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Review

Cancer-related fatigue: A critical appraisal

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ABSTRACT

This aim of this systematic review was to determine the prevalence and pattern of cancer-related fatigue (CRF), and identify factors associated with its development. Relevant literature was identified through an electronic database search using specified keywords. Included studies investigated CRF in adult cancer patients using a multidimensional fatigue measure. The methodological quality was assessed using six published standards. CRF is apparent both during and after anti-cancer therapy, however, the prevalence of CRF varied between studies. The variables associated with the development and persistence of CRF remain to be identified. Inconsistencies were evident in the pattern of CRF and its associated factors. This is likely to have arisen from the inherent difficulties in the measurement of a subjective sensation, further complicated by the myriad of outcome measures used. More methodologically sound research; assessing CRF from the commencement of therapy, considering all pertinent variables is needed.

1. Introduction

Excessive tiredness is a common complaint of today's society with some level of fatigue found in nearly all of the population.[1] For most individuals fatigue is a protective response to physical and psychological stress[2] and is easily remedied by rest. The majority of patients receiving anti-cancer therapy experience fatigue that is dissimilar from that experienced by the general population.[3] Cancer-related fatigue (CRF) has a phenomenal impact on a sufferer's life with devastating social and economical consequences, and can persist for months or even years following completion of treatment.

A lack of consensus surrounds the optimal means of assessing CRF.[4] A number of CRF instruments exist that assess fatigue as a uni-dimensional construct, however, CRF can manifest itself in many domains, consequently although these instruments may appear to demonstrate satisfactory psychometric properties, they fall short in assessing the full spectrum of CRF.[5] As a multidimensional experience, the most comprehensive approach would be to assess CRF using a multidimensional measure.[6]

A previous review conducted by Servaes and colleagues,[7] concluded that fatigue was a problem for cancer patients, but the association between CRF and tumour and treatment-related variables was difficult to establish.[7] It was proposed that this could be attributed to the myriad of fatigue measures used in the reviewed studies as both uni- and multidimensional measurement tools were included. In an

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attempt to reduce the variability in the findings, this current review only included studies that measured CRF using a multidimensional instrument. Furthermore, the body of evidence has grown substantially in recent years and an update is warranted.

In an attempt to aid clinicians in their understanding of the phenomenon as well as identifying those at most risk of developing CRF, the aims of this review were to provide clarification of the prevalence and pattern of CRF, identify factors associated with its development, and make recommendations for future research.

2. Patients and methods

Relevant literature was identified through an electronic search of Medline (1966 – September 2005), CINAHL (1982 – September 2005), AMED (1985 – September 2005), PsychINFO (1872 – September 2005), BNI (1985 – September 2005), Cochrane Library and ProQuest, using the keywords "Fatigue"[MeSH] OR "Muscle Fatigue"[MeSH] OR "Mental Fatigue"[MeSH] AND (neoplasm* OR tumor* OR tumour* OR cancer* OR Hodgkin's OR haematolog* OR radiat* OR radioth* OR chemo* OR hormone therapy OR bone marrow transplant*). The reference list of each relevant study was searched for additional papers. The search strategy identified 174 papers. Non-interventional studies presented in English that assessed fatigue in cancer patients during and/or after treatment, measured with a multidimensional tool were included. Studies investigating a sample of subjects other than adult cancer patients; studies with the primary aim of evaluating the psychometric properties of a fatigue questionnaire; studies evaluating fatigue using a multidimensional tool but failing to report the findings, studies using only a uni-dimensional fatigue scale or one or a few items from a quality of life questionnaire and reviews, editorials and comments were excluded. Following application of the inclusion/exclusion criteria, 69 studies were selected for review. Included studies were examined under two headings; those investigating fatigue during anti-cancer therapy and those examining fatigue after cancer therapy in survivors.

To provide an indication of the quality of the included studies, six standards developed by the Department of Clinical Epidemiology and Biostatistics[8] were used. These standards were devised to facilitate the critical appraisal of research investigating the prevalence, pattern and clinical characteristics of a disease, and have been applied previously in a review of CRF literature.[9] The standards can be grouped under two headings, sampling and measurement.

3. Results

3.1. CRF during anti-cancer therapy

Forty-four relevant publications were identified through the search strategy and are summarised in Table 1.[10–53] As can be seen from Table 1, some consist of the same study sample and methodology but report on a different analysis.[13–15,24,26,30,35] Consequently, 40 studies have resulted in 44 separate publications.

From the 40 studies reviewed two types of research design were employed. Eight studies were cross-sectional and 32 longitudinal. Twenty-nine studies considered fatigue in a homogenous group of cancer patients, the most common being breast cancer, investigated by 20 studies. The remaining 11 studies observed a heterogeneous sample. Twenty-three studies evaluated fatigue in female cancer patients, five in male cancer patients and 12 a mixed gender sample. The sample size ranged from 13 to 607.

Concerning treatment, 19 studies noted fatigue during chemotherapy treatment including one study that assessed a group of patients following completion of chemotherapy before initiation of autologous bone marrow/peripheral blood stem cell transplant (AT), and one study during autologous stem cell transplantation (ASCR). Eleven charted fatigue in patients receiving radiotherapy, two in patients receiving a combination of radiotherapy and chemotherapy, two with patients during hormone therapy, two during interferon alpha treatment, and two during a variety of treatments. A number of studies included a post-treatment follow-up assessment.[11,13–15,20–22,24,26,27,41,43,47,48,51] Two studies assessed fatigue solely prior to treatment.

Five studies incorporated a comparison group of non-cancer individuals to provide an indication of the severity of the cancer participants fatigue scores.

3.2. Prevalence of fatigue during anti-cancer therapy

A number of studies reported over 90% of participants experiencing fatigue.[17,36,40] In comparison, in a large cross-sectional study of cancer subjects with various diagnoses, receiving varying treatments, more than half reported experiencing fatigue in the past month.[23] In a longitudinal survey assessing fatigue during radiotherapy, 39% of patients endured significant fatigue.[48]

Prevalence reports of fatigue would be more meaningful if comparison scores of the expected 'norm' were available for evaluation purposes. In all five studies that included a comparison group of healthy individuals with no history of cancer, cancer participants experienced significantly more fatigue than the general population.[18,19,29,37]

3.3. Course of fatigue over time

The temporal variability of CRF could not be determined from all of the included studies as approximately one third was cross-sectional in design. However, a number of longitudinal surveys reported a significant increase in fatigue over time during anti-cancer therapy,[10,14,18,20,22,24,26,28,38,42,46,47,49,52,53] although two of these studies reported this increase based on a uni-dimensional fatigue assessment tool.[19,22] This finding was not supported by all investigations. In breast cancer patients receiving chemotherapy, fatigue increased significantly following the initiation of chemotherapy, but the reported fatigue did not differ significantly between the first and last measurement.[19,41] In a separate study of breast cancer patients receiving radiotherapy, CRF did not increase steadily over time, but a fluctuation in CRF severity was apparent. CRF was higher at the time of infusion than the cycle midpoint, thus leading to a repetitive pattern of high and low

Table 1 – Studies investigating CRF during anti-cancer therapy

Study	Study design (data collection points)	Sample	Sampling			Measurement			Results
			Inception cohort	Referral pattern	80% Follow up	Objective outcome criteria	Blind assessment	Extraneous variables	
Dean et al.[10]	L 5 (before, fortnightly during treatment for two months)	N = 30 Malignant melanoma, age range 20–85, 67% male. During treatment with interferon alpha.	×	✓ Two centres	Not reported	PFS	Self report	×	Pattern of fatigue consistent over the 5 points.
Monga et al.[11]	L 3 (preRT, 7–8 wks RT, 5–6 wks post RT)	N = 13 Prostate cancer, age range 60–76. During RT.	✓	×	×	NMF TA PFS	× Self report	×	During RT sig decline in NME of TA.
Berger[12]	L 6 (Days 1–4 and cycle midpoints of cycles 1, 2, 3)	N = 72 Br cancer, mean age 50 (SD 9). During CT.	✓	✓ Several centres	✓	PFS	Self report	×	Fatigue did not increase over time, but fatigue scores sig higher at time of treatment than at cycle midpoint.
Smets et al.[13]	L 3 (pre RT, 2 wks and 9 mths post RT)	N = 250 Cancer patients (various diagnoses), mean age 64 (SD 13), 58% male. During RT.	✓	✓ One centre	✓ (2 wk) × (9 mth)	MFI-20	Self report	✓	Pre RT physical condition explained most of the fatigue. Post RT physical condition and perception of burden explained fatigue.
Smets et al.[14]	L 2 (pre, 2 weeks post treatment)	N = 250 Cancer patients (various diagnoses), mean age 64 (SD 13), 58% male. During RT.	✓	✓ One centre	✓	MFI-20	Self report	✓	Fatigue scores after RT sig higher than before RT. 46% reported fatigue among three symptoms that caused them the most distress.
Visser and Smets[15]	L 3 (2 wks pre RT, 2 wks post RT, 9 mth post)	N = 250 Cancer patients (various diagnoses), mean age 64 (SD 13), 58% male. During RT.	✓	✓ One centre	✓ (2 wk) × (9 mth)	MFI-20	Self report	✓ Predictive power of depression on fatigue.	Fatigue and depression do not follow the same course over time. No strong evidence for cause–effect relationship.
Berger and Farr 1999[16]	L 6 (Days 1–4 and cycle midpoints of cycles 1, 2, 3)	N = 72 Br cancer, mean age 50 (SD 9). During CT.	✓	✓ Eight clinics	✓	PFS	Self report	✓ Activity and rest indicators.	Individuals who were less active and more nighttime awakenings reported higher fatigue.
Gaston-Johansson et al.[17]	C	N = 127 Br cancer, mean age 45 (SD 7.6). Post CT, pre AT.	× But uniform point.	✓ One centre	N/A	PFS	Self report	× for fatigue ✓ for health status	91% participants reported fatigue.

Hann et al.[18]	L 3 (baseline, mid, post treatment)	N = 41 Br cancer patients about to undergo ASCR. Mean age 51 (SD 15.4). N = 63 healthy volunteers, mean age 51 (SD 7.9).	× But uniform point.	✓ One centre	×	FSI	Self report	×	Cancer patients reported sig more fatigue than healthy volunteers with no history of cancer.
Jacobsen et al.[19]	L 3 (pre CT, completion of 2nd and 3rd cycles)	N = 54 Br cancer, mean age 51 (SD 10). During CT. Control N = 54. Mean age 54 (SD 11).	✓	×	✓ 100%	FSI (POMS-F, MSAS)	Self report	✓ MSAS	Br cancer patients experienced sig worse fatigue than non-cancer controls both before and after CT initiated.
Monga et al.[20]	L 4 (pre RT, mid, end, 4–5 wk post)	N = 36 Prostate cancer patients, mean age 67 (range 55–79). During RT.	✓	✓	Not reported	PFS	Self report	×	Fatigue scores sig higher during and immediately post RT than pre RT. At 5 wk follow up fatigue scores not sig higher then pre RT.
Berger and Higginbotham[21]	L 6 (pre cycle 3, days 1–4, 5–10, 11–21, end last cycle, 2 mths post)	N = 14 Br cancer, mean age 52 (range 32–69). During CT.	✓	✓	✓	PFS	Self report	×	Patients experienced the highest levels of fatigue during first 4 days after cycle 3.
Stone et al.[22]	L 2 (first day therapy, 3 mth later)	N = 62 Prostate ca, median age 69 (55–80). During HT.	✓	✓ One centre	✓	BFS (FSS)	Self report	✓ FSS as dependent variable.	Prevalence of severe fatigue at baseline 14%, median FSS score increased sig after 3 mth.
Stone[23]	C	N = 576 Various diagnoses, receiving different treatment. Median age 59, 37% male.	×	✓	N/A	FACT-F	Self report	✓	Fatigue affected patients' sig more than any other symptom. 58% affected by fatigue in the past month.
Ahsberg and Furst[24]	L 4 (pre RT, last week RT, 1 and 3 mth post)	N = 100 Various diagnoses, age 30–70, 9% male. During RT.	✓	✓ One centre	✓	SOFI	Nurse + self report	✓	Fatigue increased sig at end of RT compared to pre RT and decreased post RT.
Beach[25]	L 3 (pre RT, week 4 RT, end RT)	N = 74 Lung ca, 53% female. During RT.	✓	✓ One centre	×	R-PFS	Self report	×	No sig change in fatigue levels.
Furst and Ahsberg[26]	L 4 (Before, last week of RT, 1 and 3 mth post)	N = 100 Various diagnoses mean age 56, 90% female. During RT.	✓	✓ One centre	✓	MFI-20	Nurse + self report	×	Fatigue peaked at end of RT.
Geinitz[27]	L 7 (pre RT, end wk 1–5, 2 mth post RT)	N = 41 Br cancer, median age 54 (range 34–77). During RT.	×	×	Not reported	FAQ	Self report	×	FAQ values did not increase sig during treatment. (VAS sig increase wk 4, remained elevated wk5).

(*continued on next page*)

Table 1 – *continued*

Study	Study design (data collection points)	Sample	Sampling			Measurement			Results
			Inception cohort	Referral pattern	80% Follow up	Objective outcome criteria	Blind assessment	Extraneous variables	
Stone et al.[28]	L 2 (pre RT, 1 wk post RT)	N = 69 Br (34) or prostate (35) cancer, median age 63 (range 41–79). During RT.	×	✓ One centre	✓	BFS (FSS)	Self report	✓	Sig increase in BFS-physical and BFS-total after RT.
Holzner et al.[29]	L Before CT and prior to first three cycles	N = 68 Colorectal (25), lung (26), ovarian (17). Mixed gender. Mean age 61 (SD 9.5). During CT. Normative data (GenPop) N = 120. Mean age 59 (SD 10.6), 55% male.	×	✓	✓	MFI-20	Self report	×	Compared with healthy individuals, cancer participants experienced sig higher fatigue. Hb values alone do not fully account for observed fatigue.
Hwang et al.[30]	C	N = 180 Varying diagnoses, median age 68 (30–89). Male. During varying combinations of anticancer treatment, some not in active treatment.	×	✓	N/A	FACT-F (BFI)	Self report	Unclear	Fatigue present in 74% patients (BFI). Increased fatigue associated with greater symptom distress and reduced quality of life.
Kallich et al.[31]	L 4 (baseline, wk 4,8 and 12 of CT)	N = 607 Varying diagnoses, mean age 61 (SD 11), 53% female. During CT.	×	✓	✓	FACT-F	Self report	×	Patients with Hb response of 2g/dL or more, more likely to report improvements in fatigue scores.
Payne[32]	L 6 (Prior CT, 2 wk nadir, 3 mth, 2 wk nadir, 6 mth, 2 wk nadir)	N = 17 Br or ovarian ca. During CT.	✓	✓ Two centres	✓	PFS	Self report	×	Increase in fatigue at 3 mths, returned to near pre treatment at 6 mths. Overall change in fatigue not sig.
Roscoe et al.[33]	L 4 (following 4 CT cycles)	N = 78 Br cancer, mean age 52 (range 34–79). During CT.	×	✓ Three centres	×	MAF (FSCL)	Self report	×	Fatigue score correlated with circadian rhythm. Changes in fatigue score correlated with concurrent changes in circadian rhythm.
Haghighat et al.[34]	C	N = 112 Br cancer. Mean age 46 (SD 11). During or after CT.	×	✓ One centre	N/A	CFS	Self report	✓	Mean total fatigue score 18.7. Fatigue predicted by depression, pain, tamoxifen use and anxiety.

Hwang[35]	C	N = 180 male, varying diagnoses, Median age 68 (30–89). Receiving various modes and combinations of anticancer therapy.	×	✓ One centre	N/A	FACT-F (BFI)	Self report	✓	Fatigue present in 62%. Physical and psychological symptoms only independent predictors in multi-dimensional model.
Respini et al.[36]	C	N = 77 Metastatic cancer, varying diagnoses. Mean age 71, 58% female. During CT.	×	✓ One centre	N/A	FSI	×	×	76 (99%) reported fatigue in the past week.
Tchen et al.[37]	C	N = 110 Br cancer, median age 48 (range 27–60). Comparison group: N = 107 Median age 47 (range 26–62).	×	✓ Several centres	N/A	FACT-F	×	✓	Patients experienced sig more fatigue than controls.
Ahlberg et al.[38]	L (pre RT, after 30Gy, end RT)	N = 15 (63% power) Uterine ca, median age 63. During RT.	✓	✓ One centre	✓ (100%)	MFI-20	Self report	×	Fatigue increased sig during RT without sig change in cytokine level. Hb decreased sig during RT.
Ahlberg et al.[39]	C Before RT	N = 60 Uterine cancer. Due to receive RT.	✓	✓ One centre	N/A	MFI-20	Self report	✓	Experienced a low grade of fatigue and distress. Sig correlation found between fatigue and anxiety and fatigue and depression.
Can et al.[40]	L 2 (pre cycle, 7–10 days post cycle)	N = 90 Br cancer, age range 30–above 60. During CT.	×	✓ One centre		PFS	Telephone interview	✓	All patients experienced fatigue 7–10 days after the CT cycle.
De Jong et al.[41]	L 5 (start, 3rd cycle, 5th cycle, 4 + 12 wks post)	N = 157 Br cancer, mean age 47 (SD 9). During CT.	✓	✓ Six centres	✓	MFI-20	Interview	✓	Prevalence of fatigue increased sig after the start of CT. Fatigue at first and last measurements do not differ sig.
Donovan et al.[42]	L (Pre treatment 1st, 3rd, final CT cycles; 1st, 15th, final RT)	N = 159 (13 became ineligible) Br cancer, scheduled for CT and RT or RT only.	✓	✓ Two centres	✓	FSI	Self report	×	Patients who received CT reported greater fatigue than patients who received RT. Those not pre-treated with CT experienced increase in fatigue during RT.

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Table 1 – *continued*

Study	Study design (data collection points)	Sample	Sampling			Measurement			Results
			Inception cohort	Referral pattern	80% Follow up	Objective outcome criteria	Blind assessment	Extraneous variables	
Geinitz et al.[43]	L 3 (before, 2 mth after, 2.5 yrs after)	N = 41 Br cancer during RT Mean age 58.	✓	×	✓ 38/41 (93%)	FAQ	Self report	✓	No sig difference between fatigue scores 2.5 yrs after treatment and pre-treatment scores. Fatigue score 2.5 yrs post sig higher than 2 mth post.
Jacobsen et al.[44]	L 2 (pre treatment, end of treatment)	N = 90 Br cancer patients, mean age 55 (SD 10). During CT or RT.	✓	✓ Two centres	✓	FSI	Self report	✓ To identify the ability of catastrophising to predict follow-up levels of fatigue.	Greater catastrophising related to greater fatigue.
Jacobsen et al.[45]	L 2 (Baseline, Before start of 4th cycle)	N = 102 Various diagnoses, mean age 60. 77% female. During CT.	✓	✓ One centre	✓	FSI	Self report	✓	No sig change in fatigue. Greater decline in Hb sig related to greater increases in fatigue.
Kumar et al.[46]	L Baseline, each visit for CT	N = 198 Br cancer patients, mean age 50 (SD 10). During CT.	✓	✓	✓	FSI	Self report	×	Main focus weight gain. 94% patients reported an increased frequency of fatigue at end of CT, compared with 42% at start.
Trask et al.[47]	L (before, post high dose, 1, 2, 3, 6 mth post high dose)	N = 21 Malignant melanoma. Mean age 43.7 (SD 12.7) 57% male. During high dose treatment with interferon alpha.	Unclear	✓ One centre	×	R-PFS	Self report	×	Fatigue increased sig from baseline through 6 mth post high dose therapy.
Wratten[48]	L (Before, weekly during RT, 2 and 6 weeks post).	N = 54 Br cancer. Mean age 58 (SD 10). During RT.	×	✓ One centre	✓	FACT-F	Self report	✓	21 developed sig fatigue during RT. Fatigue plateaued between week 4 of RT and 2 weeks post RT.
Ahlberg et al.[49]	L (pre RT, after 30 Gy, end RT)	N = 60 Uterine cancer, mean age 66 (SD 11, range 37–84). During RT.	✓	✓ One centre	Unclear	MFI-20	Self report	✓	Fatigue increased significantly during therapy.
Bender et al.[50]	Pooled analysis. Baseline assessment data.	N = 154 Br cancer. Mean age ranged from 42.3 to 55.2 across the 3 studies. Before, during or after various combinations of anticancer therapy.	×	✓ Data from 3 separate studies	N/A	FACT-F	Self report	×	Fatigue symptoms comprised the symptom clusters across all three studies.

De Jong et al.[51]	L (start CT, 3rd, 5th cycle, 4 and 12 weeks post)	N = 157 Br cancer. Mean age 47.3 (SD 8.8, range 25–70). During CT.	✓	✓ Six centres	✓	MFI-20	Self report	Unclear, however, a statistical process was used to correct for confounders	An unequivocal pattern of mental fatigue during and after CT was not found.
Mills et al.[52]	L (start of cycle 1 and cycle 4)	N = 29 Br cancer. Mean age 49.5 (SD 11, range 34–79). During CT.	✓	✓ Multi-centre	✓	MFSI-SF	Self report	✓	Fatigue sig increased from cycle 1 to cycle 4.
Shun et al.[53]	L (before and days 2, 4, 6 of TACE)	N = 47 Hepatocellular carcinoma. Male, mean age 67.3 (SD 10.3). During TACE.	×	✓ One centre	✓	PFS	Self report	✓	Fatigue changed sig over time, peaking on second day of TACE and gradually declining.

N/A, not applicable; C, cross-sectional; L, longitudinal; sig, significant; SD, standard deviation; wk, week; mth, month.
CT, chemotherapy; RT, radiotherapy; ASCR, autologous stem cell rescue; HT, hormone therapy; AT, autologous bone marrow/peripheral blood stem cell transplant; TACE, transcatheter arterial chemoembolisation; Hb, haemoglobin; Br, breast; Ca, cancer; GenPop, general population. BFI, Brief Fatigue Inventory; BFS, Bidimensional Fatigue Scale; BSI, Brief Symptom Inventory – Anxiety and Depression Subscales; CFS, Chadler Fatigue Scale; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; FAQ, Fatigue Assessment Questionnaire; FSCL, Fatigue Symptom Checklist; FSI, Fatigue Symptom Inventory; FSS, Fatigue Severity Scale; MAF, Multidimensional Assessment of Fatigue; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; MSAS, Memorial Symptom Assessment Scale; MFI-20, Multidimensional Fatigue Inventory; PFS, Piper Fatigue Scale; POMS-F, Profile of Moods States-Fatigue Scale; R-PFS, Revised-Piper Fatigue Scale; SOFI, Swedish Occupational Fatigue Inventory; VAS, Visual Analogue Scale; NME, neuromuscular efficiency; NMF, neuromuscular fatigue; TA, tibialis anterior.

fatigue.[12] However, owing to a high attrition rate, only the first three chemotherapy cycles were considered.

A number of studies reported no increase or pattern in fatigue scores across measurement points. The studies involved lung cancer[25] and breast cancer patients.[27,45,51] The first study of breast cancer patients was based on a small sample of 41 participants, with 3 possibly receiving chemotherapy prior to radiotherapy, and the completion rate was not reported.

3.4. *Tumour/disease-related variables*

In a number of studies no association was found between tumour stage and fatigue.[18,19,22,34,42,44,48] Two studies reported no association between tumour size and fatigue,[18,53] with one of these studies[18] also reporting no link between time since diagnosis or extent of nodal involvement and fatigue. In three studies an association was found between tumour site and fatigue, in two studies lung cancer patients reported the worst fatigue[14,29] and in one study, ovarian cancer sufferers experienced worse fatigue than their breast cancer counterparts.[32] The small sample in the latter study limits the ability to generalise findings. Tumour stage was found to have a relationship with severity of fatigue in three studies.[35,40,52] Two of these studies have methodological limitations, one assessed only one cycle of chemotherapy and included no pre-treatment fatigue scores,[40] the other was a cross-sectional study, the participants received varying combinations of anti-cancer treatment, with some possibly not even in the active treatment phase.[35]

3.5. *Treatment-related variables*

Eleven studies found no relationship between fatigue and treatment-related variables such as receiving surgery,[40] type of surgery,[19,42,44] type of therapy (radiotherapy, chemotherapy or hormone therapy),[34,43,44] or treatment characteristics such as dose or fractionation for radiotherapy[14,48] or chemotherapy dose and regime.[18,19,37,40,51] In contrast, Hann et al.[18] demonstrated that a longer hospitalisation period was linked with more fatigue. Drug regime,[41,53] type of surgery, that is lumpectomy versus mastectomy,[34,41,51] time between surgery and treatment,[51], longer treatment[41,51] and current tamoxifen use[34] were all associated with fatigue. However, this latter cross-sectional study also included data from patients after treatment.

3.6. *Demographic variables*

The majority of studies reported no relationship between age,[14,19,22,34,40,42–44,48,53] gender,[14] ethnicity,[18,44,53] marital status,[18,34,36,40,44] educational level,[14,18,34,36,40] occupation,[18,40] level of income[18,40,44] and fatigue. However, two studies reported females experiencing more fatigue than males,[26,36] one demonstrated an association between increasing age and lower fatigue,[51] two between marital status and fatigue,[41,51] and two between lower education and fatigue.[44,53]

3.7. *Psychological variables*

Fourteen studies found an association between the presence of anxiety and/or depression and the existence of

fatigue.[14,18,22–24,28,31,33–36,39,43,47,51,53] Furthermore, an improvement in emotional well-being was associated with an improvement in fatigue.[42] The actual causal relationship, however, remains to be fully established. Two studies found a correlation between anxiety and depression and fatigue, however, as fatigue increased there was no concurrent increase in anxiety and depression.[15,27] Moreover, in two studies of prostate cancer patients, an increase in the level of fatigue did not relate to an increase in psychological complaints.[20,22]

The concept of a relationship between catastrophism and the level of fatigue experienced was investigated in a sample of breast cancer patients receiving chemotherapy or radiotherapy. An association between this process and fatigue was demonstrated in radiotherapy but not chemotherapy patients.[44]

3.8. *Physiological/Biological variables*

Many authors have postulated anaemia as a cause of CRF either related to the disease itself or due to anti-neoplastic therapy.[2,54–57] Indeed, a number of studies found an association between haemoglobin levels and fatigue.[31,35–37,45,48] Three small studies involving female cancer patients failed to find an association between fatigue and haemoglobin and/or cytokines.[27,32,38] In the latter study, it was interesting to note that although no correlation was found between changes in fatigue and changes in haemoglobin levels, haemoglobin did decrease significantly over the course of the therapy with a concurrent significant increase in the level of fatigue, this did not, however, occur in all studies.[49] A study involving 54 breast cancer patients undergoing radiotherapy, 15 of which had received chemotherapy previously, found fatigue to be correlated with certain cytokines such as interleukin-6. Baseline and week five fatigue also correlated with many other biological factors.[48] In addition, chemotherapy induced changes in inflammation that were linked to fatigue in breast cancer patients.[52]

3.9. *Symptom experience, sleep quality and physical activity*

Seven of the studies reviewed found an association between the presence of pain and fatigue.[14,17,19,28,29,34,49] An association between fatigue and the presence of nausea and vomiting,[28,49] dyspnoea,[23,28,29] loss of appetite[49] and/or diarrhoea[28,29,49] was also demonstrated. However, dyspnoea was not found to be related to fatigue in a sample of breast cancer patients assessed cross-sectionally either during or after chemotherapy.[34] Finally, a number of studies found an association between the level of symptom distress experienced by the participant and the severity of fatigue reported.[14,19,21,30,40,53]

As expected, several studies found an association between sleep quality, and fatigue.[14,16,19,21,29] However, three studies reported no relationship.[20,27,34]

All studies that investigated the association between physical activity or performance and fatigue concluded that poorer performance status and physical inactivity lead to increased levels of fatigue.[16,19,21,28,33]

3.10. *CRF following anti-cancer therapy*

Twenty-five relevant studies were identified and are summarised in Table 2.[58–82] Two publications reported on the same study but focused on a different outcome,[73,74] leaving 24 separate methodologies for review. Three of these examined fatigue in almost the same sample of patients.[64,67,70]

Twenty-two of the 24 studies assessed CRF on a one-off basis, however, one of these was a follow-up of a longitudinal study conducted during treatment.[62] The two remaining studies assessed fatigue twice, an initial and follow-up assessment.

Eight studies included a comparison group of healthy volunteers;[58,60–62,65,73,74] six utilised reference scores from the general population;[64,66,67,69,70,76] two compared the scores of participants with malignant and benign tumours[59,77] and one compared fatigued and non-fatigued cancer participants.[72]

Twenty-one studies involved a homogenous sample, the majority ($n = 9$) assessed breast cancer patients. Nine involved a female population, two a male population and 13 a mixed gender sample with the majority around 50% male.

The sample size ranged from 38 to 820 with a mean age range of 37–65 years. The mean time since treatment at the time of assessment varied greatly from 9 months to 12 years, with a wide variation within studies for example; 17 days–2.4 years,[63] 1 month–33 years,[75] and 1–15 years.[77]

3.11. *Prevalence of fatigue following anti-cancer therapy*

Six studies reported participants that experienced substantial or severe fatigue, with the prevalence ranging from 19% to 38%.[64,67,69,70,73,75] In comparison, in a study that reported lung cancer patients with some degree of fatigue the prevalence was 82%.[71]

These prevalence reports become more meaningful when compared to the fatigue of those without cancer. Eleven studies reported that the cancer group experienced significantly worse fatigue than the comparison group.[58–60,64–67,70,73,76,81] Andrykowski[59] demonstrated that CRF may persist over time; breast cancer patients, a mean of 25 months post-treatment consistently reported significantly more fatigue than benign breast cancer patients at an initial and four month assessment point. In contrast, three studies found no difference between the amounts of fatigue experienced by the two groups.[61,62,77] Finally, one study reported the fatigue scores of testicular cancer survivors to be higher then that of the general population, but less than scores obtained from Hodgkin's Disease Survivors.[76]

3.12. *Tumour/disease-related variables*

An almost unanimous opinion was presented regarding the association between variables related to the tumour itself and fatigue in cancer survivors. No relationship was found to exist between diagnosis,[62,65,69,75,77,79] tumour size,[58,61] time since diagnosis,[58,60,61,64,66,71,75] nodal involvement,[58,68] tumour stage,[58–61,64,66–68,71] relapse status,[64,67], presence of metastatic disease,[81] menopausal status[58,60,72] and fatigue. One study did, however, report an association between the time since a diagnosis of haematological malignancy and fatigue,

Table 2 – Studies investigating CRF after anti-cancer treatment

Study	Study design (data collection points)	Sample	Sampling			Measurement			Results
			Inception cohort	Referral pattern	80% Follow up	Objective outcome criteria	Blind assessment	Extraneous variables	
Hann et al.[58]	C	N = 43 Br cancer patients, mean 20 mths post treatment with high dose CT + BMT, mean age 44 (SD 6). Healthy volunteers N = 43, mean age 47 (SD 6).	×	✓ One centre	N/A	FSI (POMS-F)	Self report	✓ Relationship of medical and psychosocial variables to fatigue.	Br cancer patients treated with BMT reported sig more frequent and severe fatigue than the non-cancer comparison group.
Andrykowski et al.[59]	L 2 (initial and 4 mth follow up)	N = 88 Br cancer patients, 25 mths post treatment with RT ± CT. Mean age 54 (SD 9). Healthy volunteers: N = 88, benign Br problems, mean age 53 (SD 9).	×	✓ One centre	✓	PFS CFS	Self report	×	Br cancer patients reported sig more fatigue than the benign breast patients at both assessment points.
Broeckel et al.[60]	C	N = 61 Br cancer patients mean 16 mths post CT ± RT. Mean age 52(SD 11). Healthy volunteers: Mean age 51 (SD 11).	×	✓ One centre	N/A	FSI MFSI (POMS-F)	Self report	✓ Variability of fatigue severity (POMS-F) accounted for by the psychosocial variables.	Br cancer patients reported sig more severe fatigue than healthy volunteers.
Hann et al.[61]	C	N = 45 Br cancer patients (5–88 mth post RT, mean 22 mths). Mean age 64 (SD 13). Comparison group: N = 44. Mean age 60 (SD 9).	×	✓ One centre	N/A	FSI (POMS-F)	Self report	×	Fatigue experienced by women after RT not sig different to the fatigue experienced by healthy women.
Smets et al.[62]	L (9 mth follow up to Smets et al.[14])	N = 154 Cancer patients (various diagnoses) post RT. Mean age 65 (SD 12), 57% male. Comparison group: N = 139 Mean age 46 (SD 16), 44% male.	✓	✓ One centre	×	MFI-20	Self report	✓	Fatigue scores of patients did not differ sig from the fatigue score of the comparison group.
Woo et al.[63]	C Mailed survey	N = 332 Br cancer patients (17 days–28 yrs post diagnosis, mean 2.4 yrs). Had received RT ± CT ± HT, some may have still been in active treatment. Mean age 52 (SD 10).	×	✓	N/A	PFS	Self report	× Controlled for age in the ANCOVA.	Women who received combination therapy had sig higher fatigue score than those who had received RT alone.

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Table 2 – *continued*

Study	Study design (data collection points)	Sample	Sampling			Measurement			Results
			Inception cohort	Referral pattern	80% Follow up	Objective outcome criteria	Blind assessment	Extraneous variables	
Loge et al.[64]	C	N = 459 HDSs that had received RT ± CT, mean observation period 12 yrs (SD 5.5). Mean age 44 (SD 12), 56% male. GenPop: N = 2214, mean age 45 (SD 17).	×	✓	N/A	FQ	Self report	✓	HDSs sig higher fatigue scores than the control population.
Howell et al.[65]	C	N = 66 (2 groups) 100% male, diagnosed with HM. Group 1: mean age 42, mean yrs since CT 8 (1–21). Group 2: mean age 38.5, mean yrs since CT = 8 (1–17). Healthy controls: N = 44, mean age 40, 100% male.	×	Not reported	N/A	MFI-20	Self report	× Influence of independent parameters on *quality of life*.	Fatigue scores sig higher in men treated for haematological malignancy than a comparison group of healthy men.
Knobel et al.[66]	C	N = 38 Lymphoma patients treated with high dose CT + ABMT. Median age 39 (18–59), 55% male, 4–10 yrs post high dose CT.	×	✓ One centre	N/A	FQ	Self report	×	Patients cured of malignant lymphoma sig more fatigued than Norwegian reference population.
Loge et al.[67]	C	N = 421 HDSs, received RT ± CT, observation period 3–23 yrs. Age 19–74, 56% male.	×	✓	N/A	FQ	Self report	✓	26% had substantial fatigue for more than 6 mths. Fatigued HDSs had higher levels of A + D than non-fatigued HDSs.
Okuyama et al.[68]	C	N = 134 Br cancer patients, 59–1894 days post surgery. Treated with surgery ± RT ± CT. Mean age 55 (SD 10).	×	✓ One centre	N/A	CFS	Self report	✓	Fatigue determined by current physical and psychological distress rather than cancer and cancer treatment.
Servaes et al.[69]	C	N = 85 Cancer patients with varying diagnoses. Mean age 47.5 (SD 14), 56% male, mean time since treatment 3 (0.5–12.5).	×	✓ One centre	N/A	CIS	Self report	×	19% of disease free cancer patients were severely fatigued. Fatigue comparable to fatigue of CFS patients.
Knobel[70]	C	N = 92 HDSs, received RT ± CT, mean observation time 9 yrs (SD 3). Mean age 37 (SD 7), 59% male.	×	✓	N/A	FQ	Self report	✓	There is an association between fatigue and pulmonary dysfunction in HDSs.

Okuyama et al.[71]	C	N = 157 Advanced lung cancer patients, mean age 63 (SD 9), 71% male, 15–3138 days after diagnosis (median 386 days).	×	✓ Two centres	N/A	CFS (FNS)	Self report	✓	81.5% experienced some degree of fatigue (FNS). Depression, dyspnoea and appetite loss sig factors.
Bower et al.[72]	C	N = 40 (20 fatigued, 20 non-fatigued) Br cancer patients, treated with RT ± CT. Fatigued: 5.5 yrs since diagnosis, mean age 57 (SD 9) Non-fatigued: 5 yrs since diagnosis, mean age 58 (SD 10).	×	✓	N/A	FSI	Self report	Confounds that were correlated with any of the physiological markers were controlled for using ANCOVA.	Fatigued Br cancer survivors had raised serum markers associated with proinflammatory cytokine activity.
Servaes et al.[73]	C	N = 150 Br cancer patients, mean 29 mths post treatment with RT ± CT, mean age 46 (SD 6). Healthy volunteers: N = 78, mean age 48 (SD 6).	×	✓ Seven centres	N/A	CIS (fatigue severity subscale)	Self report	✓	38% breast cancer patients severely fatigued, this was sig higher than the percentage of healthy volunteers severely fatigued (11%).
Servaes[74]	C (incorporating an actometer worn for 12days)	N = 150 Br cancer patients, mean 29 mths post treatment with RT ± or CT, mean age 46 (SD 6). Healthy volunteers: N = 78, mean age 48 (SD 6).	×	✓ Seven centres	N/A	CIS (fatigue severity subscale)	Self report	×	Fatigue correlated with neuropsychological functioning (self-report).
Bartsch et al.[75]	C	N = 144 Varying diagnoses, 1 mth–33 disease duration. Received surgery/RT/CT/HT/BMT or combination. Mean age 56, 70% female.	×	✓ Three centres	N/A	MFI	Self report	×	22% reported sig symptoms of fatigue.
Fossa et al.[76]	C	N = 820 TCSs, median age 44 (range 23–75). Median 12 since orchiectomy. Ref groups: HDS N = 249 men GenPop N = 1083 men.	×	✓ One centre	N/A	FQ	Self report	✓	125 identified as having chronic fatigue. Chronic fatigue in TCSs more prevalent than in GenPop, but less prevalent than in HDSs.
Servaes et al.[77]	L 2 (2 yrs apart)	N = 170 Bone or soft tissue tumour. Malignant (N = 71, mean age 43 SD 15, 54% male) and benign (N = 99, mean age 34 SD 13, 53% male) tumours. Completed treatment 1–15 yrs ago.	×	✓ One centre	×	CIS	Self report	✓	28% were considered severely fatigued long after treatment finished. Percentage equal for malignant and benign tumours.

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Table 2 – *continued*

Study	Study design (data collection points)	Sample	Sampling			Measurement			Results
			Inception cohort	Referral pattern	80% Follow up	Objective outcome criteria	Blind assessment	Extraneous variables	
So et al.[78]	C	N = 157 Haematological malignancy, post BMT. 54% male. Mean age 40 (SD 10), mean 53 mths (SD 37, range 2–136) post BMT.	×	✓ One centre	N/A	R-PFS	Self report	×	Participants experienced a moderate level of fatigue.
Dimeo et al.[79]	C	N = 71 Patients with HM, 3–132 mths post therapy (mean 28 mths). Mean age 51 (SD 13), 41 male.	×	✓ One centre	N/A	FACT-F	Self report	✓	Fatigue related to depression and performance status.
Gelinas and Fillion[80]	C	N = 103 Br cancer patients 3–24 mths post RT ± CT ± HT. Mean age 54.	×	✓ One centre	N/A	MFI	Telephone interview	✓ Predictive capacity of stress variables to explain fatigue.	Fatigue related to many stress-process variables.
Brown et al.[81]	C	N = 38 Advanced or metastatic lung cancer. Mean age 64 (range 43–81). 61% male. Healthy volunteers N = 15. Mean age 64 (range 46–74). 47% male.	×	✓ Three centres	N/A	FACT-F	Self report	✓	Cancer patients reported sig more fatigue than the group of healthy volunteers.
So and Tai[82]	C	N = 157 HM, mean age 39.9 (SD 9.9, range 18–69). 54% male. Post HSCT.	×	✓ One centre	× Postal survey RR 71%	R-PFS	Self report	×	Most participants perceived a moderate level of fatigue (descriptive statistics employed).

N/A, not applicable; sig, significant; SD, standard deviation; RR, response rate; mth, month; yrs, years.
C, cross-sectional; L, longitudinal; CT, chemotherapy; RT, radiotherapy; HT, hormone therapy; (A)BMT, (autologous) bone marrow transplant; HSCT, hemopoietic stem cell transplantation; Br, breast; HDSs, Hodgkin's Disease Survivors; HM: Haematological Malignancy; TCSs, Testicular Cancer Survivors; GenPop, general population; A + D, anxiety and depression.
CFS, Chadler Fatigue Scale; CIS, Checklist Individual Strength; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; FNS, Fatigue Numerical Scale; FSI, Fatigue Symptom Inventory; FQ, Fatigue Questionnaire; MFI-20, Multidimensional Fatigue Inventory; MFSI, Multidimensional Fatigue Symptom Inventory; PFS, Piper Fatigue Scale; POMS-F, Profile of Moods States-Fatigue; R-PFS, Revised-Piper Fatigue Scale.

with those more recently diagnosed experiencing more fatigue.[78] Further to this, an association between menopausal status and fatigue was demonstrated in breast cancer.[80]

3.13. *Treatment-related variables*

The majority of studies found no association between treatment-related variables and fatigue. This included treatment received;[59,61,68,69,71–73,75,76] treatment parameters, that is, chemotherapy regime,[58,64,65] dose[61,62] and cycles;[64,65] radiotherapy fractionation[62] and type of irradiation;[64] length of treatment;[60,61,66,69,73] tamoxifen use;[58,60,68] time since treatment completion;[58,59,65,66,69,70,76,79] and length of hospital stay.[58]

In contrast, Hann et al.[58] found an association between fatigue and the length of time since bone marrow transplantation in breast cancer survivors. Woo et al.[63] also studied breast cancer survivors and reported greater fatigue in patients receiving combination therapy, however, this survey may have included some participants still in active treatment. Also, in patients diagnosed with a bone or soft tissue tumour, the shorter the time since treatment completion and the more operations undergone, the more fatigue experienced.[77] These findings may not represent the original sample due to a less than 80% response rate.

3.14. *Demographic variables*

Ten studies reported no association between fatigue and demographics including gender,[67,69–71,77,82] age,[58,60–62,70,71,75,77] marital status,[58,60,61,71] ethnic background,[60] educational level,[58,60–62,69–71,77] income,[58] and employment status.[60,61,71] In contrast a number of studies did find that fatigue was associated with gender,[62,66] age,[63,67,68,76,78,82] marital status,[82] education,[59,67] employment status[78,82] and income.[59,78,82] This finding is complicated by an inconsistency that exists between the direction of the association of certain variables and fatigue. For example, with testicular cancer patients[73] and participants with a haematological malignancy,[75,82] the older the subject the more fatigue reported, whereas with breast cancer patients the younger participants reported more fatigue.[63]

3.15. *Psychological variables*

All studies that examined the association of psychological variables such as anxiety and depression to fatigue concluded that a relationship existed.[58–62,64,65,67–69,72,73,75,76,79–81] One study involving patients with breast cancer did, however, produce an interesting finding. A correlation was reported between depression and fatigue with the breast cancer group demonstrating significantly higher levels of fatigue than a matched group of participants with a benign breast problem, however, the two groups did not differ with respect to the amount of depression reported.[59]

3.16. *Physiological/biological variables*

A limited number of studies examined the relationship between physiological variables and fatigue in cancer survivors. No association was demonstrated between haemoglobin levels and fatigue after anti-cancer therapy.[75,79,81] Regarding cytokines, one small study stated that fatigued breast cancer survivors had significantly higher serum levels of immune markers associated with proinflammatory cytokine activity than their non-fatigued counterparts.[72] However, only 55% of the possible non-fatigued patients were included. Three studies reported no association between the presence of proinflammatory cytokines and fatigue.[66,79,80] The first of these studies that involved lymphoma patients also reported no apparent relationship between endocrine status and fatigue.[66] The small sample included for analysis does reduce the ability to generalise the findings.

3.17. *Symptom experience, sleep quality and physical activity*

All studies reviewed reported an association between higher fatigue and poorer sleep quality[58–60,62,68,71,73] and greater fatigue and worse physical function.[61,62,69,71–73,75,78,79,81]

Following cancer management, the degree of symptom distress and the presence of certain symptoms were found to be related to fatigue. Greater symptom prevalence, severity and distress were positively associated with fatigue.[61] Pain was reported to be associated with fatigue;[62,69,71,80] dyspnoea and appetite loss were also linked to fatigue in breast cancer patients,[68] and lung cancer patients.[71] The latter study also demonstrated an association between increased sputum, cough and fatigue.[71]

Long-term oncological complications were investigated in two studies. A study of Hodgkin's Disease Survivors found an association between pulmonary dysfunction and fatigue but no association between hypothyroidism or cardiac problems and fatigue.[70] Furthermore, a relationship could not be established between oncological complications and fatigue in a sample of patients diagnosed with a bone or soft tissue tumour.[77]

4. Discussion

The purpose of this review was to clarify the prevalence of CRF as measured with a multidimensional fatigue self-report questionnaire, and determine the factors associated with its occurrence. It was also proposed that the findings of this review would improve the understanding of the symptom, and guide future research.

The methodological quality of the reviewed studies was generally acceptable; however, the recruitment of an inception cohort was not well executed. Endeavouring to determine the factors associated with the development and continuance of fatigue over time would be complicated with a sample of patients at various stages of their disease and/or treatment process. Following anti-cancer treatment, an attempt should be made to recruit participants at a uniform stage, that is, a standardised time from completion of treatment. If this is not possible then an attempt to control for the temporal differences among subjects in relation to such variables as disease or treatment should be made before interpreting the outcomes of fatigue.[9] Undeniably many studies achieved this by considering the time since diagnosis or

end of treatment as one of the predictors of fatigue in a multiple regression analysis.

A number of studies undertook a regression analysis to adjust for confounding variables and determine predictors of CRF. However, the variety of possible variables made this complicated. Nevertheless, the strict inclusion and exclusion criteria implemented by some investigators, with the sample selected to rule out other causes of fatigue, reduced the number of possible confounders initially.

The method of recruitment used by a number of studies led to a difficulty in the generalisation of findings. Many investigations involved participants from one centre and many were white, middle-aged, upper class working individuals. This does not fully represent the entire target population, thus the conclusions can only be assumed in the examined sample.

CRF was evident in cancer patients during therapy, and appears to be more severe than normal fatigue. This is illustrated by the unanimous finding in those studies that included a comparison group. A conflict of opinion surrounds the pattern of CRF during treatment and those factors associated with its development. Generally it would seem that CRF is not associated with treatment or demographic characteristics, although some investigations did demonstrate a relationship and these findings should not be totally discounted. An association would seem apparent between tumour site and fatigue, however, tumour stage seems unrelated to fatigue. Psychological variables such as anxiety and depression are associated with CRF. A correlation, however, is not the same as causation;[22,45] which is reflected by the increase in fatigue without a subsequent increase in anxiety and depression demonstrated by few studies. Regarding biological variables, haemoglobin appears to be related to fatigue, and a relationship between fatigue and cytokines was suggested, although more research is needed. It was anticipated that sleep quality would show an association with fatigue and although five studies supported this theory, three did not. Finally, symptom distress and level of physical activity appear to have a strong relationship to CRF owing to the unanimous opinion presented within the literature reviewed.

This review suggests that CRF persists following completion of anti-cancer therapy owing to the reported prevalence in the included studies, although these reports vary. The majority of studies demonstrated that the fatigue endured by cancer survivors was more severe than a comparison group of individuals with no cancer history, this inclusion is vital at this stage, as with no pre-treatment fatigue scores it would be difficult to determine the significance of the fatigue reported. Even where no difference was reported it could be suggested that the characteristics of the fatigue are different.[62] Psychological factors, physical factors, sleep and symptom burden appear to be related to CRF development; whereas tumour and treatment factors do not. The literature remains equivocal with regard to an association between demographic variables and fatigue. Further to this, those studies that did suggest an association did not concur on its direction. To date, biological factors have received little attention although haemoglobin was reported not to be unrelated to fatigue.

A number of factors could be contributing to the apparent conflict surrounding the reported prevalence of CRF. Firstly, this could be attributed to the difference in opinion in what constitutes fatigue. A number of the studies reviewed reported percentages of participants who were substantially or severely fatigued, whereas others stated the percentage of all participants experiencing fatigue, no matter how slight. This is an important factor to be aware of when interpreting the outcome. The fatigue assessment tool used could have led to inconsistent results, as each multidimensional measure differs in format, content and dimensional structure.[4] Participants are required to rate their fatigue over a certain time period, for example the past week or past month. This could lead to inconsistent findings as it requires some averaging of the fatigue experience.[59] Fatigue assessment is further complicated by the problem of subjectivity; self-report measures are subject to a recall bias and may result in either over or under-reporting of the fatigue experience. Finally, a selection bias was evident in some studies as non-participants reported higher fatigue,[13–15] which could have lead to an underestimation of the problem. Unfortunately, data on non-participants was not available in all studies.

An inconsistency was evident in the detection of the temporal changes in CRF. It is possible that fatigue may not have been assessed frequently enough to detect a change with time. Where fatigue was only assessed pre and post-treatment and no significant change in fatigue was noted, it is possible that certain fluctuations may have been missed. The small sample size in many studies may have lead to an inability to detect subtle changes in the level of fatigue.[32] Furthermore, the phenomenon of 'response shift' could have a large effect on the ability to determine patterns of fatigue; that is, as patients became accustomed to the feelings of fatigue they no longer rated them as severe.[42]

Inconsistent findings limited the ability to draw definite conclusions regarding the variables associated with the initiation and persistence of CRF. The conflicting results regarding the relationship of treatment-related variables to CRF could be due to the crude assessment of the therapy received. Many studies did not take account of the differences that exist within a particular treatment modality, for example target area, dose and fractionation for radiotherapy, and chemotherapy dose and regime. A number of studies reported no association between treatment with radiotherapy and fatigue, however, De Jong and colleagues,[41] stated that those participants that received radiotherapy in addition to chemotherapy had higher levels of fatigue than those who had chemotherapy alone. This could indicate that receiving radiotherapy leads to an increase in CRF, but it could also be the result of receiving multimodal treatment. This second opinion is supported by Woo and colleagues[63] who reported that cancer survivors who had received multimodal therapy reported higher levels of fatigue.

From the literature it would appear that anxiety and depression are associated with CRF, nevertheless, the causal relationship has yet to be established. The two phenomena are closely related as they share many of the same symptoms, which would lead to a high correlation.[7] An increase in fatigue without a concurrent increase in anxiety and depression was presented in many of the studies and would indicate that

another variable might be causing the increase in cancer-related fatigue. Anxiety and depression are therefore not the sole factors associated with CRF.

A definite relationship exists between other concurrent symptoms experienced during anti-cancer therapy and CRF. However, it is unlikely that the various symptoms associated with fatigue such as pain, nausea and vomiting, dyspnoea, cough and appetite loss cause or lead to persistent fatigue by the same mechanism.[35] Nevertheless, although symptom experience would be a unique experience to each person, the individualised, effective management of each symptom may help in the control of CRF.

This review is limited by the inclusion of only English language studies; there is a possibility that a language bias is present. Research has shown that a tendency exists for studies not showing positive results to be published in non-English language journals,[83] thus some studies showing no increase in fatigue may have been omitted. Regarding fatigue assessment, although only research utilising a multidimensional instrument was included, in many cases this was used in conjunction with a uni-dimensional scale. On occasion, it was unclear which scale the results were based on. Finally, it was unclear whether the statistical processes employed by the authors to adjust for extraneous variables; for example, multiple logistic regressions was adequate or appropriate.

Although fatigue is a symptom experienced by all people, the severity and impact of fatigue reported by people with cancer is decidedly worse and deserving of clinical attention.[84] Clinicians should be aware of the phenomenon and undertake methods of amelioration. This is made complicated by the confusion surrounding the pattern of CRF and factors associated with its development. Despite the volume of studies focused on answering these questions, inconsistencies are still evident and a general conclusion cannot be confidently made. In order to make CRF research more sound, participants should be followed longitudinally during their treatment, assessed frequently with a multidimensional CRF measure and compared with a group of healthy volunteers to aid interpretation.

Conflict of interest statement

None.

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