o item 8	HADS-A	0.77 p < 0.001	0.51 p < 0.001	Results support the validity of the MFI-20.
Stein (1998) Longitudinal.	N = 275 BC pts Control N = 70 Women with no cancer history	Received or undergoing RT, BMT, or chemotherapy	MFSI	CES-D	STAI	0.68 p < 0.05	0.58 p < 0.05	The MFSI may be useful in identifying patterns of fatigue within individuals & across treatment modalities.
Stone (2001) Longitudinal.	N = 69 Pts with breast or prostate cancer	Assessment prior to starting RT & within 1 wk of completion	FSS BFS	HADS-D w/o item 8	HADS-A	0.75 p <0.001 (at baseline)	0.50 p < 0.001 (at baseline)	No increase in FSS scores, but modest significant increase in 3 other measures of fatigue. Combination of fatigue & anxiety at baseline predicted 54% of variation in fatigue at completion of RT. Depression had strongest association with fatigue severity.
Stone (2000) Cross-sectional.	N = 227 Prostate cancer, BC, non-small-cell lung	Pts about to begin receiving treatment except for group with	FSS EORTC QLQ-C30	HADS-D w/o item 8	HADS-A	0.67 p < 0.001	0.41 p < 0.001	Severe fatigue was present in 15%, 16%, 50%, & 78%,

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
	cancer, or advanced cancer Control N = 98	advanced cancer, who were 4 wks post-treatment						respectively, of pts recently diagnosed with BC, recently diagnosed with prostate cancer, inoperable non-small cell lung cancer, & palliative care inpatients. Psychological distress, dyspnea, pain & overall disease burden accounted for 56% of fatigue.
Stone (2000) Longitudinal	N = 62 Prostate cancer patients	Pts starting first-line hormone therapy. Assessment at start of hormone therapy and 3 mo later.	FSS EORTC-QLQ C30 BFS VAS	HADS-D w/o item 8	HADS-A	0.46 P < 0.001 FSS	0.52 P < 0.001	Mean FSS scores increased after 3 mo treatment. Anxiety/ depression symptoms accounted for 28% of variance in fatigue at baseline. Increases in fatigue did not appear to be related to increases in psychological complaints.
Stone (1999) Cross-sectional	N = 95 Inpatients with advanced cancer Control N = 98 without cancer	No RT or chemotherapy in previous 4 wks.	FSS	HADS-D w/o item 8	HADS-A	0.16 ns	0.16 ns	75% of advanced cancer pts had severe subjective fatigue (fatigue greater than that of 95% of the control group). Fatigue severity associated with pain & dypsnoea; anxiety & depression were significant correlates only in controls.
Sugawara (2005) Cross-sectional.	N = 79 BC pts w/o major depression & disease free 3 yrs post surgery	Disease-free status & receiving no therapy other than tamoxifen	CFS	POMS-D	STAI	0.36 p < 0.01	0.36 p < 0.01	36.7% of disease-free BC pts without major depression exhibited fatigue, which was associated with neuroticism. Depressive symptoms & anxiety were also significantly associated.

Study	Cancer Sample & Control group	Treatment Status	Fatigue Measure	Depression Measure	Anxiety Measure	Fatigue-Depression *R or OR*	Fatigue-Anxiety *R or OR*	Key findings of study relevant to this review
Tchekmedyian (2003) Longitudinal.	N = 250 Lung cancer pts with anemiar	On chemotherapy. Assessment at baseline & after 4 wk of treatment.	FACT-F	BSI-Depression	BSI-Anxiety	−0.44 p < 0.001	−0.45 p < 0.001	Improvements in fatigue were associated with reductions in anxiety & depression. In a multiple regression model of change in anxiety & depression, change in fatigue was the only significant variable
Tsai (2007) Cross-sectional.	N = 77 Terminally ill cancer	Institutional hospice	POMS-F	HADS-D	HADS-A	0.73 p < 0.0001	0.54 p < 0.0001	Terminally ill pts had moderate to severe levels of fatigue. Fatigue was associated with overall symptom distress, depression, anxiety, & performance status.
Visser (1998) Longitudinal	N = 250 Cancer pts scheduled for RT	In RT. Assessment 2 wks pre-treatment, 2 wks post treatment, 9 mo later.	MFI-20	CES-D (mood only)		0.35 T1 0.43 T2 0.48 T3 p < 0.001		Just after RT, fatigue increased or remained stable, while depression decreased. 9 mo later, fatigue had decreased while depression was stable. No strong causal relationship was found between depression & fatigue.
Wu (2006) Cross-sectional	N = 172 BC pts	Undergoing chemotherapy	WCFS	GDS		0.60 p not reported		In this scale development study, the revised WCFS was found to be reliable & valid.
Young (2006) Cross-sectional.	N = 69 Disease-free BCpts	At least 6 mo post-treatment	MFSI FSI Structured interview	HADS-D	HADS-A	0.78, 0.79 p < 0.01	0.70, 0.75 p < 0.01	19% met draft ICD-10 criteria for cancer-related fatigue. Psychological distress & beliefs about activity predicted fatigue directly.

BDI Beck Depression Scale
BFI Brief Fatigue Inventory
BFS Bi-dimensional Fatigue Scale

BSI Brief Symptom Inventory
CFS Cancer Fatigue Scale
CES-D Center for Epidemiological Studies Depression Scale
CIS Checklist Individual Strength
EORTC QLQ-C30 European Organization for Research & Treatment of Cancer 30-Item
FACT-F Functional Assessment of Cancer Therapy-Fatigue Subscale
FAQ Fatigue Assessment Questionnaire
FNS Fatigue Numerical Scale
FQ Fatigue Questionnaire
FSCL Fatigue Symptom Checklist, 30-item
FSI Fatigue Symptom Inventory
FSS Fatigue Symptom Severity
GDS Geriatric Depression Scale
HADS-A Hospital Anxiety & Depression Scale – Anxiety
HADS-D Hospital Anxiety & Depression Scale – Depression
HDI Hamilton Depression Inventory
LASA Linear Analogue Self-Assessment
LFS-F Lee Fatigue Scale-Fatigue subscale
MAF Multidimensional Assessment of Fatigue
MSAS-SF Memorial Symptom Assessment Scale Short Form
MFI-20 Multidimensional Fatigue Inventory
MFI-15 Mulitdimensional Fatigue Inventory – Short form
MFSI Multidimensional Fatigue Symptom Inventory
PFS Piper Fatigue Scale
POMS-D Profile of Mood States depression-dejection subscale
POMS-F Profile of Mood States fatigue-inertia scale
POMS-T Profile of Mood States-tension/anxiety scale
SCL-90 Symptoms Checklist – 90
SDS Symptom Distress Scale
SF-36 Short-Form 36 Health Status Survey
SES Symptom Experience Scale
STAI Spielberger Trait Anxiety Inventory
VAS Visual Analog Scale, 100-meter
WCFS Wu Cancer Fatigue Scale
Zung SDS Zung Self-Rating Depression Scale

General fatigue scores are used for correlations when multiple fatigue types are reported
BC = Breast Cancer
CFS = Chronic Fatigue Syndrome
N/A = Not Available
RCT = Randomized controlled trial
RT= Radiotherapy
QoL= Quality of life
BMT = Bone marrow transplantation
Pt(s) = Patients

Table 2

Characteristics of Study Samples

Study characteristic	Number of studies
Cancer type/site	
Breast cancer	21
Lung cancer	4
Hematological	4
Prostate	2
Testicular	1
Mix of specific types	4
Any cancer type	23
Disease status	
Disease-free after treatment	10
Advanced cancer	6
Long-term survivorship	3
Type or stage of treatment	
Post-treatment	13
Receiving chemotherapy	7
Receiving radiotherapy	6
Bone marrow/stem cell transplant	4
Receiving palliative care	3
Currently receiving either chemotherapy or radiotherapy	2
Currently receiving hormone therapy	1
Currently receiving treatment, type not specified	3

Table 3

Mean associations with CRF across studies, weighted by sample size

	Correlation Coefficients	95% Confidence Intervals	Odds Ratios
Depression	0.56 N = 7508	0.54 → 0.58	1.16 N = 4027
Anxiety	0.46 N = 4710	0.43 → 0.49	1.19 N = 1150

Table 4

Measurement Scales Used

Measure	Number of studies
Fatigue	
Multidimensional Fatigue Inventory	9
Functional Assessment of Cancer Therapy—fatigue subscale	6
Profile of Mood States—fatigue inertia subscale	7
Fatigue Symptom Inventory	5
Visual Analog Scale, 100-meter	5
Cancer Fatigue Scale	5
European Org. for Research & Treatment of Cancer 30-Item QoL	4
Fatigue Assessment Questionnaire	3
Fatigue Symptom Inventory	3
Piper Fatigue Scale	3
Short-Form 36 Health Status Survey	3
Bi-dimensional Fatigue Scale	2
Fatigue Questionnaire	2
Fatigue Symptom Checklist, 30-item	2
Multidimensional Fatigue Symptom Inventory	2
Multidimensional Assessment of Fatigue	2
Others, each used in single study*	14
Depression	
Hospital Anxiety & Depression Scale—depression subscale	24
Center for Epidemiological Studies—depression subscale	14
Profile of Mood States—depression subscale	6
Beck Depression Scale	4
Zung Self-Rating Depression Scale	3
Symptoms Checklist-90	2
Geriatric Depression Scale	2
Others, each used in single study	5
Anxiety	
Hospital Anxiety & Depression Scale—anxiety subscale	21
Spielberger Trait Anxiety Inventory	9
Profile of Mood States—tension anxiety scale	3
Symptoms Checklist-90	2
Visual Analog Scale, 100-meter	2
Brief Symptom Inventory	1

*Brief Fatigue Inventory, Chalder Fatigue Scale, Checklist Individual Strength, Fatigue Numerical Scale, Lee Fatigue Scale, Linear Analog Self-Assessment, Memorial Symptom Assessment Scale Short Form, Symptom Distress Scale, Symptom Experience Scale, Wu Cancer Fatigue Scale, a customized test for asthenia, a single item from the Zung Self-Rating Depression Scale, a 1-item energy scale, and structured interview.