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A Literature Synthesis of Symptom Prevalence and Severity in Persons Receiving Active Cancer Treatment

Carolyn Miller Reilly, RN, PhD, FAHA,
Emory University, Atlanta GA

Deborah Watkins Bruner, RN, PhD, FAAN,
Emory University, Atlanta GA

Sandra A. Mitchell, PhD, CRNP,
National Cancer Institute, Bethesda MD

Lori M. Minasian, MD, FACP,
National Cancer Institute, Bethesda MD

Ethan Basch, MD, MSc,
Memorial Sloan-Kettering Cancer Center, New York, NY

Amylou C. Dueck, PhD,
Mayo Clinic, Scottsdale, AZ

David Cella, PhD, and
Northwestern University, Chicago, IL

Bryce B. Reeve, PhD
University of North Carolina, Chapel Hill, NC

Abstract

Purpose—Patients with cancer experience acute and chronic symptoms caused by their underlying disease or by the treatment. While numerous studies have examined the impact of various treatments on symptoms experienced by cancer patients, there are inconsistencies regarding the symptoms measured and reported in treatment trials. This article presents a systematic review of the research literature of the prevalence and severity of symptoms in patients undergoing cancer treatment.

Methods—A systematic search for studies of persons receiving active cancer treatment was performed with the search terms of “multiple symptoms” and “cancer” for studies involving patients over the age of 18 years and published in English during the years 2001 to 2011. Search outputs were reviewed independently by seven authors, resulting in the synthesis of 21 studies meeting criteria for generation of an Evidence Table reporting symptom prevalence and severity ratings.

Results—Data were extracted from 21 multi-national studies to develop a pooled sample of 4067 cancer patients in whom the prevalence and severity of individual symptoms was reported. In total, the pooled sample across the 21 studies was comprised of 62% female, with a mean age of 58 years (range: 18 to 97 years). A majority (62%) of these studies assessed symptoms in homogeneous samples with respect to tumor site (predominantly breast and lung cancer), while 38% of the included studies utilized samples with mixed diagnoses and treatment regimens. Eighteen instruments and structured interviews were including those measuring single symptoms, multi-symptom inventories, and single symptom items drawn from HRQOL or health status measures. The MD Anderson Symptom Inventory (MDASI) was the most commonly used instrument in the studies analyzed (n=9 studies; 43%), while the Functional Assessment of Cancer Therapy (FACT-G), Hospital Anxiety and Depression Subscale (HADS-D), Medical Outcomes Survey Short Form-36 (SF-36), and Symptom Distress Scale (SDS) were each employed in two studies. Forty-seven symptoms were identified across the 21 studies which were then categorized into 17 logical groupings. Symptom prevalence and severity were calculated across the entire cohort and also based upon sample sizes in which the symptoms were measured providing the ability to rank symptoms.

Conclusions—Symptoms are prevalent and severe among patients with cancer. Therefore, any clinical study seeking to evaluate the impact of treatment on patients should consider including measurement of symptoms. This study demonstrates that a discrete set of symptoms is common across cancer types. This set may serve as the basis for defining a “core” set of symptoms to be recommended for elicitation across cancer clinical trials, particularly among patients with advanced disease.

Keywords

Cancer; symptoms; systematic review

Introduction

Patients with cancer experience acute and chronic symptoms caused both by their underlying disease and by the often toxic treatments employed in oncology care.[1,2] Clinical investigators, regulators, and healthcare providers often focus on the prevention or cure of illness, whereas relief of symptoms is a paramount goal for patients. [3,4] Symptoms are a common reason healthcare is sought and an impetus for testing to definitively diagnose an illness or injury. Once treatment is implemented, symptomatic treatment toxicities frequently develop. [5]

While numerous studies have examined the impact of various treatments and medications on symptoms in patients receiving cancer treatment, a limitation in comparing these outcomes is the lack of a common or “core” set of patient-reported symptoms, consistently measured across studies. For example, one study may report an improvement in nausea with a specified treatment, another study may report worsening fatigue, leaving the clinician and patient comparing treatment efficacies and weighing side effects based upon disparate outcomes.

These differences in symptom outcomes between studies to some extent can be attributed to the use of varying symptom assessment questionnaires and strategies. While there is value to focusing on specific symptoms in particular clinical contexts (e.g., pain in patients with metastatic prostate cancer to bone), there is also value in administration of a common set of symptoms both in order to characterize the broader impact of disease and treatment on the patient experience, and to enable cross-trial comparisons and aggregation of data. Therefore, in 2011, the National Cancer Institute sponsored a scientific meeting to identify a standard core set of patient-reported symptoms to be recommended across cancer clinical trials as well as existing questionnaires that are appropriate for assessing these symptoms. As a component of this initiative, a multidisciplinary team conducted a systematic review of the literature to identify studies that measure the prevalence and severity of symptoms in patients undergoing cancer treatment.

Search Methods

A systematic electronic search of PubMed was performed with the search terms of “multiple symptoms” and “cancer” (Figure 1). The search was limited to adults over the age of 18 years, English language articles, and the years 2001 to 2011. Search outputs including the abstract were reviewed independently by seven authors, and full-text of papers deemed to be potentially relevant based on a priori criteria (i.e., containing evidence characterizing symptoms in patients being treated for cancer) for inclusion were examined. Hand searches of papers in reference lists were also performed. Studies were included if they evaluated multiple symptoms in persons receiving active cancer treatment regardless of cancer site, stage, treatment, or geographic location. The initial search retrieved 55 publications of which 19 were excluded as case studies,[6-8] studies of single symptoms,[9-12] symptoms at the end of life,[13,] presenting symptoms at the time of cancer diagnosis,[15,16] or were otherwise not research reports focused of multiple symptoms in persons with cancer.[17-24]

In 2009, Esther Kim et al[25] published a literature synthesis of cancer symptomatology in 18 studies. This paper and four additional literature reviews[26-29] identified in our systematic search were excluded from this analysis. Instead, the findings by Esther Kim et al. (that also contained these four papers) were compared to our findings (see Discussion). Unlike the Esther Kim et. al. synthesis which only included studies that used the MD Anderson Symptom Inventory (MDASI), Memorial Symptom Assessment Scales (MSAS), or the Symptom Distress Scale (SDS), this present analysis intentionally did not limit to any specific assessment instrument so that a wide array of symptoms could be collated and analyzed across a broader range of studies.

Nine publications that failed to report symptom statistics[30-38] and one publication that was a secondary study of a sample already included in this analysis[39] were excluded, resulting in 21 studies included in this analysis.[40-60] Potentially relevant data were abstracted for the review including disease/treatment, sample, instrument used to measure symptoms, and symptom prevalence and severity. Where information about prevalence and severity was not presented, the authors were contacted by e-mail to obtain the necessary detail. Data were managed using Excel.

Analysis and Synthesis Methodology

Table 1 provides a summary of the 21 studies that evaluated multiple symptoms in adult oncology patients receiving active treatment. Twelve of these studies used a cross-sectional design and 9 employed a longitudinal approach that included randomized clinical trials, a cross-over design, or structured interviews. The length of follow-up in the longitudinal studies ranged from 7 days to 18 months, with assessment time points typically concurrent with important milestones such as treatment cycles or return to the home community following allogeneic Hematopoietic Stem Cell Transplantation (HSCT).

An aggregation of the demographics for the studies is presented in Table 2 and then prevalence and severity of symptoms by paper is presented in Table 3. To allow for comparisons between the cross-sectional and longitudinal studies, where possible, mean prevalence was computed by averaging the reported values across the available time points in the longitudinal studies. When this was not possible due to missing data, the baseline values were entered into the analysis as noted on this table.

A similar procedure was used for tabulating severity, although mean severity by symptom was often not reported. In addition, many of the studies only reported those symptoms in which the severity was classified as moderate to severe. Because there was variation in the range of the severity scales among the instruments used in the studies, mean values were linearly transformed to a 0-10 scale to facilitate comparisons. Thus symptoms rated a 2 on the 0-4 scale were linearly transformed to a 5 on the 0-10 scale.

Lastly, to assess if the most commonly used instruments asked about the most compelling symptoms to patients, thresholds by number of patients queried for the symptom were constructed. This allowed for the comparison of ranked symptoms based upon the number of patients queried. Thus symptoms that were assessed in 100 or more people were ranked by frequency and severity, symptoms assessed in 500 or more people, and then a final threshold of 1000 or more people. The lowest threshold of 100 people had the most symptoms ranked while creating the threshold of 1000 people limited the number of symptoms. Some symptoms found in this synthesis did not include query by at least 100 patients and were therefore not included in this rank ordering of symptoms by threshold level.

Characteristics of These Studies

Data were extracted from the reported studies to develop a pooled sample of 4067 cancer patients in whom the prevalence and severity of individual symptoms was reported. Individual studies contributed from 16 to 1433 participants; nine (43%) studies included a sample size less than 100. All of the investigations employed convenience samples. Eleven (52%) of the studies were conducted in the United States while the remainder were multinational as listed in the Table 2. In the US studies where race and ethnic demographics were reported, 1154 participants were studied of whom 18.5% of the samples were non-white. Studies from other nations failed to distinguish race/ethnicity. In total, the pooled sample across the 21 studies was comprised of 38% male and 62% female, with a mean age of 58 years (range: 18 to 97 years).

A majority (62%) of these studies assessed symptoms in homogeneous samples with respect to tumor site (predominantly breast and lung cancer), while 38% of the included studies utilized samples with mixed diagnoses and treatment regimens. Table 2 summarizes the characteristics of participants in the included studies by cancer disease site, stage, and treatment type. Persons with breast cancer were the single largest group by cancer site (approximately 25% of patients) followed by lung (approximately 20%). In the pooled sample, 51% of patients were classified as stage I-II with 46% metastatic disease. The largest majority of study participants were treated with chemotherapy, radiation, and/or surgery. Approximately 5% additionally of the participants additionally received Hematopoietic Stem Cell Transplantation (HSCT), with symptom assessment before and after this treatment. For these two longitudinal studies, the frequency and severity of symptoms was averaged across the various assessment times for this synthesis.

Symptom Assessment Instruments

Eighteen instruments listed in Figure 2 and structured interviews were used in the 21 studies included in this synthesis. Instruments included those measuring single symptoms, multi-symptom inventories, and single symptom items drawn from HRQOL or health status measures. The MD Anderson Symptom Inventory (MDASI) was the most commonly used instrument in the studies analyzed (n=9 studies; 43%), while the Functional Assessment of Cancer Therapy (FACT-G), Hospital Anxiety and Depression Subscale (HADS-D), Medical Outcomes Survey Short Form-36 (SF-36), and Symptom Distress Scale (SDS) were each employed in two studies. The remaining instruments were represented just once.

Symptom Summary

Forty-seven symptoms were identified across the 21 studies which were then categorized into 17 logical groupings. While many studies only reported the most prevalent or severe symptoms, some reported every symptom acknowledged by patients. In an attempt to be as inclusive as possible, all symptoms reported were included in this synthesis.

A summary of the prevalence and mean severity rates (when available) for these various symptoms are provided in Table 4. This table is organized in descending order according to the prevalence of the measurement of symptom groupings as highlighted in blue. Thus, all of the studies in this synthesis measured and reported frequency and/or severity of the symptoms of fatigue and pain, 91% of the studies similarly reported symptoms of sleep issues, while only 4.5% reported on symptoms of hair loss or other appearance issues.

The pooled prevalence and mean severities reported in Table 4 were calculated by aggregating all queries for that specific symptom across studies to provide a pooled prevalence per symptom. Where possible, symptoms of the same nature but labeled differently such as anorexia and decreased appetite were combined into one symptom. This was possible when only one term was used in a study providing one statistic; however, some symptom terms which could be synonymous for each other were often reported as separate items in the same study. Examples include the terms “fatigue”, “lack of energy”, and “weakness”. Each is listed separately in this synthesis to assure the capture of constructs that may be related but distinct. Of note, while all of studies measured and thus reported the

symptom of fatigue, 59.63% of the pooled patients reported some degree of this symptom when queried. Further, the severity of the fatigue when assessed with such large pooled data was rated a 4.62 on a 0-10 scale.

Symptom Prevalence

Given the large spread of sample sizes, the variety of instruments utilized and the identification of 47 separate symptoms presented in Table 3, it was determined that the most appropriate method to rank symptoms in a systematic, unbiased, and interpretable fashion was to compare the symptom prevalence by aggregated sample size thresholds. Three thresholds were constructed for combined samples of greater than 100 patients, greater than 500 patients and greater than 1000 patients who were queried for the symptom. Thus the most inclusive threshold was 100 taking into account all symptoms in which at least 100 patients across studies were queried. Not included in this analysis then were symptoms such as irritability which was only assessed in a total of 85 patients in 2 studies or headache included in only one study of 31 patients.

As depicted in Table 5 depending upon the threshold level selected, the rank order of the prevalence changed. For a threshold of 100 patients, Nocturia was the most frequently reported symptom followed by Fatigue and Cough. When the threshold was raised to a minimum of 500 patients assessed for the symptom, Cough was replaced by Insomnia/Disturbed Sleep. Finally, when raised to a sample threshold of 1000 patients, Fatigue, Insomnia/Disturbed Sleep, and Pain are the top three most reported symptoms. Thus as will be discussed later, while nocturia was the most prevalent symptom with 74.8% of patients reporting, it was only queried in 507 patients in 2 studies.[45,49]

Symptom Severity

A similar approach was taken in evaluating the symptom severity, and is presented in Table 6. In studies with a sample threshold of 100 patients, Worry had the highest mean severity followed by Sexual Dysfunction and Edema. By comparison, when the higher threshold of 500 patients was selected, most of the symptoms in the lower threshold of 100 patients were removed and by the 1000 patient threshold, all but one symptom was replaced with the top three being Fatigue, Insomnia/Disturbed Sleep, and Anorexia/Appetite changes. As with the symptom prevalence, fewer studies assessed worry (three studies)[41,46,51] and sexual dysfunction (two studies)[45,51] resulting in a smaller patient pool, yet the compelling severity reported may indicate the need for further assessment as a routine symptom measure.

Discussion

Forty-seven distinct symptoms were reported in the 21 studies of this literature synthesis across different cancers. Most studies employed instruments that assessed for symptoms of Fatigue & Weakness (100% of studies), Pain (100% of studies), Sleep Issues (91% of studies), Anorexia & Weight loss (91% of studies), GI Issues such as nausea and vomiting (81% of studies), Affect issues such as depression and irritability (76% of studies), and Respiratory Issues such as cough and dyspnea (76% of studies). Fewer studies assessed

symptoms related to Urinary Elimination Issues (19% of studies), Skin and Wound Issues (19% of studies), Hot Flashes/sweating (14% of studies), Sexual Dysfunction (10% of studies), Fever (14% of studies), and Hair Loss/Appearance (5% of studies), yet the prevalence and severity of some of these symptoms was greater than the more commonly assessed symptoms.

This disparity is most obvious when evaluating the prevalence and severity by threshold levels. Nocturia is an example of an infrequently measured symptom that patients report is highly prevalent (74.8%) and moderately severe (4.07 on scaled of 0-10). Further analysis of the two studies that assessed for nocturia reveals that one study was completed in the US and the other in Turkey, that adequate sample sizes of 220 and 287 were included, and that various cancer sites were involved with lung being the predominant cancer.[45,49] Given the heterogeneous nature of the studies, this finding suggests that nocturia is a symptom that has been infrequently assessed, but which necessitates further systematic evaluation and consideration as a symptom to assess in a broad range of cancers. Similar arguments can be made for sexual dysfunction[45,51] and cough[45,46,48,51,53] which each were reported by patients in disparate studies (nation, cancer site, sample sizes) as highly prevalent and of moderate to high severity.

Findings from this literature synthesis are most useful when compared with the research synthesis by Esther Kim et. al.[25] Many similarities between the two syntheses exist including the similar mean age of 58 and 59 years, a predominance of heterogeneous cancer diagnoses (62% and 50%), and when reported for US studies, an approximate 18% non-Caucasian sample. Differences include a greater range of sample sizes in this present analysis (16- 1433 compared to 26-527) and a greater proportion of females in this analysis (62% vs. 48%). Whereas Esther Kim et. al. limited their review to only studies that employed the MDASI, MSAS, or the SDS, this present analysis included studies employing any symptom assessment tools.

Table 7 presents a comparison of the most prevalent symptoms in this synthesis to the top 10 identified by Esther Kim et. al. These are presented in descending prevalence for this current synthesis. All but three of the symptoms (nocturia, outlook, and weakness) included in this synthesis were also included in the Esther Kim et. al. synthesis. Unfortunately, the synthesis by Esther Kim et. al. only published the aggregation of the top 10 symptoms. As presented in this table, while the vast majority of symptoms were assessed (as indicated by the instrument used), comparisons cannot be drawn because the pooled prevalence numbers for all but the top 10 symptoms were not published. In comparing our findings to those of Esther Kim et.al., similarities in the prevalence of fatigue, insomnia, dry mouth, tiredness, feeling nervous, distress, and depression were noted, however differences are observed between the rates of irritability, pain, and worry are evident. Further, highly prevalent symptoms such as nocturia, lack of energy, outlook, cough, anorexia, dyspnea, and difficulty concentrating did not make Esther Kim et. al.'s list of the most prevalent symptoms. The Kim study did not aggregate severity data.

Limitations and Future Directions

As with any literature synthesis, findings must be tempered by acknowledging publication bias as only published manuscripts were included in this literature synthesis. Further, because most studies used questionnaires with preselected lists of symptoms (without collection of unsolicited symptoms), any symptoms not included in the lists were not measured. Therefore, systematic under-reporting of symptoms which could be prevalent and severe in a population is possible in the included studies. An example of this is nocturia, which when elicited was prevalent and severe, but was infrequently systematically elicited in studies. Future studies should include a two-step methodology, starting with qualitative work in which patients in a given population are interviewed in groups or individually to determine likely prevalent and severe symptoms, followed by questionnaire administration in a larger sample. Over-representation of studies in breast, colorectal and lung cancer may have yielded a disproportionate influence on the results, and work parallel to this paper supported by the NCI is evaluating prevalence and severity of symptoms by cancer type and stage.

It is unclear if symptoms reported in this analysis are attributable to the morbidity of cancer, to side effects of treatment, to accumulated toxicities of prior treatment, or to comorbidities. As previously noted, this is a synthesis of cross-sectional studies and longitudinal studies whereby symptoms in the longitudinal studies were average across the measurement times, and no control was made for cross-sectional sampling related to the time of symptom measurement (i.e.: at diagnosis, following treatment, or at another arbitrary point in time). In addition, attribution is beyond the scope of this paper, but is a salient consideration because the impetus for measuring symptoms in a given clinical trial may be contingent on the cause of the symptom. For example, a trial seeking to evaluate whether a cancer-related symptom improves with active treatment may yield a negative result if the principal driver of measured symptoms is toxicity or comorbidity. Therefore, any given clinical trial aiming to measure symptoms should provide a rationale specific to the population and interventions regarding why particular symptoms were selected, and their suspected cause and hypothesized direction of change.

This synthesis is focused on the prevalence and severity of symptoms and did not assess measures of health-related quality of life domains such as enjoyment of life or physical functioning. Future work will evaluate these areas.

Conclusion

Symptoms are prevalent and severe among patients with cancer. Therefore, any clinical study seeking to evaluate the impact of treatment on patients should consider including measurement of symptoms. Without such an assessment, the picture of the patient experience is incomplete.[61] Symptoms may be due to various etiologies, and understanding their trajectories in a given context is essential to profiling both the benefits and harms of treatment. This study demonstrates that a discrete set of symptoms is common across cancer types. This set may serve as the basis for defining a “core” set of symptoms to be recommended for elicitation across cancer clinical trials, particularly among patients with

advanced disease. Indeed, the NCI is currently engaged in such an activity, which serves as the impetus for this review. It is notable that a number of existing multi-symptom questionnaires already include a set of pre-specified of symptoms. It is the authors' hope that the data included in this review will assist in the design of future studies and questionnaires, and in improved methods for assessing the prevalence and severity of symptoms in cancer populations.

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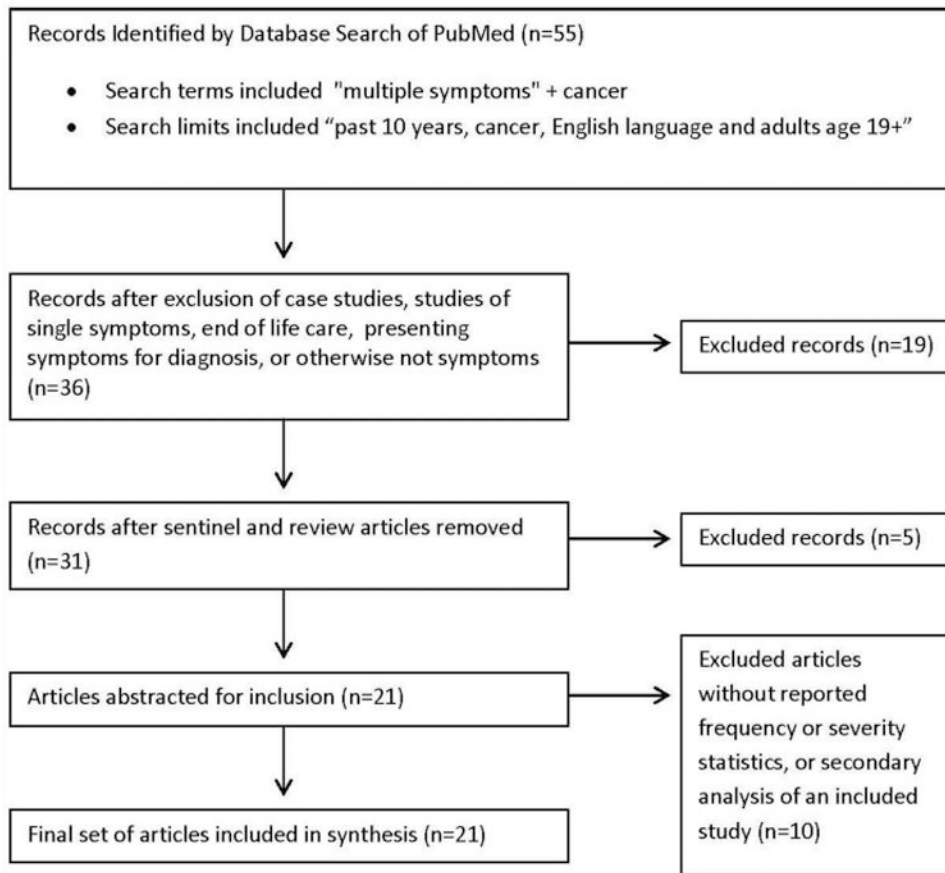


Figure 1. Search Methodology

- **Brief Pain Inventory (BPI)**
- **Cancer Symptom Experience Inventory (CSEI)**
- **Eastern Cooperative Oncology Group Performance Status (ECOG)**
- **European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC-QLQ-C30)**
- **Functional Assessment of Cancer Therapy (FACT-G)**
- **Generalized Fatigue Scale (GFS)**
- **Hospital Anxiety and Depression Subscale (HADS-D)**
- **MD Anderson Symptom Inventory (MDASI)**
- **Medical Outcomes Survey Short Form (SF-12)**
- **Medical Outcomes Survey 36 (SF-36)**
- **Memorial Symptom Assessment Scales (MSAS)**
- **Patient Disease Symptom/ Sign Assess Scale (PDSA)**
- **Physical Symptom Experience Tool (PSET)**
- **Pittsburgh Sleep Quality Index (PSQI)**
- **Profile of Mood States (POMS)**
- **Renal Cell Carcinoma Symptom Index (RCC-SI)**
- **Side Effect Checklist (SEC)**
- **Structured Interviews (SI)**
- **Symptom Distress Scale (SDS)**

Figure 2. Instrument List

Table 1

Evidence table

Evidence Source/Citation	Sample Characteristics (n, age, stage, treatment type, phase of care, special population)	Outcome Measure(s) of Symptoms, Functioning and/or HRQL	Study Design/Analytic Approach	Symptoms and Symptom Dimensions (provide %s or #s as they relate to prevalence, severity, duration, and/or interference)	Comments and Caveats
Anderson (2007)	100 patients during the acute phase of autologous PBSC transplantation with multiple myeloma or non-Hodgkin's lymphoma	MD Anderson Symptom Inventory (MDASI-BMT) and the Eastern Cooperative Oncology Group Performance Status (ECOG PS) were completed at baseline, 3-4 days into conditioning, day of transplant, day of nadir, and 30days post transplant. The Profile of Mood States (POMS) and the Functional Assessment of Cancer Therapy– Bone Marrow Transplant (FACT-BMT) at BL and 30 days.	Longitudinal, descriptive	The time point associated with the most reported disturbances was Nadir: The top five symptoms at each time point rated by patients as moderate to severe were: BL 29% fatigue, 21% pain, 17% distress, 14% weakness, 13% sadness; Conditioning: 34% disturbed sleep, 22% fatigue, 22% loss appetite, 14% nausea, 13% weakness.; Transplant:34% loss appetite, 32% fatigue, 26% disturbed sleep, 25% nausea, 23% weakness. Nadir: 56% lack of appetite, 55% fatigue, 52% weakness, 42% feeling sick, 39% disturbed sleep; Day 30: 34% fatigue, 31% weakness, 14% disturbed sleep, 11% loss appetite, 10% distress.	Cancer diagnosis was a significant predictor of changes in symptoms over time. The patterns of fatigue, pain, sleep disturbance and lack of appetite were significantly different for patients with multiple myeloma as compared with patients with non-Hodgkin's lymphoma.
Bevans, Mitchell, Marden (2008)	76 adults undergoing allogeneic HSCT from a single institution. Mean age of 40 years (SD 13.5 years). 67% of the sample was male; 30% of the sample was Hispanic; two thirds were undergoing transplant for acute or chronic leukemia, lymphoma or multiple myeloma. 66% were in a complete remission at the time of transplant, while 34% had progressive disease.	Symptom Distress Scale (SDS)	Longitudinal study with data about the symptom experience collected pre-transplant, day 0 (after HSCT conditioning), and days 30 and 100 post-transplant	The most prevalent symptoms at baseline were fatigue and worry (both 68%), at day 0, the most prevalent symptom was appetite change (88%), and fatigue was most prevalent at days 30 (90%) and 100 (81%). Symptoms that were severely distressing including worry (16% severely distress at baseline), insomnia (32% severely distressed at day 0), appetite change (22% severely distressed at day 30) and fatigue (11% severely distressed at day 100). The SDS was highest at day 0 (mean 26.6 SD 7.6), when the highest number of symptoms were reported. Symptoms formed clusters comprised of fatigue, appearance change and worry at baseline, and fatigue, insomnia, and bowel changes at days 0 and 30. Examining the symptom experience over time, it is apparent	Though not consistently the most prevalent or distressing, GI complications, including bowel changes, nausea, and appetite limitations were noted across the treatment trajectory.

Evidence Source/Citation	Sample Characteristics (n, age, stage, treatment type, phase of care, special population)	Outcome Measure(s) of Symptoms, Functioning and/or HRQL	Study Design/Analytic Approach	Symptoms and Symptom Dimensions (provide %s or #s as they relate to prevalence, severity, duration, and/or interference)	Comments and Caveats
Chen ML, Chang HK (2004)	121 patients with breast (40%), head and neck (33%), or esophageal cancer (27%) that were hospitalized in Northern Taiwan for chemotherapy (76%), symptom management (20%) and follow-up or surgery (4.1%). Male=55%. Mean Age=52.19 (SD 10.44) Range=26-81. Cancer stage= II (15%), III (17%), IV (33%), missing (36%).	Patient Disease Symptom/Sign Assessment Scale (PDSA), Hospital Anxiety and Depression Subscale (HADS-D)	Cross-sectional, descriptive	that HSCT patients tend to present for transplantation with low symptom distress, and experience that HSCT patients tend to present for transplantation with low symptom distress, and experience that HSCT patients tend to present for transplantation with low symptom distress, and experience that HSCT patients tend to present for transplantation with low symptom distress, and experience	Using HADS-D to measure depression decreases the likelihood of confounding the assessment of depression with physical symptoms caused by cancer and its treatment since HADS-D does not use physical symptoms to measure depression.
Chen (2007)	329 multi-disease site pts. Study from Taiwan 29% breast; 25% GI; 76% local disease without mets; time since dx 1-31 mos with median of 14 mos; 53% had chemo; 73% had RT	MDASI-Taiwanese-13 common ca related symptoms measured on scale 1-10 assessed in primary study but only 9 symptoms used in this secondary CFA analysis based on previous EFA (Chen & Tseng 2006)	Secondary analysis of Cross sectional study; Confirmatory factor analysis	Insomnia was the most prevalent symptom (67%), followed by pain (62%), anorexia (47%), fatigue/weakness (40%), nausea/vomiting (24%), wound/pressure sore (17%), dyspnea (14%), edema (8.3%), and elimination problems (2.5%), and change in consciousness (0%). The average number of symptoms for total sample was 2.83 (median 3.0, range: 0/7). 55% reported 3 or more. 25% were classified as depressed (HADS-D cutoff of 11). The average number of symptoms observed total sample was 3.77 (median 3.5), depressed patients had average number of 3.77 (median=3.5) and non-depressed had 2.52 (median/2.0). Depressed patients showed a significantly higher occurrence rate than that of non-depressed patients in insomnia, pain anorexia fatigue, wound/pressure sore. Patients simultaneously experiencing insomnia, pain, anorexia, and fatigue had a higher risk of depression (odds ratio 5.03)	
Ferreira (2008)	115 outpatients with cancer, who had not received cancer treatment in the last 30 days who reported at least 2 symptoms. Female=61%, Mean age= 57.2(SD 13.5).	Karnofsky Performance Status scale (KPS), Beck Depression Inventory (BDI), the Brief Pain Inventory	Cross-sectional, descriptive study	mean # of symptoms per pt = 6.6 (range 0-13); prevalence 72% dry mouth; 70% fatigue 63% sleep disturbance 3 clusters: sickness including pain, fatigue, disturbed sleep & drowsiness; GI including N&V & lack of appetite; Emotional including distress & sadness	Prevalence and mean of symptoms as follows: pain 100%, 7.36; fatigue 87%, 41.50; Insomnia 73%, 57.39; constipation 51%, 36.52; lack of appetite 50%, 37.97; dyspnea 44%, 24.19; depression 44%, 14.43; nausea

Evidence Source/Citation	Sample Characteristics (n, age, stage, treatment type, phase of care, special population)	Outcome Measure(s) of Symptoms, Functioning and/or HRQL	Study Design/Analytic Approach	Symptoms and Symptom Dimensions (provide %s or #s as they relate to prevalence, severity, duration, and/or interference)	Comments and Caveats
Hayes (2010)	N=287, Australian women age 74 or younger (mean 54), early stage, all post surgery (PS) by 4 mo+, 87% had one or more LNs dissected w median of 12 LNs examined	PRO: FACT-B+4 (arm subscale), Disability of Arm, Shoulder, Hand (DASH) collected at 6 mo and q3 mo x4. Objective measures: ROM, Exercise protocol, Bio-impedance Spectroscopy (BIS) to measure LE	Descriptive study, prospective, longitudinal, population-based sample through cancer registry in Queensland, Australia	Numbness (19-29%) & swelling (13-23%) most common symptoms. Multiple symptoms were 1.7x more common in LE pts and by 18mo PS, having LE doubled chance of 1 or more symptoms. By 18 mo the differences were minimal, except those w LE reported more tingling, swelling, numbness	1 in 2 women reported moderate to extreme pain, tingling, weakness, stiffness, poor ROM, swelling, and/or numbness at 6 mo PS, but 51% reported at least 1 complaint 12 mo later
Hoffman (2007)	n = 80 newly diagnosed with lung cancer; 2 CCOPs and 2 Comprehensive CA centers; age range 41-83, mean 63; Caucasian 95%; Early stage - 10%; Late Stage 90%;	Given (co-author) Cancer Symptom Experience Inventory (15 symptoms; occurrence, severity, interference).	secondary data analysis from baseline of randomized clinical trial; explore relationship among pain, fatigue, insomnia, and gender.	Most Frequent (%): Fatigue 97; Pain 69; Nausea 53; Constipation 53; insomnia 51; poor appetite 50; cough 49; dry mouth 44 diff breathing 44; diarrhea 30; diff concentrating 26; coordination 24 vomiting 23; fever 11; mouth sores 8	
Karabulu (2010)	287 Turkish pts from a university hospital. 56% male, 66% had Stage II disease; mean duration since tx was 3 yrs +/- 2.5 yrs; 39% GI, 17% lung, 14% AML/ ALL, 13% H&N, 12% breast. 72% had chemo only, 2% RT only & 8% chemoRT	MDASI- Turkish	cross-sectional design using hierarchical cluster analysis to identify symptom clusters and regression analysis to assess predictors of clusters	prevalence: fatigue 95.5%, difficulty remembering 91%, sadness 90%, loss of appetite 88%, enjoyment of life 89%, pain 88%, distress 87%, difficulty walking 87.5%, dry mouth 87.5%. Overall 37.5% had moderate and 12.5% had severe symptoms. Mean MDASI scores for 13 symptom items were 5 and 4.4 for the 6 interference items. 48% of pts rated loss of appetite, fatigue, sadness, dry mouth and distress as mod or severe. Loss of appetite was most prevalent symptom. The 6 interference symptoms formed a cluster (gen activity, mood, work relations with others, walking, enjoyment with life); a second cluster was formed with sleep disturbance, difficulty remembering, pain, distress, sadness, fatigue, dry mouth and appetite loss. A third cluster was formed with nausea, vomiting, SOB, numbness, drowsiness.	

Evidence Source/Citation	Sample Characteristics (n, age, stage, treatment type, phase of care, special population)	Outcome Measure(s) of Symptoms, Functioning and/or HRQL	Study Design/Analytic Approach	Symptoms and Symptom Dimensions (provide %s or #s as they relate to prevalence, severity, duration, and/or interference)	Comments and Caveats
Kenefick (2006)	N=55, age 60 or older (mean 68), 61%white, 37% AA, stage I or II BCA,	Symptom Distress Scale (SDS) Longitudinal data collection at hospital discharge and 3 & 6 mo post discharge.	Secondary, descriptive analysis from larger study of a home care nursing intervention on QOL of older pts newly diagnosed with several types of cancer.	SDS scores range from 13 to 65 and mean total SDS were 23.81 at discharge from hospital and 20.52 at 3 mo, and 18.6 at 6 mo. Most frequent sx were fatigue, frequency of pain, outlook and insomnia. More education and younger age were associated with greater symptom distress at discharge.	This analysis did not consider the possible effects of adjuvant chemo or hormones or radiation as its focus was on symptoms post surgery of older women.
Keene Sarenmalm (2007)	N=56, age 55 & older (mean 65), newly diagnosed w local, regional or distant recurrent BC-A (29 had loco-regional recurrence) (1/3 had past hx of anxiety and/or depression)	MSAS, MSAS-PHYS, MSAS-PSYCH, TMSAS (total symptom burden), MSAS-GDI, HADS, Sense of Coherence (soc) measures coping capacity, PACIS, QLQ-C30, IBCSG-QOL	Descriptive study, pts recruited prospectively from 2 oncology centers, correlation analyses with multiple regressions for developing prediction model	65% reported 10-23 symptoms (avg 14). Prevalent sx >50%: lack of energy (67%), difficulty sleeping (61%), pain (59%), worrying (59%), problems w sexual interest/activity (59%) feeling sad (57%), dry mouth (52%)	Stat sig correlations among highly related symptoms were worrying and feeling nervous, worrying and feeling sad, nausea & lack of appetite, difficulty swallowing & feeling bloated.
Kim (2008)	N=282, women w BCA all stages, age >30, (mean 55), 92% white, initiating rx of at least 3 cycles of chemo (44%) or 6 wks of XRT (56%)	General fatigue scale, POMS, Pittsburgh Sleep Quality Index, Side Effect Checklist. Time points- baseline pre-rx and 48 hours post rx 2 and 3.	Secondary analysis of data from RCT of cognitive behavioral rx on fatigue (1999-2002 at 2 ca ctrs), factor analysis for symptom clusters	Common factoring identified a psychoneurological symptom cluster at 1st time point: depressed mood, cognitive disturbance, fatigue, insomnia, and pain and was generalizable to all subgroups. Symptom cluster at 2nd time point included upper-GI symptoms (nausea, vomiting, decreased appetite)	Confounding variables on symptom clustering included varying CTX regimens, XRT dose, hormonal rx, surgery type and time lapse since surgery were not controlled for
Kiteley (2006)	n = 16 at lung cancer clinic in Toronto mean age 67; 9 men, 7 women; chemo before 1st interview - 4; btwn interviews - radiation -9, rad and chemo 2, surgery and rad 1, surgery only 1, chemo alone 1	spontaneous reports and probes on symptoms (21 in total were identified)	semi-structured interview to describe their symptom experiences; interview at time of diagnosis and second interview 2 months later.	Out of N = 16, symptoms with greater than 25% include (#s are reported at Baseline & 2 Months later: fatigue = 14, 15; pain = 10, 9; shortness of breath = 9, 7; loss of appetite = 8, 11; cough = 8, 8; insomnia = 8, 9; mucous = 8, 9; weight loss = 8, 8; wheeze = 7, 4	fatigue and pain most troublesome symptoms; most often cited combo of symptoms was respiratory symptoms (wheeze, cough, mucus, shortness of breath)
Nejmi (2010)	165 cancer patients in Morocco (Arabic-speaking); mean age 48.7; 56% female; 8% receiving chemotherapy/14% receiving radiotherapy; 32% Stage II-III/68% Stage IV; 95% ECOG PS 2-4 (39% ECOG PS 4); 21% gastrointestinal/19% breast/15%	MD Anderson Symptom Inventory Arabic version (MDASI-A); Eastern Cooperative Oncology Group Performance Status (ECOG PS)	Cross-sectional, descriptive, mixed methods	Mean score (0-10 scale, in order of mean severity high to low): pain (9.62); fatigue (7.05); lack of appetite (6.07); disturbed sleep (5.35); dry mouth (5.07); sadness (4.85); distress (4.33); shortness of breath (3.89); numbness (3.76); drowsiness (3.28); nausea (3.03); difficulty remembering (2.85); vomiting (2.43). % with score >= 5 (moderate or severe; in order of incidence high to low): pain (100%);	Interview format; very poor performance status overall

Evidence Source/Citation	Sample Characteristics (n, age, stage, treatment type, phase of care, special population)	Outcome Measure(s) of Symptoms, Functioning and/or HRQL	Study Design/Analytic Approach	Symptoms and Symptom Dimensions (provide %s or #s as they relate to prevalence, severity, duration, and/or interference)	Comments and Caveats
Reyes-Gibby (2007)	48 patients with locally advanced pancreatic cancer receiving chemoradiation 5040 cGY in 28 fractions, capecitabine and bevacizumab) on a phase I protocol. Median of 58 years of age 9range 41-80), 92% Caucasian, equally divided between males and females. KPS was preserved (100% of teh sample with KPS>80%), however 74% had one or more comorbidities.	gynecological/12% lung/8% unknown/7% genitourinary gynecological/12% lung/8% unknown/7% genitourinary gynecological/12% lung/8% unknown/7% genitourinary	Longitudinal, descriptive, with symptoms and their interference with usual function measured at baseline, weekly during treatment, and at the time of the first clinical assessment after chemoradiation	fatigue (86%); lack of appetite (79%); disturbed sleep (69%); dry mouth (68%); sadness (62%); distress (54%); shortness of breath (47%); numbness (46%); drowsiness (43%); nausea (35%); difficulty remembering (35%); vomiting (25%). % with score ≥ 7 (severe; in order of incidence high to low): pain (96%); fatigue (65%); lack of appetite (48%); dry mouth (30%); sadness (31%); shortness of breath (29%); distress (28%); disturbed sleep (24%); numbness (22%); drowsiness (16%); nausea (16%); difficulty remembering (16%); vomiting (15%). 95% of the patients reported at least one of the 13 symptoms at initial presentation. The highest mean score was observed for fatigue, followed by lack of appetite and pain. The most commonly reported symptoms at moderate to severe intensity over the course from presentation, during treatment and after treatment were fatigue, lack of appetite, pain, nausea and sleep disturbance. At entry to the study, 51% of the sample reported multiple symptoms that were of moderate to severe intensity, with the proportion reporting symptoms of moderate to severe intensity decreasing to 20% at the time chemoradiotherapy was concluded. Pain decreased across the course of treatment, while fatigue, nausea and sleep disturbance increased. Fatigue and appetite changes formed a distinct grouping.	
Shi (2010)	Forty-two patients with breast, head and neck, lung, gynecological, gastrointestinal, prostate, or brain cancer in their third to eighth week of chemoradiation. Majority female, white, >55yrs, breast cancer; 50% metastatic cancer.	To examine the effects of recall on symptom severity ratings by comparing ratings made using 24-hour and seven-day recall periods of the MD Anderson Symptom Inventory (MDASI). Eastern Cooperative Oncology Group	Cross-over design	The five most severe symptoms from both recall periods were fatigue, sleep disturbance, drowsiness, lack of appetite, and pain. Paired t-tests did not find any significant difference between the 24-hour and seven-day recall periods. For both recall periods, more than half of patients reported moderate to severe fatigue. Percentages did not differ significantly between the 24-hour and seven-day recall periods.	Comparing the 24-hour and seven-day recall periods, the correlation coefficient for total symptom severity was 0.888. All correlation coefficients for symptom severity items were >0.7 except for distress (r = 0.67). The percentages of moderate to severe symptoms (rated >5) were consistent for both recall

Evidence Source/Citation	Sample Characteristics (n, age, stage, treatment type, phase of care, special population)	Outcome Measure(s) of Symptoms, Functioning and/or HRQL	Study Design/Analytic Approach	Symptoms and Symptom Dimensions (provide %s or #s as they relate to prevalence, severity, duration, and/or interference)	Comments and Caveats
Sun (2008)	45 patients actively receiving treatment for either hepatocellular carcinoma (HCC) or pancreatic cancer. The mean age was 59 years, and 64% were male. 51% Caucasian, 22% Asian, 18% Hispanic, and 4% African American participants. >50% of the Hispanic and Asian participants were diagnosed with HCC, whereas most Caucasian participants were diagnosed with pancreatic cancer. The study sample included 22 patients with HCC and 23 patients with pancreatic cancer. The majority of participants had stage III (26%) or IV (61%) disease at the time of accrual; 82% had been diagnosed recently, and 13% had recurrent disease.	Patients were followed from baseline for three months, with outcome measures repeated monthly. Outcome measures included the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) and the Functional Assessment of Chronic Illness Therapy-Spirituality Subscale (FACT-Sp-12).	Descriptive, longitudinal study. Descriptive analysis of demographic, treatment, and symptom data was conducted, followed by two-way repeated measures analysis of variance of FACT-Hep and FACT-Sp-12 scale scores by diagnosis and treatment type.	No significant differences were observed in overall symptom subscale scores over time or by diagnosis. In the HCC group, the overall symptom subscale score decreased over time from baseline, one-, and two-month evaluations, but was increased at three months. For the pancreatic cancer group, overall scores stabilized between one month and two months and then decreased by the three-month evaluation. These changes were not statistically significant. Overall, symptom scores were high for weight loss, appetite, fatigue, ability to perform usual activities, and abdominal pain and tended to worsen over time.	Pearson's correlations between the disease-specific symptom subscale and each of the QOL subscale scores were computed for all four evaluations, including baseline. Results at baseline suggest that symptoms were highly correlated with physical well-being (0.72), functional well-being (0.73), and overall FACT-Hep scores (0.93).
Wang SY, Tsai CM, Chen BC, Lin CH, Lin CC (2008)	n = 108 lung cancer in Taiwan; oncology in and outpatient units (3 sites); mean age 68; radiation -81%; localized cancer 74%	Taiwanese version of MDASI	cross-sectional	Most Severe (mean score, range 0 -10): fatigue 6.68, sleep disturbance 6.04; lack of app 5.83; short breath 5.59; distress 5.27; drowsiness 5.19; dry mouth 5.11; pain 5.10; sadness 4.87; diff remembering 4.65; numbness 4.01; nausea 2.48; vomiting 1.35	
Wang (2010)	1433 patients were included in analyses: 524 patients from the United States, 249 from China, 256 from Japan, 226 from Russia, and 178 from Korea. Percent female: US-55, China-54, Japan-42, Russia-62, Korea-40. Mean age(SD) US-55(15.0), China-51(12.8), Japan-62(12.1), Russia-61(14.3).	M. D. Anderson Symptom Inventory (MDASI), ECOG	Cross sectional, descriptive	Cross-nationally, fatigue was consistently the most prevalent moderate to severe symptom (rated 5 on the MDASI 0-10 scale). Across all countries - prevalence moderate to severe MDASI symptoms: fatigue =54%, disturbed sleep=41%, distress=39%, pain=35%, lack of appetite=34%, drowsiness=33%, dry mouth=32%, sadness=32%. Treatment-induced symptoms such as nausea, vomiting, and numbness were	The results of this study indicate that national and linguistic (country) variations in patient responses to the MDASI are small relative to individual patient-related factors. Analysis of MDASI symptom and interference ratings from cancer patients in five countries revealed that the variance of the

Table 2

Characteristics of papers included in synthesis

Study	Location	Study design		Race			Gender		Cancer Locations/ Types	Cancer Stage			Treatment				Age			
		Cross-sectional	Longitudinal	Sample size	White	Non-White	Male	Female		Number specified when provided	I-II	III-IV	Mets	Surgery	Chemotherapy	Radiation	Biologic agents	HSCCT	min	max
Anderson (2007)	US	1	1	100	81	20	60	40	H				100				100	24	75	54
Bevans, Mitchell, Marden (2008)	US	1	1	76	35	41	51	25	H						76		76	18	71	40
Chen ML, Chang HK (2004)	Taiwan	1		121			66	55	B=48; D=33; E=40	18	60	43					26	81	52	
Chen (2007)	Taiwan	1		329			146	175	A=6; B=93; C=79; E=57; H=55; I=24; L=7			77	197	173	233		22	97	61	
Ferreira (2008)	Brazil	1		115			46	69	B=44; C=6; E=8; G=15; I=27; J=12; L=1			73	74	57	61				57	
Gift (2004)	US	1		220	200	20	130	90	I	84	136		92	95	139		65	89	72	
Harding (2007)	US	1		31	30	1	17	14	G	14	15	15	20	1					55	
Hayes (2010)	Australia	1	1	285				285	B				287	114	200	171			74	54
Hoffman (2007)	US	1		80	76	4	44	36	I	1	67						41	83	63	
Karabulut (2010)	Turkey	1		287			160	127	B=34; C=113; E=37; F=15; H=39; I=49	197	90		51	274	73					
Kenefick (2006)	US	1	1	57	35	22	0	57	B	54	3								58	
Keene Sarenmalm (2007)	Sweden	1		54			0	54	recurrent B	32	24		10	7	42		55	79	65	
Kim (2008)	US	1	1	282	258	24	0	282	B	220	31		125	157			30	83	50	
Kiteley (2006)	Canada	1	1	16			9	7	I				2	7	12		50	89	66	
Nejmi (2010)	Morocco	1		165			72	93	B=32; C=35; E=12; F=25; G=12; H=4; I=20; K=6; L=19	53	112		6	13	23		18	84	49	
Reyes-Gibby (2007)	US	1	1	37	44	4	25	23	C								41	80	58	
Shi (2010)	US	1	1	42	25	17	10	32	A, B, C, E, F, J	19	23	19							60	
Sun (2008)	US	1	1	45	23	22	29	16	C	6	39		10	29	6				59	
Wang SY, et. al (2008)	Taiwan	1		108			69	39	I	16	21	28	10	25	30		41	90	68	
Wang (2010)	US, China, Japan, Russia, Korea	1		1433			513	920	Multicancer, not defined			754		736						
Wang XS, et. al (2010)	US	1		184	146	38	87	97	C&D	31	85		10	112	25		20	84	60	

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Cancer Type/Location: A = Brain/CNS ; B = Breast; C = Digestive/Gastrointestinal; D = Esophageal; E = Head & Neck; F = Gynecologic; G = Genitourinary/Renal; H = Hematologic; I = Lung; J = Prostate; K = stem; L = Other/Unknown

Table 4
Summary of pooled prevalence and pooled mean severity rates (when available)

	Number of Patients Reporting Symptom	Total sample of Patients Queried	Pooled Prevalence (%)	Mean Severity
Fatigue & Weakness (100% of studies)				
Generalized Fatigue	2177	3651	59.63	4.62
Tiredness/Drowsiness	999	2310	43.25	3.37
Lack Of Energy	36	54	66.67	
Weakness	222	636	34.91	5.00
Pain (100% of studies)				
Generalized/unspecified pain	1880	3914	48.03	3.44
Headache	7	31	22.58	
Abdominal Pain				5.44
Sleep Issues (91% of studies)				
Insomnia/Disturbed Sleep	1792	3675	48.76	4.15
Anorexia & Weight loss (91% of studies)				
Weight Loss	129	321	40.19	5.94
Anorexia/Appetite changes	1539	3388	45.43	3.89
GI Issues (81% of studies)				
Bloating	9	54	16.67	0.98
Bowel Changes	108	260	41.54	2.13
Constipation	117	349	33.52	2.25
Feeling Sick	18	100	18.00	2.20
N&V	61	236	25.85	1.20
Nausea	670	1672	40.07	2.50
Vomiting	392	1459	26.87	2.09
Diarrhea	52	349	14.90	1.15
Affect (76% of studies)				
Depression/Sadness	983	2856	34.42	2.70
Irritability	44	85	51.76	
Worry	58	161	36.02	7.75
Feeling Nervous	23	54	42.59	
Distress	887	2149	41.28	2.36
Outlook	35	57	61.40	2.00
Respiratory Issues (76% of studies)				
Cough	208	401	51.87	5.13
Wheezing	5	16	31.25	
Difficulty breathing/Dyspnea	681	1560	43.65	2.78
Impaired Cognition (67% of studies)				
Difficulty Concentrating/Remembering	693	1590	43.58	3.05

	Number of Patients Reporting Symptom	Total sample of Patients Queried	Pooled Prevalence (%)	Mean Severity
Oral & Swallowing Issues (62% of studies)				
Altered Taste	87	274	31.75	3.50
Dry Mouth	1248	2610	47.82	3.49
Oral Lesions	12	234	5.13	0.45
Dysphagia	69	274	25.18	3.13
Neurologic Issues (57% of studies)				
Poor Coordination	55	300	18.33	5.37
Mobility	29	285	10.18	
Dizziness	80	305	26.23	4.68
Numbness/Tingling	364	875	41.60	2.21
Unspecified Neurologic	4	184	2.17	
Edema (29% of studies)				
Edema	102	711	14.35	6.57
Urinary Elimination Issues (19% of studies)				
Urinary problems	14	85	16.47	4.25
Nocturia	379	507	74.75	4.07
Skin and Wound Issues (19% of studies)				
Skin changes	7	54	12.96	
Wound/Pressure Sore	21	121	17.36	
Itching	13	134	9.70	4.15
Hot Flashes/sweating (14% of studies)				
Hot Flashes/sweating	156	556	28.06	6.47
Fever (14% of studies)				
Fever	19	111	17.12	2.81
Sexual Dysfunction (10% of studies)				
Sexual Dysfunction	101	274	36.86	6.90
Hair Loss/Appearance (5% of studies)				
Hair Loss/Appearance	34	161	21.12	

Table 5

Rank ordering of symptom prevalence by sample threshold

	Number of Patients Reporting Symptom	Total sample of Patients Queried	Prevalence ordering of symptoms in Sample >1000	Prevalence ordering of symptoms in Sample >500	Prevalence ordering of symptoms in Sample >100	Pooled Prevalence
Generalized Fatigue	2177	3651	1	2	2	59.6
Insomnia/Disturbed Sleep	1792	3675	2	3	4	48.8
Pain	1880	3914	3	4	5	48.0
Dry Mouth	1248	2610	4	5	6	47.8
Anorexia/Appetite changes	1539	3388	5	6	7	45.4
Difficulty breathing/Dyspnea	681	1560	6	7	8	43.7
Difficulty Concentrating/Remembering	693	1590	7	8	9	43.6
Tiredness/Drowsiness	999	2310	8	9	10	43.2
Distress	887	2149	9			41.3
Nausea	670	1672	10			40.1
Nocturia	379	507		1	1	74.8
Cough	208	401			3	51.9
Numbness/Tingling	364	875		10		41.6

Table 6

Rank ordering of symptom severity by sample threshold

	Number of Patients Reporting Symptom	Total sample of Patients Queried	Prevalence ordering of symptoms in Sample >1000	Prevalence ordering of symptoms in Sample >500	Prevalence ordering of symptoms in Sample 100	Mean Severity
Generalized Fatigue	2177	3651	1	4	10	4.62
Insomnia/Disturbed Sleep	1792	3675	2	5		4.15
Anorexia/Appetite Changes	1539	3388	3	7		3.89
Dry Mouth	1248	2610	4	8		3.49
Pain	1880	3914	5	9		3.44
Tiredness/Drowsiness	999	2310	6	10		3.37
Difficulty Concentrating/Remembering	693	1590	7			3.05
Difficulty breathing/Dyspnea	681	1560	8			2.78
Depression/Sadness	983	2856	9			2.70
Nausea	670	1672	10			2.50
Edema	102	711		1	3	6.57
Weakness	222	636		3	8	5.00
Hot Flashes/Sweating	156	556		2	4	6.47
Nocturia	379	507		6		4.07
Cough	208	401			7	5.13
Weight Loss	129	321			5	5.94
Dizziness	80	305			9	4.68
Poor Coordination	55	300			6	5.37
Sexual Dysfunction	101	274			2	6.90
Worry	58	161			1	7.75

Table 7

Comparison of Prevalence statistics between this literature synthesis and Esther Kim et. al.

	Pooled Prevalence	Mean Severity	Esther Kim et. al. Prevalence
Nocturia	74.75	4.07	*
Lack Of Energy	66.67		MSAS
Outlook	61.4	2	*
Generalized Fatigue	59.63	4.62	62%
Cough	51.87	5.13	MSAS
Irritability	51.76		37%
Insomnia/Disturbed Sleep	48.76	4.15	41%
Generalized/unspecified pain	48.03	3.44	36%
Dry Mouth	47.82	3.49	42%
Anorexia/Appetite changes	45.43	3.89	MDASI, MSAS, SDS
Difficulty breathing/Dyspnea	43.65	2.78	MDASI, MSAS, SDS
Difficulty Concentrating/Remembering	43.58	3.05	MDASI, MSAS, SDS
Tiredness/Drowsiness	43.25	3.37	36%
Feeling Nervous	42.59		45%
Numbness/Tingling	41.6	2.21	MDASI & MSAS
Bowel Changes	41.54	2.13	MSAS & SDS
Distress	41.28	2.36	34%
Weight Loss	40.19	5.94	MSAS
Nausea	40.07	2.5	MDASI, MSAS, SDS
Sexual Dysfunction	36.86	6.9	MSAS
Worry	36.02	7.75	54%
Weakness	34.91	5	*
Depression/Sadness	34.42	2.7	39%

Key for symptom assessment in the Esther Kim et. al. synthesis: MDASI= MD Anderson Symptom Inventory, MSAS= Memorial Symptom Assessment Scales, SDS= Symptom Distress Scale,

*
=not assessed