Associations Between Multiple Chronic Conditions and Cancer-Related Fatigue: An Integrative Review

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Problem Identification: To summarize the current state of nursing knowledge related to the association of multiple chronic conditions (MCCs) and cancer-related fatigue (CRF) in patients with solid tumors during chemotherapy.

Literature Search: A systematic literature search of PubMed, CINAHL®, EMBASE, Cochrane, and ProQuest Dissertations and Theses for primary nursing research from January 2000 to June 2012 that examined the prevalence and/or severity of CRF with MCCs or a single comorbidity.

Data Evaluation: The studies were appraised for the clarity and focus of the research question and the appropriateness of the method and research design. A 13-item quality criteria checklist evaluated the data from each article on a 0–2 scale (0 = poor, 1 = fair, 2 = good).

Data Analysis: Of 329 abstracts, 21 studies were included in the analysis. The association of MCC and CRF was mostly reported in aggregate, with a mean of three MCCs per patient.

Presentation of Findings: Having one or more other comorbidities was significantly associated with the prevalence and severity of CRF. Specifically, arthritis, hypertension, and cardiac disease, although not consistently or clinically defined across studies, are associated with an increased prevalence and severity of CRF. The association of MCC and CRF prevalence and severity was inconsistent because of the variability in the measures used and the time span identified to measure changes.

Implications for Nursing Practice: Awareness of the prevalence of MCCs is essential to support patients experiencing CRF. Holistic nursing assessment of the patient's symptoms—with an awareness of MCCs—would help improve symptom management to limit the effect of CRF.

Key Words: fatigue; symptoms; integrative review

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Cancer-related fatigue (CRF) is a persistent symptom present at diagnosis, during treatment, and for months or years post-treatment (Berger et al., 2013). Although CRF may occur in combination with other cancer-related symptoms, patients identify it as the most disturbing (Curt et al., 2000; Hoffman, Given, von Eye, Gift, & Given, 2007; Ryan et al., 2007). During chemotherapy treatments, more than 30% of patients experience CRF so severe that it affects treatment decisions (Barsevick, Frost, Zwinderman, Hall, & Halyard, 2010; Cleeland, 2007; Curt et al., 2000; Donovan, McGinty, & Jacobsen, 2013; Portenoy & Itri, 1999). Patients consistently report feelings of uselessness and frustration caused by CRF that affect quality of life (QOL) and limit their perceptions of their ability to participate in symptom management strategies (Curt et al., 2000; Goldstein et al., 2012; Gupta, Lis, & Grutsch, 2007; Minton et al., 2013). The pathogenesis of CRF is not fully understood (Mustian et al., 2007; Ryan et al., 2007). One of the many factors could be the interaction between the mechanisms of CRF and the pathogenesis of other chronic comorbidities.

Eighty-one percent of patients with cancer report at least one comorbidity (Rothrock et al., 2010), and 32% have more than two comorbidities (Ogle, Swanson, Woods, & Azzouz, 2000). Multiple chronic conditions (MCCs) are defined as "the existence of two or more concurrent chronic conditions in one person"(U.S. Department of Health and Human Services [USDHHS], 2010, p. 2). Chronic conditions are defined as those that "last a year or more and require ongoing medical attention and/or limit activities of daily living" (USDHHS, 2010, p. 2). The wide range of chronic conditions (e.g., arthritis, diabetes, heart disease, hypertension, lung disease) may have a synergistic effect that increases fatigue severity and decreases QOL (Institute of Medicine [IOM], 2012).

Effective management of a coexisting cancer diagnosis with other chronic illnesses is a challenge (Tinetti et al., 2011). Symptoms associated with MCCs can overlap and confound the healthcare provider's evaluation of a patient's health status, QOL, and symptom management abilities (IOM, 2012). MCCs present a potential for increased symptom severity, increased symptom burden, and decreased QOL (IOM, 2012). The current

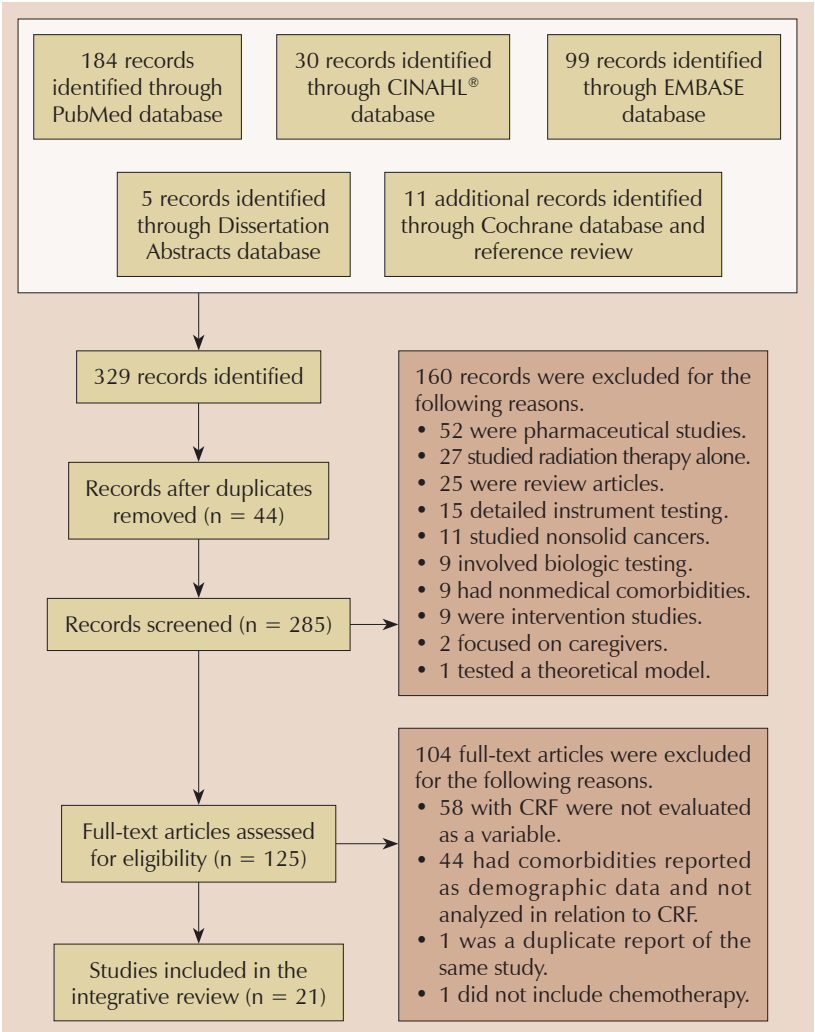
integrative review examines research that describes the associations between MCCs and CRF in adults with solid-tumor cancers who are currently or have previously received chemotherapy.

Literature Search

A preliminary PubMed search to explore the association of CRF and MCCs and to identify database search terms resulted in 48,408 titles and abstracts using the search "cancer-related fatigue AND chronic disease." PubMed, CINAHL®, EMBASE, and the Cochrane databases then were searched and limited to research published from January 2000 through June 2012. The time frame was chosen to reflect increased nursing involvement in symptom management research after the creation of the National Institute of Nursing Research. Common to each database were the search limits of English-language publications and human studies. Searches were truncated to capture publications that were not yet indexed during the last year of the search (2012). The ProQuest Dissertations and Theses database was searched for doctoral dissertations to address publication bias within the results of the other database searches (Whittemore & Knafl, 2005).

Inclusion and Exclusion Criteria

Studies were included if they were primary quantitative, qualitative, or mixed-method research studies that examined the prevalence and/or severity of CRF associated with an aggregate number of MCCs or individual physical conditions. Because of the persistence of CRF through survivorship, studies that included patients undergoing active chemotherapy or who had completed chemotherapy but were followed for long-term CRF were included to examine potential long-term associations with MCCs. Cognitive comorbidities (e.g., dementia, Alzheimer disease) were excluded because CRF is measured by self-report (Mitchell, 2010).



CRF—cancer-related fatigue; PRISMA—Preferred Reporting Items for Systematic Reviews and Meta-Analysis

Figure 1. PRISMA Strategy for Integrative Review

Search Results

Three hundred and twenty-nine records that met inclusion criteria were reviewed for duplicates (n = 44), resulting in 285 potential abstracts, including articles identified from a hand-search of the Cochrane database results and reference lists. Following abstract review, 160 articles were excluded, resulting in 125 articles of which the full text was read. In the majority of excluded articles, CRF was not an evaluated outcome variable (n = 58) or MCCs were reported as demographic data but not analyzed (n = 44) (see Figure 1). Twenty-one studies were included in the final analysis: 13 quantitative, 6 secondary analyses, and 2 mixed-methods studies.

Three of the secondary analyses (Gift, Jablonski, Stommel, & Given, 2004; Gift, Stommel, Jablonski, & Given, 2003; Kozachik & Bandeen-Roche, 2008) were from the same parent study included in the current integrative review (Given, Given, Azzouz, Kozachik, & Stommel, 2001). The three other secondary analyses each were derived from different data sets (Bender et al., 2008; Hoffman et al., 2007; Liu, Ercolano, Siefert, & McCorkle, 2010).

All of the studies examined CRF but differed in the focus of their analysis. Five studies examined CRF independent of other cancer-related symptoms (Andrykowski, Donovan, Laronga, &

Jacobsen, 2010; Bower et al., 2000, 2006; Karakoç & Yurtsever, 2010; Orre et al., 2008). Ten studies focused on clusters of multiple symptoms (including CRF), and the published results allowed analysis of the specific association of MCCs and CRF (Barbera et al., 2010; Beck, Towsley, Caserta, Lindau, & Dudley, 2009; Bender et al., 2008; Brant et al., 2011a, 2011b; Gift et al., 2003, 2004; Hershey, 2011; Liu et al., 2010; Sarna et al., 2008). CRF prevalence was evaluated in all included articles; however, severity was only evaluated in eight (Andrykowski et al., 2010; Gift et al., 2003, 2004; Hershey, 2011; Hoffman et al., 2007; Karakoç & Yurtsever, 2010; Kozachik & Bandeen-Roche, 2008; Sarna et al., 2008) (see Table 1).

Knowledge Translation

Knowledge of multiple chronic conditions (MCCs) associated with increased cancer-related fatigue (CRF) severity is essential to effective symptom management.

The heterogeneity of the specific conditions and potential interactions warrants inclusion of MCC assessment and coordinated care management.

During chemotherapy, CRF often is an expected side effect; however, fatigue also can be related to a patient's MCCs. On average, one or more MCCs are associated with increased CRF.

Data Evaluation

Prior to analysis, a systematic method to evaluate the scientific rigor and quality of the sample was identified to support unbiased and complete synthesis (Whittemore & Knafl, 2005). The studies were appraised for the clarity and focus of the research question and the appropriateness of the method and research design to answer the question. The appraisal included the clarity of conceptual definitions and the use of an appropriate theoretical framework, sampling methods, instrument reliability and validity, appropriate statistical analysis for the level of data reported, threats to validity, and an evaluation of the study's quality (Whittemore, 2005). A 13-item quality criteria checklist was used to evaluate the data from each article on a three-point scale ranging from 0 (poor) to 2 (good) (McNamara & Shaw, 2007). The scores for specific criteria then were summed for an overall quality score, with a maximum possible score of 26.

Sample Characteristics

The 21 studies included more than 80,000 patients ($\bar{X}$ age = 62.9 years) identified as 88% Caucasian and 61% women. Race was not reported in six studies (Barbera et al., 2010; Bower et al., 2006; Gift et al., 2003; Given et al., 2001; Kozachik & Bandeen-Roche, 2008; Liu et al., 2010). Three studies were international, reflecting Turkish (Karakoç & Yurtsever, 2010), Korean (Kim et al., 2008), and Norwegian (Orre et al., 2008) nationalities. The most common solid-tumor cancer diagnoses were represented. Four studies exclusively involved patients with breast cancer (Andrykowski et al., 2010; Bower et al., 2000; Kim et al., 2008) or lung cancer (Gift et al., 2003, 2004; Hoffman et al., 2007; Sarna et al., 2008). Patients with gynecologic (GYN) (Liu et al., 2010) or testicular (Orre et al., 2008) cancer were studied individually in two separate articles. The remaining 11 studies examined CRF with samples that included patients with gastrointestinal (GI), genitourinary, GYN, lung, prostate, and breast cancers (Barbera et al., 2010; Beck et al., 2009; Bender et al., 2008; Brant et al., 2011a, 2011b; Deimling, Bowman, & Wagner, 2007; Given et al., 2001; Hershey, 2011; Karakoç & Yurtsever, 2010; Kozachik & Bandeen-Roche, 2008). Six studies did not report cancer stage (Barbera et al., 2010; Beck et al., 2009; Bender et al., 2008; Karakoç & Yurtsever, 2010; Orre et al., 2008; Reyes-Gibby, Aday, Anderson, Mendoza, & Cleeland, 2006). Six other studies grouped the American Cancer Society staging and reporting system into early and late stages rather than more specific stage designations, with more than 50% of participants considered to have early-stage cancer (Bower et al., 2000, 2006; Given et al., 2001; Hershey, 2011; Kozachik & Bandeen-Roche, 2008; Liu et al., 2010). The remaining nine studies reported specific stage information (Andrykowski et al., 2010; Brant et al., 2011a, 2011b; Deimling et al., 2007; Gift et al., 2003, 2004; Kim et al., 2008; Sarna et al., 2008).

Although current chemotherapy or a history of chemotherapy treatment were inclusion criteria, cancer treatments also varied, reflecting the complexity of cancer treatment regimens. Only three studies (Bender et al., 2008; Hoffman et al., 2007; Karakoç & Yurtsever, 2010) reported chemotherapy as an independent treatment. Fifteen studies' participants experienced multiple treatment modalities, all of which included chemotherapy (Andrykowski et al., 2010; Beck et al., 2009; Bower et al., 2000, 2006; Brant et al., 2011a, 2011b; Deimling et al., 2007; Gift et al., 2003, 2004; Given et al., 2001; Hershey, 2011; Kim et al., 2008; Orre et al., 2008; Sarna et al., 2008). One study, using a nationally representative survey, did not report specific treatment information but assumed a history of chemotherapy treatments (Reyes-Gibby et al., 2006).

Data Analysis

An integrative review aims to interpret and synthesize primary research to answer a specific question

Table 1. Summary of Articles Included in the Integrative Review

Study	Purpose	Design	Patient Population	Findings
Andrykowski et al., 2010	To identify CRF prevalence at CTX initiation and at 6 and 42 months post-CTX	Longitudinal prospective	304 women with breast cancer	Increased number of MCCs associated with increased CRF occurrence ($p < 0.05$) at T4
Barbera et al., 2010	To determine how patient characteristics affect cancer symptoms and functional performance	Descriptive cross-sectional	45,118 patients with breast, GI, GU, GYN, lung, and other cancers	Mean CRF score increases with one or more MCCs ($p = 0.05$)
Beck et al., 2009	To examine symptom experience, HRQOL, and functional performance of rural and urban older adult cancer survivors in the first three months after completion of initial treatment	Mixed methods	52 patients with breast, GI, GYN, prostate, and other cancers	Total number of MCCs correlated with CRF occurrence ($p < 0.05$); arthritis was associated with increased CRF severity ($p < 0.05$)
Bender et al., 2008	To compare chronic health symptoms in patients with and without cancer	Secondary analysis	1,040 patients with rheumatoid arthritis or urinary incontinence without cancer or with breast, GI, GU, GYN, lung, prostate, and other cancers	MCCs increase CRF occurrence.
Bower et al., 2000	To describe CRF in breast cancer survivors compared to the general population	Descriptive cross-sectional	1,957 cancer-free breast cancer survivors	Arthritis (OR =1.35, $p = 0.03$) and hypertension (OR = 1.35, $p = 0.04$) predict CRF.
Bower et al., 2006	To identify the prevalence, persistence, and potential predictors of CRF at 5–10 years after breast cancer diagnosis	Time-ordered cross-sectional	763 cancer-free breast cancer survivors from a previous study (Bower et al., 2000)	At T1, hypertension (OR = 1.8; 95% CI [1.14, 2.86]) and cardiac disease (OR = 1.89; 95% CI [83, 4.28]) predict CRF; at T2, hypertension predicts CRF (OR = 1.75; 95% CI [1.08, 2.2]).
Brant et al., 2011a	To examine trajectories of pain, CRF, depression, distress, and sleep disturbance during the first six cycles of CTX	Longitudinal prospective cohort comparative	118 newly diagnosed patients with GI, lung, and other cancers	At T1, increased number of MCCs was associated with increased CRF severity ($p < 0.01$); number of MCCs predicts inter-individual differences seen over CTX cycles ($p < 0.01$)
Brant et al., 2011b	To examine post-CTX symptom trajectories in cancer survivors	Longitudinal	100 patients with GI, lung, and other cancers	No significant association between MCCs and CRF
Deimling et al., 2007	To determine age- and cancer-related correlates of pain and CRF	Descriptive cross-sectional	295 patients with breast, GI, and prostate cancers	MCCs correlated with less energy ($p \leq 0.01$); MCCs explained 5% of variance in energy
Gift et al., 2003	To determine changes in symptom cluster prevalence and severity at three and six months postdiagnosis	Secondary analysis	112 patients with lung cancer six months after diagnosis	No significant association between MCCs and CRF
Gift et al., 2004	To determine if differences in the number of symptoms are predicted by stage, MCCs, treatments, and gender	Secondary analysis	220 newly diagnosed patients with lung cancers	Number of MCCs predicts CRF severity ($p = 0.004$)
Given et al., 2001	To identify the prevalence and predictors of pain and CRF at four time points over one year	Longitudinal descriptive	841 newly diagnosed patients with breast, GI, lung, and prostate cancer	Three or more MCCs predicts CRF (OR = 0.62, 95% CI [0.46, 0.82])

(Continued on the next page)

CI—confidence interval; CRF—cancer-related fatigue; CTX—chemotherapy; GI—gastrointestinal; GU—genitourinary; GYN—gynecological; HRQOL—health-related quality of life; MCCs—multiple chronic conditions; OR—odds ratio; T—time

Table 1. Summary of Articles Included in the Integrative Review *(Continued)*

Study	Purpose	Design	Patient Population	Findings
Hershey, 2011	To determine how cancer diagnosis and treatment affect diabetes self-management. A subanalysis evaluated presence and severity of CRF.	Mixed methods pilot study (unpublished dissertation)	29 patients with breast, GI, GYN, lung, prostate, and other cancers	Qualitative theme linked CRF to decreased diabetes self-management; no quantitative analysis of MCCs
Hoffman et al., 2007	To determine frequency and severity of pain, CRF, and insomnia	Secondary analysis	80 newly diagnosed patients with breast, GI, lung, and prostate cancers	No significant association between MCCs and CRF
Karakoç & Yurtsever, 2010	To determine CRF severity in older adult patients with cancer during CTX	Descriptive cross-sectional	71 patients with breast, GI, prostate, and other cancers in Turkey	No significant association between MCCs and CRF
Kim et al., 2008	To determine prevalence of CRF and depression	Descriptive cross-sectional	2,403 women with breast cancer in Korea	CRF correlated with GI ($p < 0.001$) and renal ($p = 0.018$) comorbidities; GI comorbidities predict CRF (OR = 2.08; 95% CI [1.33, 3.24])
Kozachik & Bandeen-Roche, 2008	To determine if demographics, cancer type, stage, treatments, and MCCs predict pain, CRF, and/or insomnia more than one year after diagnosis	Secondary analysis	236 newly diagnosed breast, GI, prostate, and lung cancer	Number of MCCs at T1 increases CRF (RRR = 2.22; 95% CI [1, 4.94]). No association was found between the number of MCCs and CRF at T2, T3, and T4.
Liu et al., 2010	To explore patterns of symptoms over time	Secondary analysis	66 newly diagnosed women with GYN cancer	No significant association between MCCs and CRF
Orre et al., 2008	To examine correlates of CRF	Descriptive correlation	1,431 patients with testicular cancer in Norway	MCCs were associated with prevalence of CRF ($p < 0.001$); MCCs were not significant predictors of CRF (OR = 1.48; 95% CI [0.91, 2.73]).
Reyes-Gibby et al., 2006	To determine prevalence of CRF, pain, and depression in adults with a history and without a history of cancer	Descriptive cross-sectional	Health and Retirement Study of 17,210 adults in a community with and without a history of cancer	Number of MCCs predicts CRF: 0 MCC, OR = 1; 1 MCC, OR = 2.432; 2 MCCs, OR = 4.796; 3 MCCs, OR = 9.985 ($p < 0.0001$)
Sarna et al., 2008	To describe changes in symptoms at one, two, and four months after thoracotomy	Descriptive exploratory repeated measures	86 patients with lung cancer	At one ($p < 0.001$) and four ($p < 0.01$) months, number of MCCs was associated with CRF severity.

CI—confidence interval; CRF—cancer-related fatigue; CTX—chemotherapy; GI—gastrointestinal; GU—genitourinary; GYN—gynecological; HRQOL—health-related quality of life; MCCs—multiple chronic conditions; OR—odds ratio; T—time

(Whittemore & Knafl, 2005). The data from each study in the current integrative review were extracted, classified, and systematically evaluated for quality and content (Whittemore & Knafl, 2005). Analysis and synthesis of each study's results led to the development of three main themes to describe the associations between MCCs and CRF in adults with solid-tumor cancer who are currently or have previously received chemotherapy: (a) instrumentation variability limits comparisons of MCCs' prevalence and association with CRF across studies; (b) MCCs were reported as the mean, range, or aggregate number of MCCs present, with limited reporting of the prevalence of specific conditions; and (c) analysis of the association of MCCs and CRF is limited by the reporting methods; however, cancer survivors with one or more MCCs more frequently report CRF than survivors without MCCs. When individual conditions were examined, arthritis and hypertension were found to be associated with CRF.

Instrumentation Variability

Cancer-related fatigue measures: Within this integrative review sample of 21 studies, seven multi-item CRF

instruments were used by six studies (Andrykowski et al., 2010; Beck et al., 2009; Karakoç & Yurtsever, 2010; Kim et al., 2008; Orre et al., 2008; Sarna et al., 2008). CRF was measured by a single question in four studies (Brant et al., 2011a, 2011b; Liu et al., 2010; Reyes-Gibby et al., 2006). Single-item CRF measures included within a multiple-symptom instrument were used by nine studies (Barbera et al., 2010; Bender et al., 2008; Gift et al., 2003, 2004; Given et al., 2001; Hershey, 2011; Hoffman et al., 2007; Kozachik & Bandeen-Roche, 2008; Sarna et al., 2008). Of those nine studies, three used the 32-item Physical Symptom Experience instrument with five gender-specific items deleted so it applied to patients of both genders (Gift et al., 2003, 2004; Given et al., 2001). The time frame for patients to report CRF ranged from the current state (Barbera et al., 2010; Brant et al., 2011a, 2011b; Kim et al., 2008), to the past two weeks (Gift et al., 2003, 2004; Given et al., 2001), to

Table 2. CRF Assessment: Instruments, Definition, and Time Frame

Study	CRF Instrument	Total Items	CRF Items	Term to Describe CRF	Scale	Time Frame of CRF Report
Andrykowski et al., 2010	FSI FCS	14 10	14 10	Fatigue Fatigue	0–10 NR	NR
Barbera et al., 2010	ESAS	9	1	Tiredness	0–10	Current state
Beck et al., 2009	GFS	7	7	Fatigue	NR	Today and most days
Bender et al., 2008	Modified CCI	32	1	Fatigue	Present or not present	NR
Bower et al., 2000	SF-36®	36	4	Vitality	Total score 0–100	Past four weeks
Bower et al., 2006	SF-36®	36	4	Vitality	Total score 0–100	Past four weeks
Brant et al., 2011a	Single item	1	1	Fatigue	0–10	Current state
Brant et al., 2011b	Single item	1	1	Fatigue	0–10	Current state
Deimling et al., 2007	Single item	1	1	Energy	0–3	Typical week
Gift et al., 2003	PSE	32	1	Fatigue	0–4	Past two weeks
Gift et al., 2004	PSE	32	1	Fatigue	0–4	Past two weeks
Given et al., 2001	PSE	32	1	Fatigue	0–4	Past two weeks
Hershey, 2011	Symptoms of illness checklist	24	1	Fatigue	0–5	Past one week
Hoffman et al., 2007	CSE	1	1	Fatigue	0–10	NR
Karakoç & Yurtsever, 2010	Lee fatigue VAS	18	18	Fatigue and energy	0–10	NR
Kim et al., 2008	BFI	9	9	Fatigue	0–10	Current, usual, and past 24 hours
Kozachik & Bandeen-Roche, 2008	PSE	37	1	Fatigue	0–4	Past two weeks
Liu et al., 2010	Self-report	1	1	Fatigue	Yes or no	NR
Orre et al., 2008	FQ	13	13	Fatigue	Total sum	Time last felt well
Reyes-Gibby et al., 2006	Single item	1	1	Troublesome fatigue	Yes or no	NR
Sarna et al., 2008	Schwartz CRF Lung cancer symptom	6 6	6 1	Fatigue	1–5 Yes or no	Past 2–3 days Past four weeks

BFI—Brief Fatigue Inventory; CCI—Charlston Comorbidity Index; CRF—cancer-related fatigue; CSE—Cancer Symptom Experience; ESAS—Edmonton Symptom Assessment System; FCS—Fatigue Catastrophizing Scale; FQ—fatigue questionnaire; FSI—Fatigue Symptom Inventory; GFS—General Fatigue Scale; NR—not reported; PSE—Physical Symptom Experience; VAS—visual analog scale

the past four weeks (Bower et al., 2000, 2006; Sarna et al., 2008), to a typical week (Deimling et al., 2007) (see Table 2).

Multiple chronic condition measures: Nondefined demographic questions were used to identify MCCs in seven studies (Beck et al., 2009; Bower et al., 2000, 2006; Karakoç & Yurtsever, 2010; Kim et al., 2008; Orre et al., 2008; Reyes-Gibby et al., 2006). A modified version of the Charlson Comorbidity Scale was used in three studies (Barbera et al., 2010; Bender et al., 2008; Sarna et al., 2008). Two studies used a comorbidity questionnaire (Hershey, 2011; Hoffman et al., 2007). The remaining eight studies each used a different method to identify MCCs (Andrykowski et al., 2010; Deimling et al., 2007; Gift et al., 2003, 2004; Given et al., 2001; Kozachik & Bandeen-Roche, 2008; Liu et al., 2010) (see Table 3).

Reporting Methods for Multiple Chronic Conditions

Patients from the current data sample reported an average of three MCCs (Bender et al., 2008; Brant et al., 2011a, 2011b; Deimling et al., 2007; Hershey, 2011; Sarna et al., 2008), with a range of 0–9 MCCs (see Table 4).

Thirteen studies reported the prevalence of specific chronic conditions in patients with CRF (Beck et al., 2009; Bender et al., 2008; Bower et al., 2006; Brant et al., 2011a, 2011b; Gift et al., 2003, 2004; Hershey, 2011; Hoffman et al., 2007; Kim et al., 2008; Kozachik & Bandeen-Roche, 2008; Reyes-Gibby et al., 2006; Sarna et al., 2008). Based on the frequencies reported in those 13 studies, 32% of the patients reported arthritis or hypertension and 21% reported diabetes or cardiac disease (see Table 5).

Analysis of the Association of Multiple Chronic Conditions and Cancer-Related Fatigue

Prevalence: The prevalence of CRF significantly increased when patients reported having one (odds ratio [OR] = 2.432, $p < 0.0001$), (Reyes-Gibby et al., 2006), two (OR = 4.796, $p < 0.0001$) (Reyes-Gibby et al., 2006), or three or more MCCs (OR = 0.62, 95% confidence interval [CI] [0.46, 0.82]) (Given et al., 2001). In long-term survivors of testicular cancer, a 33% increase ($p = 0.001$) in CRF prevalence was associated with MCCs, but the number or type of MCCs was not reported (Orre et al., 2008). Beck (2009) identified the total number of MCCs as significantly correlated with the prevalence of CRF ($r = 0.31$, $p < 0.05$). Gift et al. (2003) found no significant association between MCCs and CRF prevalence in patients with lung cancer (n = 220) three to six months postdiagnosis. When a secondary analysis of the same data set examined the first four to six weeks postdiagnosis (n = 220), the aggregate number of MCCs was found to predict CRF (sum of squares = 86.8, df = 9, F = 2.84, $p = 0.004$) (Gift et al., 2004). The association of MCCs

Table 3. Multiple Chronic Condition Measures

Study	Comorbidity Instrument	Data Collection Method
Andrykowski et al., 2010	CCI	Self-report (18 items)
Barbera et al., 2010	Modified CCI	Chart review (12 items)
Beck et al., 2009	Demographic questions	Self-report
Bender et al., 2008	Comorbidity questionnaire	Self-report based on physician diagnosis more than five years after the condition identified (32 items)
Bower et al., 2000	Demographic questions	Self-report
Bower et al., 2006	Demographic questions	Self-report
Brant et al., 2011a	Self-report	Self-report
Brant et al., 2011b	Self-report	Self-report verified by chart review
Deimling et al., 2007	Health Conditions Index	Self-report (27 items)
Gift et al., 2003	NR	NR
Gift et al., 2004	Interview	Self-report (11 items)
Given et al., 2001	Aging and Health in America Survey	Self-report (15 items)
Hershey, 2011	Comorbidity questionnaire	NR (14 items)
Hoffman et al., 2007	Comorbidity questionnaire	Self-report (14 items)
Karakoç & Yurtsever, 2010	NR	NR
Kim et al., 2008	Demographic questions	Self-report
Kozachik & Bandeen-Roche, 2008	Condensed Aging and Health in America Survey	Self-report (15 items)
Liu et al., 2010	Comorbidity Index	Self-report (20 items)
Orre et al., 2008	Self-report	Self-report
Reyes-Gibby et al., 2006	Self-report	Self-report
Sarna et al., 2008	Modified CCI	Self-report (11 items)

CCI—Charlston Comorbidity Index; NR—not reported

and CRF prevalence was not reported by nine studies (Barbera et al., 2010; Brant et al., 2011a, 2011b; Deimling et al., 2007; Given et al., 2001; Hershey, 2011; Hoffman et al., 2007; Liu et al., 2010; Sarna et al., 2008).

Four studies analyzed the association of specific MCCs and CRF prevalence (Beck et al., 2009; Bower et al., 2000, 2006; Kim et al., 2008). Arthritis was identified as a significant predictor of CRF (OR = 1.35, p = 0.03) (Bower et al., 2000). Hypertension predicted CRF (OR = 1.35, p = 0.04) (Bower et al., 2000) and was associated with persistent CRF after completion of chemotherapy (OR = 1.75, CI [1.08, 2.2]) (Bower et al., 2006). In addition, cardiac (p = 0.049) (Bower et al., 2006), GI (p < 0.001), and renal conditions (p = 0.018) all were associated with CRF (Kim et al., 2008).

Severity: Four studies reported CRF severity as directly proportional to the number of MCCs (Barbera et al., 2010; Brant et al., 2011a; Deimling et al., 2007; Gift et al., 2004). Of the 45,118 patients who completed the Ontario Cancer Registry Symptom Assessments, the mean CRF score increased with the presence of more than one MCC in 6,284 patients (Barbera et al., 2010). Increased CRF severity was found in patients who were beginning chemotherapy treatment for newly diagnosed lung, breast, or GI cancer who reported more than 2.5 MCCs (range = 0–8) (Brant et al., 2011a). In long-term cancer survivors, increased CRF severity was significantly correlated to the number of MCCs (r = –0.18, p < 0.01); however, the specific number of MCCs was not reported (Deimling et al., 2007). Three studies found no significant associations between MCCs and CRF severity (Andrykowski et al., 2010; Gift et al., 2003; Karakoç & Yurtsever, 2010).

When specific MCC associations with CRF severity were analyzed, three studies (Beck et al., 2009; Bower et al., 2000, 2006) reported significant increases in CRF severity with arthritis and hypertension (arthritis and hypertension, p < 0.05; arthritis, p = 0.03 and hypertension, p = 0.04; and arthritis, p < 0.03, respectively). Increased CRF severity also was noted with cardiac conditions (p = 0.03) (Bower et al., 2006).

Cancer-related fatigue changes over time: CRF was found to persist more than three years postchemotherapy in patients with breast cancer and MCCs (Andrykowski et al., 2010). Three studies reported no significant differences related to the number of MCCs and CRF over time (Beck et al., 2009; Brant et al., 2011b; Liu et al., 2010). Having more than one MCC was associated with significant increases in CRF prevalence (p < 0.05) (Andrykowski et al., 2010; Beck et al., 2009) and severity (p < 0.01) (Brant et al., 2011a; Sarna et al., 2008). Having more than three MCCs was associated with a 48% increase in CRF prevalence over time (Given et al., 2001). In Brant et al. (2011a), a greater number of MCCs significantly increased CRF severity over time (p < 0.05),

Table 4. Number of MCCs Reported

Study	N	Aggregate MCCs			$\bar{X}$ MCCs
		Total	n	%	
Andrykowski et al., 2010	304	0 1 ≥ 2	203 78 23	66 26 8	NR
Barbera et al., 2010	45,118	0 ≥ 1	38,834 6,284	86 14	NR
Beck et al., 2009	52	1 ≥ 3	NR NR	89 25	NR
Bender et al., 2008	1,040	NR	NR	NR	6.8
Bower et al., 2000	1,957	NR	NR	NR	NR
Bower et al., 2006	763	NR	NR	NR	NR
Brant et al., 2011a	118	0 1 2 3 4 5–8	4 31 37 25 10 11	– 26 31 21 9 9	2.5
Brant et al., 2011	100	1	Range = 0–6	73	2.24
Deimling et al., 2007	295	0–1 2–3 4–5 6–7 8–11	49 103 83 41 19	17 35 28 22 6	3.7
Gift et al., 2003	112	NR	NR	NR	NR
Gift et al., 2004	220	NR	Range = 0–9	NR	NR
Given et al., 2001	841	0 1 2 ≥ 3	61 133 193 368	8 18 26 48	NR
Hershey, 2011	29	NR	Range = 0–5	NR	2.67
Hoffman et al., 2007	80	NR	NR	NR	2
Karakoç & Yurtsever, 2010	71	0 ≥ 1	27 44	38 62	NR
Kim et al., 2008	2,403	NR	NR	NR	NR

(Continued on the next page)

MCCs—multiple chronic conditions; NR—not reported

Note. Sample N and percentages may not add to total sample N or 100% because of individual study reporting methods.

Table 4. Number of MCCs Reported *(Continued)*

Study	N	Aggregate MCCs: Total	Aggregate MCCs: n	Aggregate MCCs: %	$\bar{X}$ MCCs
Kozachik & Bandeen-Roche, 2008	236	0–3	NR	66	NR
Liu et al., 2010	66	0 1 2 ≥ 3	9 13 5 39	14 20 7 59	NR
Orre et al., 2008	1,431	NR	NR	NR	NR
Reyes-Gibby et al., 2006	17,210	0 1 2 3 4 5 6	242 565 632 358 148 54 5	12 28 32 18 7 3 1	NR
Sarna et al., 2008	86	0 1–2 3–4	72 57 15	77 61 16	1.45 (SD = 1.18)

MCCs—multiple chronic conditions; NR—not reported

Note. Sample N and percentages may not add to total sample N or 100% because of individual study reporting methods.

but the specific number of MCCs was not reported. Kozachik and Bandeen-Roche (2008) identified increased CRF associated with MCCs at baseline measurement, but noted no associations at the other time points.

Presentation of Findings

To determine the state of the science and develop recommendations, conclusions must be developed based on the validity of the data (Whittemore & Knafl, 2005). As such, the goal of the current integrative review was to draw conclusions about the association of MCCs and CRF. Limitations affecting the researchers' ability to draw those conclusions were identified.

One key limitation is the variability of CRF and MCC measures and assessment time frames. Associations between nonequivalent concepts cannot be effectively identified (Waltz, Strickland, & Lenz, 2005). Although no one instrument is appropriate for all studies, common constructs support comparisons. Only six studies identified a theoretical framework (Brant et al., 2011a, 2011b; Gift et al., 2003, 2004; Hershey, 2011; Hoffman et al., 2007), and only two identified a conceptual definition for CRF (Andrykowski et al., 2010; Orre et al., 2008). As a result, the current integrative review found CRF was defined by the instrument rather than the instrument reflecting the studies' research purposes and questions (Burns & Grove, 2009), bringing construct validity into question when determining whether the CRF instrument is measuring CRF as the research intended (Waltz et al., 2005).

In addition, assessing CRF with one item contained within multisymptom measures that assess the entirety of a patient's symptom experience does not provide depth for any one specific symptom (Dittner, Wessely, & Brown, 2004). The ease of answering one question about fatigue limits respondent burden and is useful when CRF is a secondary outcome of interest or when the study focuses on just the presence or absence of CRF (Barsevick, Cleeland, et al., 2010). In studies where changes in the prevalence and severity of CRF is a concept of interest, more discriminating measures that reflect the complex nature of CRF would be more appropriate and allow differentiation between fatigue associated with MCCs and CRF.

MCC measurement limitations also were noted. When identifying specific conditions associated with CRF, drawing comparisons is difficult when the measurements used to assess MCC do not provide a congruent list across studies (Burns & Grove, 2009). One specific issue was the modification of known MCC measurements without description or rationale for the modifications (Barbera et al., 2010; Sarna et al., 2008). Conceptual clarity also is needed to define specific MCCs. Even when the studies identified specific MCCs, variation existed between labels used for specific conditions (e.g., heart disease versus cardiac disease), limiting comparison across studies to a general grouping of physiologic systems (Extermann, 2000). For example, Beck et al. (2009), Bower et al. (2000), and Bower et al. (2006) all reported a significant association between arthritis and CRF severity; however, arthritis was not defined as rheumatoid or osteoarthritis, two clinically different and incomparable conditions. Comparisons cannot be drawn (or conclusions generalized) without congruent MCC labeling throughout all measurements. That said, an association between CRF with arthritis, hypertension, or cardiac conditions was identified (Beck et al., 2009; Bower et al., 2000, 2006).

Although the heterogeneity of the cancer diagnoses of the sample supports the generalizability of the findings, the inability to group diagnoses by stage and treatment type challenges comparisons of MCCs and CRF associations within specific diagnoses. Because the majority of the sample was identified as early stage, a positive association between MCCs and CRF in these patients seems more likely. In addition, the sample's limited racial diversity requires additional data to compare results among cultures and races. The six secondary analyses (Bender et al., 2008; Gift et al., 2003, 2004; Hoffman et al.,

Table 5. Individual Chronic Conditions Reported

Study	N	Total Reported Per Condition
Beck et al., 2009	52	20 arthritis, 23 cardiac, 13 diabetes, 4 neuromuscular, and 5 pulmonary
Bender et al., 2008	1,040	150 arthritis, 157 cardiac, 22 diabetes, 40 GI, 134 GU, 32 headache, 18 pulmonary, and 12 renal
Bower et al., 2000	1,957	None reported
Brant et al., 2011a[a]	118	36% cardiac, 19% GI, 14% pulmonary, and 20% vision/hearing deficit
Brant et al., 2011b[a]	100	49% cardiac, 21% GI, and 14% pulmonary
Gift et al., 2003	112	27 arthritis, 44 cardiac, 41 pulmonary, and 63 vision/hearing deficit
Gift et al., 2004	220	46 arthritis, 208 cardiac, 24 diabetes, 33 GU, 79 pulmonary, and 94 vision/hearing deficit
Hershey, 2011	29	29 diabetes
Hoffman et al., 2007	80	26 arthritis, 44 cardiac, 6 diabetes, 15 GU, and 24 pulmonary
Kim et al., 2008	2,403	341 cardiac, 118 diabetes, 210 GI, 294 neuromuscular, 25 pulmonary, and 22 renal
Kozachik & Bandeen-Roche, 2008	236	166 arthritis, 656 cardiac, and 388 vision/hearing deficit
Orre et al., 2008	1,431	None reported
Reyes-Gibby et al., 2006	17,210	1,442 arthritis, 2,001 cardiac, 364 diabetes, and 274 pulmonary
Sarna et al., 2008	86	11 arthritis, 36 cardiac, 12 diabetes, and 48 pulmonary

GI—gastrointestinal; GU—genitourinary
[a] Only percentages were reported.
Note. Patients could choose more than one condition.

2007; Kozachik & Bandeen-Roche, 2008; Liu et al., 2010) presented an over-representation of the same geographic area (the midwestern United States), limiting the results' generalizability (Clarke & Cossette, 2000).

Implications for Practice

Awareness of MCC prevalence is essential to support patients experiencing CRF. During chemotherapy, CRF often is an expected side effect; however, fatigue is a multidimensional symptom that can be attributed to exacerbations of MCCs (Mitchell, 2010). Although care must be exercised in drawing comparisons from the current integrative review, having one or more other chronic conditions in addition to a solid tumor cancer diagnosis seems to increase patients' reports of CRF. The contribution of MCCs to CRF severity and prevalence should be considered when developing symptom management plans. The persistence of CRF in long-term cancer survivors also must be considered when counseling patients about self-reported CRF.

Although statistically significant differences were not always noted, patient identification of increased CRF needs to be evaluated as more than an expected side effect of chemotherapy. Clinically meaningful differences were noted by Barbara et al. (2010) and Sarna et al. (2008). Scores on assessment tools may not fully reflect the effect of CRF severity on a patient's QOL. Additional assessment is required to ascertain potential contributing factors to CRF severity aside from chemotherapy. Holistic nursing assessment of patients' symptoms—with awareness of MCCs—would support symptom management to limit the effect of CRF.

Future Research

A breadth of research reports data about patients' MCCs and the occurrence of CRF, but do not examine their associations. This integrative review excluded 32 primary studies that examined CRF and reported MCCs but did not analyze their association. The multiple CRF measures and variable time frames limits conclusions across studies and requires further research to elucidate the association of CRF and MCCs (Burns & Grove, 2009).

A meta-analysis of the existing research, grouping studies with equivalent CRF measurements, cancer staging classifications, diagnoses, treatments, and MCC measurements, would provide a more confident analysis of the state of the science. In lieu of a meta-analysis, research guided by clear construct definitions and using valid and reliable measurement tools should be conducted to examine the associations between the specific conditions identified in this article. Although the current integrative review included four longitudinal studies, the inconsistency of the time points measured limited conclusions about the association of MCCs and CRF before, during, and after chemotherapy. Additional research examining the same adults with solid tumors throughout multiple cycles of chemotherapy would better elucidate the association of MCCs and CRF over time.

In addition, investigators are beginning to examine the pathogenesis of CRF with inflammation proposed as a component (Bower & Lamkin, 2012; Cameron et al., 2012; Chrousos, 2000; Miaskowski et al., 2010). Inflammation already has been linked to symptoms associated with arthritis and diabetes (Hammer, Motzer,

Voss, & Berry, 2010; Hammer & Voss, 2012; Srirangan & Choy, 2010; Sternberg, Chrousos, Wilder, & Gold, 1992). Additional research of potential shared inflammatory pathways between MCCs and CRF could provide insight on their association and inform intervention development and testing.

Conclusion

The presence of one or more comorbidities was significantly associated with the prevalence and severity of CRF. Arthritis, hypertension, and cardiac disease, although not consistently defined, are associated with the increased prevalence and severity of CRF. Future research will clarify the association of MCCs and CRF throughout multiple chemotherapy time points and inform the development of tailored interventions to improve patients' QOL.

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