Symptom clusters in patients receiving chemotherapy: A systematic review

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ABSTRACT

Background and purpose Since 2001, symptom cluster research has grown considerably. However, because multiple methodological considerations remain, ongoing synthesis of the literature is needed to identify gaps in this area of symptom science. This systematic review evaluated the progress in symptom clusters research in adults receiving primary or adjuvant chemotherapy since 2016.

Methods Eligible studies were published in English between 1 January 2017 and 17 May 2021; evaluated for and identified symptom clusters 'de novo;' and included only adults being treated with primary or adjuvant chemotherapy. Studies were excluded if patients had advanced cancer or were receiving palliative chemotherapy; symptoms were measured after treatment; symptom clusters were pre-specified or a patient-centred analytic approach was used. For each study, symptom instrument(s); statistical methods and symptom dimension(s) used to create the clusters; whether symptoms were allowed to load on more than one factor; method used to assess for stability of symptom clusters and associations with secondary outcomes and biomarkers were extracted.

Results Twenty-three studies were included. Memorial Symptom Assessment Scale was the most common instrument and exploratory factor analysis was the most common statistical method used to identify symptom clusters. Psychological, gastrointestinal, and nutritional clusters were the most commonly identified clusters. Only the psychological cluster remained relatively stable over time. Only five studies evaluated for secondary outcomes.

Discussion While symptom cluster research has evolved, clear criteria to evaluate the stability of symptom clusters and standardised nomenclature for naming clusters are needed. Additional research is needed to evaluate the biological mechanism(s) for symptom clusters.

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Key messages

What was already known?
- Gastrointestinal and psychological clusters are common.

What are the new findings?
- Nutritional cluster was commonly identified.

What is their significance?
a. Clinical
   - Psychological clusters are relatively stable over time.
   - Gastrointestinal clusters appear to fluctuate over time.

b. Research
   - Standardised nomenclature for symptom clusters is needed.
   - Evaluation of biological mechanisms for symptom clusters is needed.

INTRODUCTION

As the incidence of new cancer cases and mortality rates increase globally,[1] the symptom burden of oncology patients remains high. For example, in one study,[2] 50% of patients receiving chemotherapy experienced an average of 13 symptoms. Equally important, co-occurring symptoms and/or symptom clusters result in increased distress,[3] decreased functional status,[4] poorer quality of life (QOL)[5] and increased mortality.[6 7] Given that 50% of oncology patients may experience these negative effects, research on how and why symptoms co-occur is vital to the development of effective interventions.

In 2001, Dodd and colleagues[8] were the first to introduce the concept of a symptom cluster into oncology symptom science. Since then, symptom cluster research has increased dramatically.[9–12] While the definition of a symptom cluster has evolved,[8 13] most recently, it was defined as the co-occurrence of two

or more symptoms that are stable and independent of other clusters, and may share underlying mechanisms and/or outcomes.[9] This research has grown to include the identification of symptom clusters in children[14] and adolescents[15]; in patients with advanced cancer;[16 17] and in patients receiving active treatment.[11] An emerging area of research is the evaluation of biomarkers[18] and molecular mechanisms[19–21] associated with symptom clusters.

While this research provides important foundations in our understanding of cancer-related symptom clusters, two key methodological issues remain unresolved; namely: which statistical approach provides the most consistent identification of symptom clusters (eg, cluster analysis, exploratory factor analysis (EFA)) and how the dimension(s) of the symptom experience that are used to create the clusters (ie, occurrence, severity, frequency, distress) influence the number and types of symptom clusters identified. Resolution of these issues is key to the development of effective interventions for symptom clusters.[9] In addition, consistent identification of symptom clusters will facilitate the investigation of their underlying mechanisms.

While Skerman and colleagues suggested that factor analysis methods were the optimal approach to create symptom clusters,[22] cluster analysis[23] and more recently network analysis (NA)[24] have been used. Factor analysis methods, like EFA, are used to identify latent constructs or factors (ie, symptom clusters) that account for the strength of the relationships between variables (ie, symptoms).[25] This type of factor analysis is exploratory in nature as it does not test hypotheses on the nature of the relationships among the variables. Cluster analysis methods (eg, hierarchical cluster analysis (HCA)), use measures of correlation or distance to group related variables (ie, symptoms).[22] An emerging analytical approach for identifying symptom clusters is NA. With this approach, relationships between multiple variables or nodes (ie, symptoms) are quantified and illustrated graphically.[26] Unique strengths of NA are its potential to identify 'core' symptoms (ie, symptoms that have a high impact on the network or cluster) and relationships among symptom clusters.[27–29]

Consensus is lacking on which dimension(s) (ie, occurrence, severity, frequency, distress) of the symptom experience should be used to identify symptom clusters.[9] For example, in one review,[11] a significant amount of variability was found in the dimensions used to identify symptom clusters. This type of evaluation is important because the specific dimension used may influence the number, types and composition of the symptom clusters that are identified, making comparisons across studies difficult. While each symptom dimension provides unique information, little is known about how the symptom clusters identified using different dimensions may affect various patient outcomes or the mechanisms that underlie various symptom clusters.

In the most recent review of symptom clusters research in oncology patients receiving chemotherapy,[11] findings from studies published between 2000 and 2016 were synthesised. However, the impact of symptom clusters on outcomes (eg, QOL, functional status) and associations with underlying mechanisms were not evaluated. As noted in an expert panel report,[9] ongoing synthesis of symptom clusters research is warranted to identify gaps in this area of scientific inquiry. Therefore, the purpose of this systematic review was to evaluate the progress in symptom clusters research in adult patients receiving primary or adjuvant chemotherapy since 2016. Specifically, this paper will: (1) describe the most common instrument(s), statistical approaches and symptom dimensions used to evaluate symptom clusters; (2) describe the number and types of symptom clusters identified using different dimensions of the symptom experience; (3) determine whether symptom clusters change over time; and (4) describe associations between symptom clusters and patient-reported outcomes (PROs) and biological mechanisms.

METHODS

Search strategy

This review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[30] Studies that were published between 1 January 2017 and 17 May 2021 were retrieved from the Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, Embase, PubMed and Web of Science databases. The search strategy for each database is listed in table 1.

Study selection

Identified studies were downloaded into a prespecified Endnote Library for review and duplicates were removed. Studies were retained for review if they met the following eligibility criteria: (1) evaluated for and identified at least one symptom cluster; (2) included only adults (aged ≥18 years); (3) included only oncology patients who were being treated with primary or adjuvant chemotherapy; (4) were published in English; (5) had a cohort, case–control, cross-sectional or longitudinal design; and (6) identified symptom clusters 'de novo' (ie, used a statistical method to identify clusters). Studies were excluded if they: (1) were published prior to 1 January 2017; (2) included patients with advanced cancer (ie, stage IV) or those receiving palliative chemotherapy; (3) measured symptoms after the completion of treatment; (4) used pre-specified symptom clusters (ie, did not use a statistical method to identify clusters); (5) used a patient-centred analytic approach (eg, latent class analysis); or (6) were a systematic review, meta-analysis, conference abstract, dissertation work, case-report or qualitative study. The title and abstract of each study were reviewed by a single author (CSH) for eligibility based on our prespecified inclusion and exclusion criteria.

Table 1 Summary of search strategy

Database	Search terms
Cochrane Library	'symptom cluster' OR 'symptom clusters' OR ('symptom' AND 'cluster') OR ('symptom' AND 'clusters') OR ('symptoms' AND 'clusters') in All Text AND cancer OR neoplasm in All Text AND chemotherapy OR CTX in All Text NOT reviews NOT protocols. Restricted to 1 January 2017 to 17 May 2017
Cumulative Index to Nursing and Allied Health Literature	('symptom cluster' or 'symptom clusters' or 'symptom' AND 'cluster' or 'symptom' AND 'clusters' or 'symptoms' AND 'clusters') AND (cancer OR neoplasm) AND (chemotherapy OR CTX). Limiters: Published date: 1 January 2017 to 31 May 2021; Language: English
Embase	('symptom cluster' OR 'symptom clusters' OR ('symptoms' AND 'clusters') OR ('symptom' AND 'clusters') OR ('symptom' AND 'cluster')) AND (cancer OR neoplasm) AND (chemotherapy OR ctx). Search limited to 1 January 2017 to 17 May 2021; Language: English
PubMed	((((('symptom cluster'[All Fields]) OR ('symptom clusters'[All Fields])) OR ((((('symptom'[All Fields])) AND ('cluster'[All Fields]))) OR ((('symptom'[All Fields])) AND ('clusters'[All Fields]))))) OR ((('symptoms'[All Fields])) AND ('clusters'[All Fields])))))) AND ((cancer[All Fields])) OR (neoplasm[All Fields]))))) AND ((chemotherapy[All Fields])) OR (CTX[All Fields]))). Filter applied: 1 January 2017 to 17 May 5; Language: English
Web of Science	Topic=(symptom cluster* OR *symptom clusters*) OR Topic=(symptom* AND cluster*) OR Topic=(symptom* AND clusters*) OR Topic=(symptoms* AND clusters*) AND Topic=(cancer* OR neoplasm*) AND (chemotherapy* OR CTX*) AND Topic=(chemotherapy* OR CTX*). Restricted to: 1 January 2017 to 17 May 2021; Language: English

The first (CSH) and senior (CAM) authors reviewed the full text of the remaining articles against the inclusion and exclusion criteria.

Data extraction

The prespecified study characteristics that were extracted are detailed in box 1. Separate evaluations were done for cross-sectional (online supplemental table 1) and longitudinal (online supplemental table 2) studies. Two reviewers (CSH and CAM) independently reviewed each study and consensus was reached on the data included in the tables.

Assessment of methodological quality

Each study's methodological quality was assessed using the National Heart, Lung, and Blood Institute's (NHLBI) National Institute of Health Quality Assessment Tool for Observational and Cross-Sectional Studies.[31] Questions on this tool were designed to enable researchers to critically appraise the internal validity of research studies. Each question is answered with 'yes', 'no' or 'cannot determine, not reported or not applicable'. Items that receive a 'no' or indeterminable response are considered a study weakness that may introduce bias. As recommended by the NHLBI tool guidelines, this potential risk of bias must be further evaluated by a reviewer and is factored into the final rating of 'good', 'fair' or 'poor'. Two reviewers (CSH and CAM) independently assessed the quality of each study and combined their results in a shared Excel spreadsheet. All studies that met the inclusion and exclusion criteria were included in this review regardless of the methodological quality assessment rating.

Box 1 Pre-specified study characteristics for extraction

Study characteristics: author(s), year published, purpose(s), study design, country, sample size
Patient characteristics: age, gender, ethnicity, race, employment status, inpatient/outpatient status, cancer diagnosis, cancer treatment, timing of symptom assessment(s)
Methods: symptom instrument(s), statistical methods used to create the clusters, symptom dimension(s), whether symptoms were allowed to load on more than one factor and method used to assess for stability of symptom clusters
Associations with other patient-reported outcomes (PROs) and biomarkers
Study findings: symptom clusters identified, specific symptoms within each cluster, PROs, biomarkers
Strengths and limitations

RESULTS

Study selection

The initial search resulted in 574 articles. Following the removal of duplicates, 319 articles remained. Next, the title and abstract of each study were reviewed against our inclusion and exclusion criteria and 283 studies were excluded. The first (CSH) and senior (CAM) authors reviewed the full text of the remaining 36 articles against the inclusion and exclusion criteria. Following these steps, 23 articles were retained for data extraction and are included in this systematic review (figure 1).

Methodological quality of studies

Nine of the 13 cross-sectional studies received a 'good' quality rating, four received a 'fair' rating and none received a poor rating (table 2). Across the four studies that received a 'fair' rating, two sources of bias were: lack of reporting of whether the participation rate of eligible persons was at least 50% (item 3) and lack of clarity on whether the timing of the symptom assessment around the receipt of chemotherapy was sufficient in order to see an effect (item 7). All of the longitudinal studies received a 'good' rating. Of note, seven of the

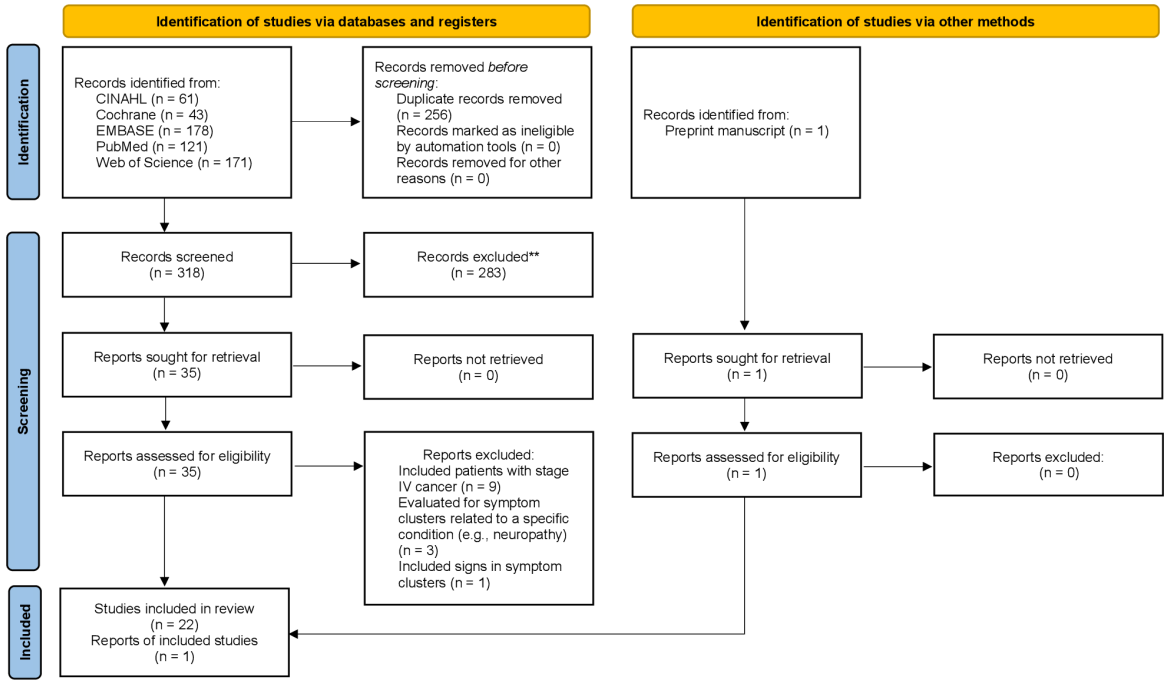

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram to determine the final selection of studies that evaluated for symptom clusters in patients receiving adjuvant chemotherapy, 2017–2021. From Page *et al*.[30]

10 longitudinal studies either lost >20% of patients to follow-up or did not report this information.

Cross-sectional study results

Study characteristics

Of the 23 studies included in this review, 13 used a cross-sectional design to identify symptom clusters in oncology patients receiving chemotherapy (online supplemental table 1). Seven studies were conducted in the USA,[29 32–37] two in China,[38 39] two in Thailand,[40 41] one in Austria,[42] and one in Turkey.[43] Sample sizes ranged from 96[41] to 1328.[29] Across these studies, the majority of patients were female (weighted grand mean 76.8%), outpatients, not working, had a weighted grand mean age of 55.0 years, and were relatively homogeneous in terms of ethnicity and race.

Five studies evaluated for symptom clusters in patients with heterogeneous types of cancer.[29 32 33 35 42] Of the eight studies that evaluated for clusters in patients with homogeneous types of cancer, four evaluated patients with breast cancer,[34 36 40 41] one with bladder cancer,[39] one with leukaemia,[38] one with lymphoma,[43] and one with lung cancer.[37]

Symptom instrument(s)

In terms of the instruments, nine of the 13 studies used the Memorial Symptom Assessment Scale (MSAS).[29 32 33 35–38 40 43] Of these nine studies, six used a modified version of the MSAS[29 32 33 35–37] and one used a condensed version.[38] One study used multiple symptom assessment tools to assess for clusters;[34] specifically, the Breast Cancer Prevention Trial Symptom Checklist, the Beck Depression Inventory-II, the Brief Pain Inventory, the Patient's Assessment of Own Functioning, and the Profile of Mood States. One study each used the Edmonton Symptom Assessment Scale,[41] the MD Anderson Symptom Inventory (MDASI),[39] and the Rotterdam Symptom Checklist.[42]

Statistical approach

Nine of the 13 studies used EFA to identify symptom clusters.[32–37 39 41 42] Of the remaining studies, two used principal component analysis (PCA),[38 40] one used HCA[43] and one used NA.[29]

Symptom dimension(s)

In terms of the symptom dimension(s), three of the 13 studies used only severity[34 39 41] and three used only distress.[32 38 42] Of the seven remaining studies, two used both occurrence and severity;[36 37] one used severity and distress;[40] one used frequency, severity and distress;[43] and three used occurrence, severity, and distress.[29 33 35]

Occurrence

Across the five studies that used occurrence,[29 33 35–37] a psychological cluster was identified. The number of symptoms ranged from five to 12. Worrying, feeling nervous, feeling sad, and feeling irritable were common across the five studies. A respiratory or lung cancer-specific cluster was identified across three of the five studies.[29 35 37] The number of symptoms ranged from four to nine. Shortness of breath, difficulty breathing and cough were common across the three studies.

Table 2 Quality assessment by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institute of Health Quality Assessment Tool for Observational and Cross-sectional Studies

Author(s), year	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Final quality
Cross-sectional studies (n=13)															
Chen *et al*, 2021[38]	Y	Y	NR	Y	N	Y	CD	NA	Y	N	Y	NA	NA	NA	Fair
Cherwin and Perkhounkova, 2017[32]	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	NA	NA	NA	Good
Chongkham-ang *et al*, 2018[40]	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	Y	NA	NA	NA	Good
Han *et al*, 2019[33]	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	NA	NA	NA	Good
Li *et al*, 2019[34]	Y	Y	NR	Y	N	Y	Y	NA	Y	N	Y	NA	NA	NA	Good
Matzka *et al*, 2018[42]	Y	Y	NR	Y	N	Y	CD	NA	Y	N	Y	NA	NA	NA	Fair
Papachristou *et al*, 2019[29]	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	NA	NA	NA	Good
Pozzar *et al*, 2021[35]	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	NA	NA	NA	Good
Ren *et al*, 2017[39]	Y	Y	Y	Y	N	CD	CD	NA	Y	N	Y	NA	NA	NA	Fair
Sezgin and Bektas, 2020[43]	Y	Y	NR	Y	Y	Y	CD	NA	Y	N	Y	NA	NA	NA	Fair
Sullivan *et al*, 2017[36]	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	NA	NA	NA	Good
Vuttanon *et al*, 2019[41]	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	Y	NA	NA	NA	Good
Wong *et al*, 2017[37]	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	NA	NA	NA	Good
Longitudinal studies (n=10)															
Albusoul *et al*, 2017[45]	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	Y	NA	Good
Berger *et al*, 2020[46]	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	Y	NA	Good
Browall *et al*, 2017[51]	Y	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	NA	NR	NA	Good
Han *et al*, 2019[33]	Y	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	NA	NR	NA	Good
Kim, 2018[54]	Y	Y	NR	Y	N	Y	Y	NA	Y	Y	Y	NA	Y	NA	Good
Li *et al*, 2020[48]	Y	Y	NR	Y	N	Y	Y	NA	Y	Y	Y	NA	N	NA	Good
Lin *et al*, 2019[53]	Y	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	NA	N	NA	Good
Russell *et al*, 2019[49]	Y	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	NA	NR	NA	Good
Sullivan *et al*, 2018[11]	Y	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	NA	NR	NA	Good
Wiggenraad *et al*, 2020[52]	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	N	NA	Good

Study methodological quality ratings: good, fair and poor.

NHLBI of the National Institute of Health Quality Assessment Tool for Observational and Cross-Sectional Studies Criteria: item 1 (clear research question); item 2 (define study population); item 3 (participation rate at least 50%); item 4 (uniform eligibility criteria); item 5 (sample size justification); item 6 (exposure assessed prior to outcome measurement); item 7 (sufficient timeframe to see an effect); item 8 (examine different levels of exposure); item 9 (clearly defined exposure measures); item 10 (exposure assessed more than once over time); item 11 (clearly defined outcome measures); item 12 (outcome assessors were blinded to exposure status of participants); item 13 (loss to follow-up less than 20%); item 14 (key confounding variables measured and adjusted statistically)

CD, cannot determine; NA, not applicable; n, no; NR, not reported; Y, yes.

A nutritional or weight change cluster was identified across all five studies.[29 33 35–37] The number of symptoms ranged from two to seven. While no common symptoms were identified across the five studies, increased appetite,[29 33 35 37] weight gain,[29 33 35 37] and weight loss[29 35–37] were found in four of them. A gastrointestinal cluster was identified in three studies.[33 35 36] However, no common symptoms were identified across the three studies.

Severity

Ten studies used severity to evaluate for clusters.[29 33–37 39–41 43] Of the eight studies that named the clusters, all identified a psychological cluster (ie, emotion-related, psychological, psychourinary).[29 33–37 39 40] The number of symptoms ranged from two to nine. Feeling sad, sadness, or depression was the only symptom that was identified across all of the studies.

Six studies identified a cluster related to nutritional status or weight (ie, nutritional, weight, weight change).[29 33–37] The number of symptoms ranged from two to six. While no symptoms were common across all six studies, weight loss[29 34–37] and weight gain[29 33 35–37] were each identified in five of them.

A gastrointestinal or gastrointestinal and energy related cluster was identified in five of the eight studies.[33 34 36 39 40] The number of symptoms ranged from two to eight. While no symptoms were common across all of the studies, nausea was identified in four of the five studies.[33 34 39 40]

Distress

Eight studies evaluated for clusters using the distress dimension.[29 32 33 35 38 40 42 43] Similar to occurrence and severity, a type of psychological cluster (ie, anxiety and depression, emotion, energy and pain related, emotions, psychological, psychological/gastrointestinal) was identified in seven of the studies that named the clusters.[29 32 33 35 38 40 42] The symptoms within this cluster ranged from three to 12. Feeling nervous or anxious and feeling sad or depressed mood were common symptoms across all seven studies.

Five studies identified a type of nutritional cluster (ie, appetite, nutritional, nutrition impaired, weight change).[29 32 33 35 38] The symptoms ranged from two to seven. Lack of appetite was common across four of the five studies.[29 32 35 38]

Multiple dimensions

Seven studies evaluated for differences in clusters across two or more symptom dimensions.[29 33 35–37 40 43] Of the six studies that named the clusters,[29 33 35–37 40] a type of psychological cluster (ie, emotion related, emotion, energy and pain related, psychological/gastrointestinal, psychological) was common across all six studies and dimensions. Feeling irritable, feeling nervous, feeling sad, and worrying were the common symptoms across the six studies and dimensions.

A type of nutritional cluster (ie, nutritional, image and nutrition, discomfort and nutrition, weight change) was identified across all six studies and dimensions. Weight loss was the common symptom across all symptom dimensions in five of the six studies.[29 35–37 40]

Evaluation of the stability of symptom clusters across symptom dimensions

Of the six studies that named the clusters and evaluated for clusters using two or more dimensions,[29 33 35–37 40] all of them evaluated the stability of the clusters across dimensions. Five studies[33 35–37 40] used the method described by Kirkova and Walsh.[44] The sixth study[29] evaluated for stability through visualisation of differences in the network's structures.

Analysis of secondary outcomes

In the four studies that evaluated for associations between clusters and other PROs,[32 38 39 42] all of them used QOL. In addition, one evaluated for associations with patients' functional status.[38] None of the cross-sectional studies evaluated for associations between symptom clusters and biological mechanisms.

Longitudinal study results

Study characteristics

Of the 23 studies included in this review, 10 used a longitudinal design to evaluate for symptom clusters in oncology patients receiving chemotherapy (online supplemental table 2). Six studies were conducted in the USA,[45–50] two in Sweden,[51 52] one in China,[53] and one in South Korea.[54] Sample sizes ranged from 51[54] to 540.[50] Across these studies, the majority of the patients were female (weighted grand mean 84.4%), currently employed, had a weighted grand mean age of 55.1 years, and were relatively homogeneous in terms of ethnicity and race.

Only one study evaluated for symptom clusters in a sample of patients with heterogeneous cancer diagnoses.[47] Of the nine studies that evaluated for clusters in patients with homogeneous diagnoses, six evaluated patients with breast cancer,[45 46 48 50–52] one with acute myelogenous leukaemia,[53] one with brain cancer,[54] and one with lung cancer.[49]

Symptom instrument(s)

In terms of the instruments, seven of the 10 studies used the MSAS.[47 49–54] Of these seven studies, three used a modified version of the MSAS.[47 49 50] Two studies used the Hospital Anxiety and Depression Scale, the Symptom Experience Scale, and the Medical Outcomes Study Short-Form Survey v2.[45 46] One study used the Breast Cancer Prevention Trial Symptom Checklist, the Beck Depression Inventory-II, the Brief Pain Inventory, the Patient's Assessment of Own Functioning, and the Profile of Mood States.[48]

Statistical approach

In terms of the statistical methods, eight of the 10 studies used EFA.[45–50 53 54] The remaining two studies used PCA.[51 52]

Symptom dimension(s)

In terms of the symptom dimension(s), four studies used only the severity dimension.[45 46 48 54] While two studies evaluated for clusters using both occurrence and severity,[49 50] two used occurrence, severity, and distress.[47 53] The remaining two studies created a symptom burden score (ie, the average of the frequency, severity, and distress scores for each symptom on the MSAS).[51 52]

Occurrence

Four studies used occurrence to identify clusters across three timepoints.[47 49 50 53] For three of these studies,[47 49 50] these timepoints were: approximately one week before the second or third cycle of chemotherapy (T1), approximately one week after chemotherapy administration (T2), and approximately two weeks after chemotherapy administration (T3). For the fourth study,[53] these timepoints were: within six days of the start of induction chemotherapy (T1a), one to seven days during induction chemotherapy (T2a), and one to seven days after induction chemotherapy (T3a).

A psychological cluster was identified across all four studies and all three timepoints, except for one study where the cluster was not identified until T2a.[53] Feeling nervous and feeling sad were common across each study and timepoint. In addition, difficulty concentrating, feeling irritable, and worrying were common to the three studies that identified a psychological cluster at T1.[47 49 50] Across these four studies, the symptoms within this cluster remained relatively consistent across time.

While a nutritional or weight change cluster was identified across all four studies, it was not identified at each timepoint. For three of the studies,[47 49 50] lack of appetite was present at T2 and lack of appetite and weight gain were present at T3. Except for one study,[53] the symptoms identified within this cluster were relatively consistent across timepoints within each study.

While an epithelial, epithelial/gastrointestinal, or body image cluster was identified across all four studies, it was not identified at each timepoint and the symptoms within this cluster changed over time. Hair loss was identified at T2 in three studies.[47 49 50] Itching was identified at T3 and T3a in three studies.[47 50 53] Changes in skin was identified across all four studies at T3 and T3a.[47 49 50 53]

A gastrointestinal cluster was identified across three studies at one or more timepoints.[47 50 53] However, this cluster was not identified at each timepoint and no common symptoms were consistent across each of the three studies. Abdominal cramps appeared across two of the studies that identified this cluster at T1.[47 50]

Severity

Eight studies used severity to identify clusters across three or four timepoints.[45–50 53 54] Of the two studies that evaluated for clusters over four timepoints, one evaluated for clusters throughout all cycles of chemotherapy (ie, prior to the first cycle to post-chemotherapy)[45] and the other evaluated for clusters from prior to and at 18 months post-chemotherapy.[48] Five of the remaining six studies evaluated for clusters over three timepoints around the receipt of active treatment (eg, prior to and post-chemotherapy).[47 49 50 53 54] The sixth study evaluated for clusters after the completion of chemotherapy (ie, prior to chemotherapy to one year after initial chemotherapy treatment).[46]

While no single cluster was common across the eight studies, a gastrointestinal cluster was identified across seven of them.[45–48 50 53 54] This cluster was not identified across all timepoints and no common symptoms were identified. In addition, a type of psychological cluster (ie, negative emotion, negative emotion and decreased vitality, psychological, psychoneurocognitive) was identified in six of the eight studies.[47–50 53 54] This cluster was not identified across all of the timepoints. However, when the cluster was identified, feeling sad or depression was consistent across all of the studies.

Distress

Only two studies evaluated for clusters using distress across three timepoints.[47 53] A psychological cluster was identified across both studies and at two of the three timepoints. Across these timepoints, feeling nervous and feeling sad were consistent. While an epithelial or body image cluster was identified across both studies, it was not present across all three timepoints. When the cluster did occur, itching was identified across both studies and timepoints.

Burden score

In the two studies that used a symptom burden score to identify clusters, one evaluated for clusters over four timepoints across multiple cycles of chemotherapy[51] and the other evaluated for clusters over three timepoints prior to the start of the second cycle of chemotherapy to 12 months post cycle two.[52] An emotional cluster was identified across both studies and timepoints. Feeling sad was common across both studies and all timepoints. While a physical cluster was identified across both studies and timepoints, no common symptoms were identified.

Multiple dimensions

Four studies evaluated for clusters using two or more dimensions over three timepoints.[47 49 50 53] In three of these studies,[47 49 50] a psychological cluster was

identified across all of these studies, dimensions and timepoints. In the fourth study,[53] this cluster occurred with some variability across timepoints and dimensions. Feeling nervous and feeling sad occurred consistently across studies, dimensions, and timepoints.

While an epithelial, epithelial/gastrointestinal, or body image cluster was identified across all four studies, it was not stable across dimensions or timepoints. Only changes in skin appeared across dimensions and studies at the third timepoint (ie, two weeks postcycle two or three, one to seven days after induction).[47 49 50 53] In addition, gastrointestinal and nutritional or weight change clusters were identified across three of the four studies.[47 50 53] No common symptoms were identified consistently across studies, dimensions and/or timepoints for either cluster.

Evaluation of the stability of symptom clusters across symptom dimensions and/or timepoints

Six studies[47–50 53 54] used the method described by Kirkova and Walsh[44] to evaluate the stability of symptom clusters across dimensions and timepoints. Two studies[45 46] relied on an investigator's appraisal of the stability. The remaining two studies[51 52] did not report on a method to evaluate stability.

Analysis of secondary outcome(s)

In the only longitudinal study that evaluated for associations between symptom clusters and a PRO,[46] measures of QOL were used. In the only study that evaluated for associations between symptom clusters and biological mechanisms,[54] levels of lipid peroxidation were examined in patients with primary brain tumours.

DISCUSSION

This systematic review evaluated the progress of symptom clusters research in adult patients receiving primary or adjuvant chemotherapy from 2017 through 2021. Given the relative infancy of symptom cluster research, this type of ongoing review and synthesis is needed to advance this area of scientific inquiry. This discussion focuses on how the science has evolved since the previous review.[11]

Symptom assessment instruments

The MSAS was the most common instrument used in 69.6% of the studies. While it was found to be one of the most commonly used instruments in the previous review,[11] its use grew from 26.3% to 69.6%. This growth may be due to the multiple strengths of the MSAS. First, because it evaluates 32 common symptoms, it is cited as one of the most comprehensive instruments to use in research and clinical practice.[55] In addition, the MSAS evaluates multiple dimensions of the symptom experience (ie, occurrence, severity, frequency, distress); has well established validity and reliability;[56] and is available in more than eight languages (eg, Arabic,[57] Chinese,[58] Spanish[59]).

In contrast with the previous review that noted that the MDASI was used in 26.3% of the studies,[11] it was used in only 4.3% of the studies in this review. This change may be due to a shift among researchers to use more comprehensive symptom instruments. Instruments like the MDASI (13 symptoms) and the Edmonton Symptom Assessment Scale (nine symptoms) are limited because they assess a relatively small number of symptoms using only severity ratings. Given that oncology patients receiving active treatment report an average of 13 unrelieved symptoms,[2] and the optimal symptom dimension to evaluate for symptom clusters has yet to be determined, use of a comprehensive, multidimensional instrument is warranted.

Statistical approaches

EFA was the most common method used in 73.9% of the studies,[32–37 39 41 42 45–50 53 54] followed by PCA in 17.4%.[38 40 51 52] These findings are consistent with the previous review that reported that 68.4% of the studies used a factor analytic approach.[11] Given that one conceptual basis for the use of EFA is that symptoms cluster together because they share common underlying mechanism(s),[22 60] EFA is preferred over HCA or PCA.

One of the key strengths of EFA is that it allows symptoms to load on more than one factor. As a result, the authors of the previous review recommended that the most common symptoms that load on more than one cluster be identified.[11] Of the studies that used EFA, 10 allowed for symptoms to load on multiple factors.[33 35–37 42 46 47 49 50 53] While the symptoms that loaded on more than one factor were not specified in most studies, in the two studies that evaluated for symptom clusters in patients with lung cancer,[37 49] difficulty concentrating, feeling nervous, feeling sad, swelling of the arms and legs, and worrying cross-loaded on multiple clusters. For the four studies that evaluated for clusters in patients with breast cancer,[36 46 50 53] change in the way food tastes cross-loaded in three studies[36 50 53] and difficulty concentrating cross-loaded in two.[46 53]

Symptom dimensions

While severity was the most common dimension used to create the clusters (78.3%),[29 33–37 39–41 43 45–50 53 54] 43.5% used distress,[29 32 33 35 38 40 42 43 47 53] 39.1% used occurrence,[29 33 35–37 47 49 50 53] 8.7% used a burden score,[51 52] and 4.3% used frequency.[43] Only 47.8% of the studies evaluated for symptom clusters using two or more symptom dimensions.[29 33 35–37 40 43 47 49 50 53]

Among the 10 studies that evaluated for clusters using two or more dimensions and named the clusters,[29 33 35–37 40 47 49 50 53] psychological and nutritional clusters were the two common clusters identified across all of the studies and dimensions. However, none of the

symptoms within these clusters were consistent across studies. This finding may be partially explained by the variability in cancer diagnoses across the studies. In the previous review,[11] the authors were unable to compare the number and types of clusters identified across dimensions due to the fact that only 15.8% (n=3) of the studies used two or more dimensions. The growth in the number of studies from 15.8% to 47.8% may be a result of multiple reports recommending that research be done on the stability of symptom clusters across the different dimensions.[9–11]

Number and types of symptom clusters

Across the 23 studies included in this review, the number of clusters identified ranged from two to eight. A psychological cluster was the most common cluster identified in 82.6% of the 23 studies in this review.[29 32–40 42 47–54] Similar to the previous review,[11] feeling sad or depressed was common across 18 of the 19 studies, while feeling anxious or nervous was common across 16.

Consistent with the previous review,[11] a gastrointestinal cluster was another common cluster identified in 69.6% of the studies.[29 33–36 39 40 42 45–48 50 51 53 54] Nausea was the most common symptom in this cluster that occurred in 13 of the 16 studies, followed by diarrhoea in eight. This finding is similar to the previous review[11] that identified nausea as one of the most common symptoms across 10 of the 13 studies.

In a departure from the previous review that identified a nutrition or nutritional cluster in only 15.8% of the studies,[11] a nutritional or weight change cluster was identified across 56.5% of the studies in this review.[29 32–38 47–50 53] Lack of appetite was the most common symptom in 12 of the 13 studies,[29 32 34–38 47–50 53] followed by weight loss in 11.[29 34–38 47–50 53]

The emergence of a nutritional or weight cluster may be due to the inclusion of an increased number of symptoms related to these two problems. For example, in nine of the 13 studies that identified a nutritional or weight change cluster, the MSAS was modified to include additional symptoms (eg, abdominal cramps, increased appetite, weight gain).[29 32 33 35–37 47 49 50] Weight gain was common across nine studies[29 33 35–37 47–50] and increased appetite was common across six.[29 33 35 37 47 49] Additional research is needed to determine the optimal number, as well as the most common and disease and treatment-specific symptoms, to assess in order to obtain more specific and mechanistically based symptom clusters.

In factor analytic methods, factor loading scores are standardised partial regression coefficients that provide an estimate of the strength of the association between a variable (ie, symptom) and a factor (ie, symptom cluster) while controlling for the impact of other factors.[25] This score is used to determine which symptoms load on which factors using a predetermined cut-off that indicates a meaningful relationship. While factor loadings of ≥0.30 or ≥0.40 are commonly accepted,[61] it is not clear what the optimal minimum factor loading score should be to include a symptom within a cluster.

In this review, ≥0.40 was the most common minimum factor loading score (n=11),[33 34 36–38 40 47–50 53] followed by ≥0.30 (n=3),[35 45 46] and ≥0.50 (n=1).[52] Of note, seven studies did not report this score. In the studies that used a minimum factor loading score of 0.40, two to eight symptom clusters were identified. While no clear pattern emerged in terms of sample size, this wide gap may be due to differences in the instruments used (eg, disease specific vs cancer specific); the type of treatment (eg, adjuvant vs induction chemotherapy); or the timing of the symptom assessments (eg, during chemotherapy, post-chemotherapy). Two of the three studies that used a factor loading of 0.30 identified only two clusters (n=219,[45] n=219[46]) and the third identified five (n=232).[35] This difference may be due to the fact that two of these studies[45 46] used only 10 symptoms to evaluate for clusters.

Unique symptom clusters

While it is important to identify which clusters are consistent across cancer types and treatments, it is equally important to identify clusters that are unique to a specific cancer and/or treatment. A hormonal or vasomotor cluster was identified in 26.1% of the studies.[29 34–36 48 50] Of note, four of these studies evaluated for clusters in women with breast cancer[34 36 48 50] and one in women with a gynaecological cancer.[35] In the sixth study,[29] the majority of women had either breast (40.2%) or gynaecological cancer (17.3%)

Changes in symptom clusters over time

Ten studies evaluated for changes in clusters over three[46 47 49 50 52–54] or four timepoints.[45 48 51] While three studies evaluated for clusters beyond the completion of chemotherapy (eg, six months post-chemotherapy),[46 48 52] the other seven studies evaluated for clusters around and during active treatment.[45 47 49–51 53 54] Of these studies, six reported a psychological or emotional cluster that remained relatively stable over time.[47–52] In contrast, six studies identified a gastrointestinal cluster that varied over time.[45–48 51 53]

Methods to evaluate the stability of symptom clusters across dimensions and/or over time

Stability was evaluated using the method proposed by Kirkova and Walsh[44] in 81.1% of the studies that evaluated for differences in symptom clusters across two or more dimensions,[33 35–37 40 47 49 50 53] and in 60% of the longitudinal studies[47–50 53 54] that evaluated for the stability across dimensions and timepoints. The method proposed by Kirkova and Walsh[44] specifies that 75% of the symptoms in a cluster should be in agreement in order for a symptom cluster to

be stable across timepoints or dimensions. In addition, the most 'prominent or important symptom(s)' needs to be present.[44] (p. 1012) While the majority of studies that evaluated for stability of symptom clusters across dimensions or time used Kirkova and Walsh's method, the criteria were applied with relative subjectivity (eg, described clusters as 'relatively stable'[50] (p. 47); described symptoms within clusters as 'relatively stable'[53] (p. 787)).

This subjectivity may be due in part to a lack of clarity and consensus on the definition of 'stability'. Similar to Kirkova and Walsh,[44] in their definition of a symptom cluster, Kim and colleagues[13] used stability as a characteristic to describe the group of symptoms within the cluster. In contrast, other researchers have described stability in terms of the type of cluster that is identified. Skerman and colleagues[22] suggested that for a cluster to be stable, it must be 'reproducible' (ie, replicated in a similar sample) or appear reliably over time. Barsevick[12] went further to describe stability as how consistently clusters appeared across statistical methods, within homogeneous populations, or over time. From these descriptions, it is unclear if stability refers to the the stability of a specific cluster itself (eg, gastrointestinal, nutritional) across time and/or symptom dimensions, or the symptoms within the cluster. Adding to this confusion, only one of these reports provided criteria to evaluate stability.[44]

Building on Barsevick's description, we suggest that the term *stability* should be used to describe whether or not the same clusters are identified across study samples, dimensions and/or over time. While *consistency* should be used to describe whether the symptoms within a cluster remain the same across these conditions. The use of separate terms to describe these characteristics of symptom clusters may provide clarity and move the science forward. In addition, consensus on how stability is used in the definition of a symptom cluster research warrants consideration.

Secondary outcomes and biomarker evaluation

Of the five studies that evaluated for associations between symptom clusters and other PROs,[32 38 39 42 46] all used measures of QOL. In addition, Chen and colleagues[38] examined the relationships between symptom clusters and functional performance. Cherwin and Perkhounkova[32] examined how symptom clusters impact symptom interference with daily life and QOL. Of the 23 studies included in this review, only one[54] evaluated for associations between symptom clusters and a biological mechanism.

Limitations

Despite the strict criteria that were employed to ensure a comprehensive review of the literature, only one author made the initial study selection and only two authors did the data extraction. Therefore, it is possible that some studies and/or information were missed. Because the majority of the studies in this review included patients who were homogeneous in terms of gender, race, ethnicity, and cancer diagnosis, our findings may not generalise to all patients with cancer. In addition, because this review focused on adults with stage I to III cancer, our findings may not generalise to patients with advanced cancer or cancer survivors. Finally, 34.8% of the studies came from a single, large study of patients undergoing chemotherapy and may influence the findings of this review.

CONCLUSIONS

This review highlighted numerous areas of growth within symptom clusters research, and identified multiple areas that warrant consideration. One ongoing issue in symptom cluster research is the lack of consistent methods for naming the clusters. In 2016,[10] Miaskowski stressed that a standardised nomenclature needed to be developed in order to facilitate comparisons of clusters across studies. However, as demonstrated in this review, a large amount of variability exists in how clusters were named. For example, the psychological cluster had 10 different names. In addition, researchers must name their clusters to allow for comparisons. In this review, symptom clusters were unnamed in 8.7% of the studies[41 43] compared with 26.3% in the previous review.[11]

We identified only one study that evaluated for symptom clusters using NA.[29] An advantage of NA is that it allows for an examination of the strengths of the relationships among the symptoms within a cluster and how symptom clusters relate to each other within the network. Additional research using NA is needed to explore the inter-relationships among symptoms within clusters and whether these relationships differ based on the dimension used.

One of the aims of this review was to describe associations between symptom clusters and biological mechanisms. Of the 23 studies included in this review, only one study evaluated for associations between symptom clusters and a biological mechanism.[54] Investigation of the mechanisms that underlie symptoms and symptom clusters is a key priority set by the National Institute of Nursing Research.[62] Future research needs to incorporate the evaluation of biological mechanisms that may underlie symptom clusters in order to better understand why these symptoms cluster and to develop interventions to target clusters of symptoms rather than single symptoms.

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Supplemental Table 1. Cross-sectional studies of symptom clusters in samples of patients who received chemotherapy

Author, year, purpose and design	Sample size, patient characteristics, time of symptom assessment	Symptom assessment instrument(s); number of symptoms on instrument; statistical analysis method; symptom dimension(s) used to create symptom clusters; analysis of additional outcomes	Number of symptom clusters, specific symptoms within each cluster Evaluation of additional outcomes	Strengths and Limitations
Chen et al., 2021 Purpose(s): Identify the symptom clusters of adult patients with acute leukemia undergoing chemotherapy Analyze the relationship between the symptom clusters and functional performance and QOL Design: cross-sectional Location: China	*n* = 132 Mean age: 39.2 (±13) years Range: NR Female: 58.3% Ethnicity: NR Race: NR Employment status: Working 27.3% Not working 72.7% Inpatients: *n* = 132 Outpatients: *n* = 0 Diagnosis: AML 53.0% ALL 47.0% Treatment: CTX 100.0%	Instrument(s): Chinese version of the Condensed MSAS: 14 symptoms Criteria used to exclude symptoms: Yes Analysis: PCA Dimension(s): Distress Symptoms allowed to load on more than one factor: No Minimum factor loadings required to include symptom within cluster: 0.40	4 symptom clusters identified: Psychological cluster: feeling nervous, worrying, feeling sad Nutrition-impaired cluster: weight loss, nausea, lack of appetite, shortness of breath, feeling drowsy, difficulty concentrating Pain-fatigue-sleep cluster: pain, lack of energy, difficulty sleeping Dry mouth-constipation cluster: constipation, dry mouth	Strengths: Evaluated for associations between symptom cluster factor scores and other patient reported outcomes Evaluated for symptom clusters in patients with hematologic cancers Used a valid and reliable symptom inventory Limitations: Cross-sectional study design

	Time of symptom assessment: Not specified	Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: NA Analysis of secondary outcomes: Functional performance status assessed with the Barthel ADL Index QOL assessed with the FACT-Leukemia version 4	Additional outcomes: ADL score was negatively correlated with the psychological, nutrition-impaired, and pain-fatigue-sleep symptom clusters Total QOL score was negatively correlated with the psychological, nutrition-impaired, and pain-fatigue-sleep symptom clusters	Relatively small sample size Lack of consistent timepoint for symptom assessment Recruited patients from only one hospital Used only a single dimension to evaluate for symptom clusters
Cherwin & Perkhounkova, 2017 Purpose(s): Describe GI symptom clusters based on symptom distress using a GI comprehensive symptom assessment Explore how distress-based GI symptom clusters impact symptom	*n* = 105 Mean age: 56.7 (±15.3) years Range: 18-86 years Female: 43.8% Ethnicity: Non-Hispanic or Latino 95.2% Hispanic or Latino 1.0% Missing 3.8% Race: White 96.2% Black or African American 1.0% Asian 1.0% America Indian or Alaskan Native	Instrument(s): MSAS (modified): 41 symptoms; 30 clinically relevant symptoms used in the analysis Criteria used to exclude symptoms: Yes Analysis: EFA Dimension(s): distress Symptoms allowed to load on more than one factor: No	6 symptom clusters identified: Image cluster: image change, skin change Fatigue cluster: feeling drowsy, lack of energy, shortness of breath, feeling dizzy Emotions cluster: difficulty concentrating, feeling nervous, feeling sad,	Strengths: Used symptom distress to create symptom clusters Evaluated for associations between symptom cluster factor scores and other patient reported outcomes Evaluated symptom clusters in patients with types of hematologic cancers

interference with daily life and QOL Design: cross-sectional Location: United States	1.0% Missing 1.6% Employment status: NR Inpatients: NR Outpatients: NR Diagnosis: Lymphoma 83.8% Leukemia 10.5% Leukemia & lymphoma 3.8% Myelodysplastic syndrome 1.9% Type of treatment: Standard CTX 88.6% Reduced CTX 11.4% Time of symptom assessment: Day 7 of CTX	Minimum factor loadings required to include symptom within cluster: NR Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: NR Analysis of additional outcomes: Symptom Interference Subscale of the MDASI Fox Simple QOL Scale	hair loss, swelling of arms or legs Bloating cluster: belching, feeling bloated, diaphoresis Worry cluster: worrying, numbness Appetite cluster: lack of appetite, nausea, taste changes Additional outcomes: Compared to no distress, patients with mild or greater than mild bloating symptom distress scores were significantly more likely to report greater symptom interference Relationship between appetite symptom distress scores and symptom interference was moderated by CTX emetogenicity Compared to no distress, patients with greater than mild	Used a valid and reliable symptom inventory Limitations: Cross-sectional design Relatively small sample size Primarily a non-Hispanic, Caucasian sample Used only a single dimension to evaluate for symptom clusters

			appetite symptom distress scores were significantly more likely to report lower QOL	
Chongkham-ang, et al., 2018 Purpose(s): Evaluate the occurrence, frequency, severity, and distress of multiple symptoms in Thai women with breast cancer receiving CTX Evaluate for similarities in symptom clusters that were identified based on ratings of severity and distress Design: cross-sectional Location: Thailand	*n* = 322 Mean age: 52.0 (±9.2) years Range: 41-60 years Female: 100.0% Ethnicity: Thai 100.0% Race: NR Employment status: Farmers 28.9% Inpatients: *n* = 0 Outpatients: *n* = 322 Diagnosis: Breast cancer = 100.0% Type of treatment: CTX 100.0% Time of symptom assessment: Day 7 after CTX	Instrument(s): Thai-MSAS: 32 symptoms Criteria used to exclude symptoms: Yes Analysis: PCA Dimension(s): severity, distress Symptoms allowed to load on more than one factor: No Minimum factor loadings required to include symptom within cluster: 0.40 Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: Yes Analysis of additional outcomes: N/A	4 symptom clusters identified using severity: Emotion-related cluster: worrying, feeling sad, feeling nervous, feeling irritable, difficulty sleeping, difficulty concentrating, feeling drowsy, sweats GI and energy related cluster: nausea, vomiting, difficulty swallowing, feeling bloated, dizziness, lack of energy, shortness of breath, lack of appetite Image and nutrition related cluster: changes in skin, hair loss, “I don’t look like myself,” mouth sores, change in the way food tastes, weight	Strengths: Recruited patients from eight different hospitals Relatively large sample size Utilized a valid and reliable symptom assessment instrument Symptom clusters were created using two dimensions of the symptom experience Limitations: Cross-sectional design Recruited outpatients from only one region (Northern Thailand)

			loss, constipation, dry mouth <u>Pain and discomfort related cluster</u>: pain, numbness/tingling in hands/feet, itching, problems with urination, cough 4 symptom clusters identified using symptom distress: <u>Emotion, energy, and pain related cluster</u>: worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, difficulty concentrating, lack of energy, feeling drowsy, pain, numbness/tingling in hands/feet, shortness of breath, sweats <u>GI related cluster</u>: nausea, vomiting, difficulty swallowing, lack of appetite, dizziness <u>Image related cluster</u>: "I don't look like	

			myself," changes in skin, hair loss Discomfort, nutrition, and elimination related cluster: itching, mouth sores, constipation, dry mouth, problems with urination, weight loss, cough, feeling bloated, change in the way food tastes Evaluation of additional outcomes: N/A	
Han et al., 2019 Purpose(s): Describe the occurrence, severity, and distress of 38 symptoms Identify whether the number and types of symptom clusters differed based on the symptom dimensions used to create the clusters Design: cross-sectional	*n* = 339 Mean age: 57.9 (±11.8) years Range: NR Female: 45.1% Ethnicity and Race: White 68.7% Black 9.0% Asian or Pacific Islander 11.5% Hispanic, Mixed, or other 10.8% Employment status: Working 33.3% Not working 66.7% Inpatients: *n* = 0 Outpatients: *n* = 399	Instrument(s): MSAS (modified): 38 symptoms Criteria used to exclude symptoms: Yes Analysis: EFA Dimension(s): occurrence, severity, distress Symptoms allowed to load on more than one factor: Yes	4 symptom clusters identified across each symptom dimension: *Occurrence symptom clusters* Psychological cluster: lack of energy, difficulty concentrating, feeling nervous, feeling drowsy, feeling sad, worrying, feeling irritable, changes in skin CTX-related cluster: dry mouth, nausea,	Strengths: Symptom clusters were created using multiple dimensions of the symptom experience Evaluated symptom clusters in patients with types of gastrointestinal cancers Utilized a valid and reliable symptom inventory Limitations:

Location: United States	Diagnosis: Colon 46.4% Rectal 20.1% Pancreatic 18.5% Esophageal 5.3% Gastric 4.8% Gallbladder/bile duct 2.5% Liver 1.5% Small intestine 1.5% Anal 1.3% Other 6.3% Treatment: Adjuvant CTX 91.5% Neoadjuvant CTX 8.5% Time of symptom assessment: Within 7 days prior to start of 2nd or 3rd cycle of CTX	Minimum factor loadings required to include symptom within cluster: 0.40 Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: Yes Analysis of additional outcomes: N/A	itching, lack of appetite, weight loss, change in the way food tastes, changes in skin, dizziness GI cluster: feeling bloated, abdominal cramps, constipation Weight change cluster: Increased appetite, weight gain *Severity symptom clusters* Psychological cluster: lack of energy, difficulty concentrating, feeling nervous, feeling drowsy, feeling sad, worrying, feeling irritable, problems with sexual interest or activity CTX-related cluster: dizziness, weight loss, lack of appetite, itching, hair loss, change in the way food tastes, “I don’t look like myself,” changes in skin	Cross-sectional design Heterogeneity in types of GI cancers

			GI cluster: nausea, feeling bloated, diarrhea, abdominal cramps Weight change cluster: increased appetite, weight gain *Distress symptom clusters* Psychological cluster: difficulty concentrating, feeling nervous, feeling sad, worrying, feeling irritable, lack of energy, feeling drowsy, difficulty sleeping, pain, sweats CTX-related cluster: dizziness, change in the way food tastes, lack of appetite, weight loss, itching, “I don’t look like myself,” changes in skin, hair loss Weight change cluster: increased appetite, weight gain	

			GI cluster: diarrhea, abdominal cramps Additional outcomes: N/A	
Li et al., 2019 Purpose(s): Examine and compare the differences in symptoms and symptom clusters between postmenopausal women with early stage breast cancer who did and did not receive chemotherapy prior to aromatase inhibitor therapy Design: cross-sectional Location: United States	Total sample: *n* = 339 CTX Group: *n* = 111 No CTX Group: *n* = 228 Mean age: Total sample: 61.2 (±6.2) years CTX Group: 59.3 (±5.5) years No CTX Group: 62.1 (6.3) years Range: NR Female: 100.0% Ethnicity: NR Race: White 96.5% Black 3.5% Employment status: Working 70.4% Not working 29.6% Inpatients: NR Outpatients: NR Diagnosis: Breast cancer 100.0% Treatment: CTX 32.7% No CTX 67.3	Instrument(s): Breast Cancer Prevention Trial Symptom Checklist: 42 symptoms Profile of Mood States: 2 symptoms (i.e., fatigue, anxiety) Brief Pain Inventory: 1 symptom Beck Depression Inventory-II: 2 symptoms (i.e., depression, changes in sleep pattern) Patient's Assessment of Own Functioning: 1 symptom Criteria used to exclude symptoms: Yes Analysis: EFA Dimension(s): severity Symptoms allowed to load on more than one factor: No	8 symptom clusters identified within the CTX Group: Cognitive cluster: difficulty concentrating, easily distracted, forgetfulness, perceived cognitive Musculoskeletal cluster: joint pain, general aches, muscle stiffness, general pain Psychological cluster: depression, anxiety, fatigue, avoidance of social affairs Urinary cluster: difficulty with bladder control when laughing or crying, difficulty with bladder control at other times	Strengths: Utilized valid and reliable symptom inventories Compared differences in the severity of symptom clusters between women who did or did not receive CTX prior to aromatase inhibitor therapy Limitations: Cross-sectional design Primarily a Caucasian sample Used a single dimension to evaluate for symptom clusters Relatively small sample size for the group that received CTX (Group 1)

	Time of symptom assessment: After completion of CTX but prior to start of aromatase inhibitory therapy	Minimum factor loadings required to include symptom within cluster: 0.40 Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: N/A Analysis of additional outcomes: N/A	Vasomotor cluster: hot flashes, night sweats Sexual cluster: pain with intercourse, vaginal dryness GI cluster: diarrhea, nausea Weight cluster: weight loss, decreased appetite 7 symptom clusters identified within the No CTX Group: Cognitive cluster: difficulty concentrating, easily distracted, forgetfulness, perceived cognitive Musculoskeletal cluster: joint pain, general aches, muscle stiffness, general pain, swelling of hands or feet Psychological cluster: depression, anxiety, fatigue, avoidance of	

			social affairs, change in sleep pattern Urinary cluster: difficulty with bladder control when laughing or crying, difficulty with bladder control at other times Vasomotor cluster: hot flashes, night sweats Sexual cluster: pain with intercourse, vaginal dryness Weight cluster: weight loss, decreased appetite Additional outcomes: N/A	
Matzka et al., 2018 Purpose(s): Identify symptom clusters in patients with cancer undergoing treatment Investigated which of the symptom clusters explained	*n* = 304 Mean age: 57.4 (±14.5) years Range: 18-88 years Female: 59.0% Ethnicity: NR Race: NR Employment status: NR	Instrument(s): German – Rotterdam Symptom Checklist: 30 symptoms Criteria used to exclude symptoms: NR Analysis: EFA Dimension(s): distress	4 symptom clusters identified: Fatigue and pain cluster: tiredness, lack of energy, low back pain, sore muscles, shortness of breath, depressed mood	Strengths: Used symptom distress to create symptom clusters Evaluated for associations between mean summated symptom scores for each symptom cluster

most of the variation in QOL in patients with cancer undergoing treatment while accounting for psychosocial resources Design: cross-sectional Location: Austria	Inpatients: NR Outpatients: NR Diagnosis: Lymphoid, hematopoietic, and related tissue 26.0% Breast 21.1% Digestive organs 17.8% Female genital organs 9.0% Respiratory and intrathoracic organs 6.0% Others 20.1% Type of treatment: CTX 75.0% Chemo-radiation 25.0% Time of symptom assessment: NR	Symptoms allowed to load on more than one factor: Yes Minimum factor loadings required to include symptom within cluster: NR Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: N/A Analysis of additional outcomes: German – Connor-Davidson Resilience Scale Multidimensional Scale of Perceived Social Support TSO	Anxiety and depression cluster: despairing about the future, anxiety, worrying, nervousness, tension, depressed mood, irritability Nausea and vomiting cluster: nausea, vomiting, lack of appetite Cancer therapy-related toxicity cluster: Sore mouth/pain when swallowing, tingling hands or feet, loss of hair, burning/sore eyes, difficulty concentrating, dry mouth Additional outcomes: The fatigue and pain, nausea and vomiting, and cancer therapy-related symptom clusters were each negatively associated with overall QOL Among patients with low TSO scores, the	and other patient reported outcomes Utilized a valid and reliable symptom inventory Limitations: Cross-sectional design Recruited patients from a single medical center Symptom clusters were created using a single dimension of the symptom experience Timing of symptom assessments were not specified Heterogeneity in the types of cancer diagnoses included in analysis Used only a single dimension to evaluate for symptom clusters

			nausea and vomiting and cancer therapy-related toxicity clusters were negatively associated with overall QOL Among patients with medium TSO scores, the anxiety and depression and nausea and vomiting clusters were negatively associated with overall QOL Among patients with high TSO scores, the fatigue and pain and cancer therapy-related toxicity clusters were negatively associated with overall QOL	
Papachristou et al., 2019 Purpose(s): Evaluate the relationships among 38 symptoms using Network Analysis Explore if network structures for occurrence,	*n* = 1328 Mean age: 57.2 (±12.4) years Range: NR Female: 77.7% Race or Ethnicity: White 69.5% Non-white 30.5% Employment status:	Instrument(s): MSAS (modified): 38 symptoms Criteria used to exclude symptoms: Yes Analysis: Network analysis	6 symptom clusters identified using symptom occurrence: Psychological cluster: difficulty sleeping, worrying, feeling sad, feeling irritable, feeling nervous, difficulty concentrating, lack of	Strengths: Symptom clusters were created using multiple dimensions of the symptom experience Utilized a valid and reliable symptom inventory

severity, and distress have different properties Design: cross-sectional Location: United States	Working 35.1% Not working 64.9% Inpatients: *n* = 0 Outpatients: *n* = 1328 Diagnosis: Breast 40.2% Gastrointestinal 30.7% Gynecological 17.3% Lung 11.8% Treatment: CTX 100.0% Time of symptom assessment: Within 7 days prior to start of 2nd or 3rd cycle of CTX	Dimension(s): occurrence, severity, distress Symptoms allowed to load on more than one factor: N/A Minimum factor loadings required to include symptom within cluster: N/A Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: Yes Analysis of additional outcomes: N/A	energy, feeling drowsy Hormonal cluster: sweats, hot flashes, problems with sexual interest/activity Respiratory cluster: shortness of breath, difficulty breathing, cough, chest tightness Nutritional cluster: weight gain, weight loss, increased appetite CTX-related cluster: itching, hair loss, changes in skin, I don't look like myself, change in the way food tastes, lack of appetite, mouth sores, difficulty swallowing, dry mouth, vomiting, nausea, dizziness, constipation Pain and abdominal cluster: diarrhea, abdominal cramps, feeling bloated,	Evaluated for symptom clusters using a new analytic method Limitations: Cross-sectional design Heterogeneity in types of cancers

			swelling of arms or legs, pain, numbness/tingling in hands/feet, problems with urination 5 symptom clusters identified using symptom severity: <u>Psychological cluster</u>: difficulty sleeping, worrying, feeling sad, feeling irritable, feeling nervous, difficulty concentrating, lack of energy, feeling drowsy, problems with sexual interest/activity <u>Hormonal cluster</u>: sweats, hot flashes <u>Respiratory cluster</u>: shortness of breath, difficulty breathing, cough, chest tightness <u>Nutritional cluster</u>: weight gain, weight loss, increased appetite, nausea,	

			vomiting, lack of appetite <u>CTX-related cluster</u>: itching, hair loss, changes in skin, I don't look like myself, change in the way food tastes, mouth sores, difficulty swallowing, dry mouth, dizziness, constipation, swelling of arms or legs, problems with urination, diarrhea, abdominal cramps, numbness/tingling in hands/feet, pain, feeling bloated 7 symptom clusters identified using symptom distress: <u>Psychological cluster</u>: difficulty sleeping, worrying, feeling sad, feeling irritable, feeling nervous, difficulty concentrating, problems with sexual interest/activity	

			Hormonal cluster: sweats, hot flashes Respiratory cluster: shortness of breath, difficulty breathing, cough, chest tightness Nutritional cluster: weight gain, weight loss, increased appetite, nausea, vomiting, lack of appetite, change in way food tastes CTX-related cluster: mouth sores, difficulty swallowing, dry mouth, dizziness, constipation, swelling of arms or legs, problems with urination, numbness/tingling in hands/feet, pain, lack of energy, feeling drowsy GI cluster: diarrhea, abdominal cramps, constipation, feeling bloated	

			Epithelial cluster: hair loss, I don't look like myself, itching, skin changes Additional outcomes: N/A	
Pozzar et al., 2021 Purpose(s): Describe ratings of symptom occurrence, severity, and distress for 38 symptoms in a sample of patients with gynecological cancer receiving CTX Identify and compare the number and types of symptom clusters identified using these ratings Design: cross-sectional Location: United States	*n* = 232 Mean age: 59.6 (±12.7) years Range: NR Female: 100.0% Ethnicity and Race: White 77.1% Black 3.5% Asian or Pacific Islander 8.8% Hispanic, Mixed, or other 10.6% Employment status: Working 31.0% Not working 69.0% Inpatients: *n* = 0 Outpatients: *n* = 232 Diagnosis: Ovarian/fallopian tube/primary peritoneal 65.4% Uterine (including endometrial) 32.9% Other 5.7% Treatment: Adjuvant CTX 100.0%	Instrument(s): MSAS (modified): 38 symptoms Criteria used to exclude symptoms: Yes Analysis: EFA Dimension(s): occurrence, severity, distress Symptoms allowed to load on more than one factor: Yes Minimum factor loadings required to include symptom within cluster: 0.30 Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints:	5 symptom clusters identified across each symptom dimension: *Occurrence symptom clusters* Hormonal cluster: sweats, hot flashes, problems with sexual interest or activity, abdominal cramps, difficulty concentrating, feeling irritable, feeling drowsy, pain, feeling bloated Respiratory cluster: difficulty breathing, shortness of breath, pain, cough, dry mouth, numbness/tingling in hands/feet, feeling bloated, dizziness, difficulty sleeping	Strengths: Symptom clusters were created using multiple dimensions of the symptom experience Evaluated symptom clusters in patients with gynecological cancers Utilized a valid and reliable symptom inventory Limitations: Cross-sectional design Heterogeneity in types of gynecological cancers

	Time of symptom assessment: Within 7 days prior to start of 2nd or 3rd cycle of CTX	Kirkova and Walsh, 2007 <u>Analysis of additional outcomes</u>: N/A	<u>Psychological cluster</u>: worrying, hair loss, feeling sad, "I don't look like myself", changes in skin, weight loss, change in the way food tastes, itching, lack of appetite, dizziness, feeling irritable, feeling nervous <u>GI cluster</u>: diarrhea, abdominal cramps, constipation, sweats, itching, hot flashes <u>Weight change cluster</u>: weight gain, increased appetite, lack of appetite, weight loss *Severity symptom clusters* <u>Hormonal cluster</u>: sweats, hot flashes, problems with sexual interest or activity, difficulty concentrating, pain <u>Respiratory cluster</u>: difficulty breathing, shortness of breath, pain, cough	

			Psychological cluster: worrying, feeling sad, feeling irritable, feeling nervous, abdominal cramps GI/epithelial cluster: lack of appetite, change in the way food tastes, weight loss, changes in skin, constipation, nausea, dizziness, itching, "I don't look like myself", hair loss Weight change cluster: weight gain, increased appetite, weight loss *Distress symptom clusters* Hormonal cluster: sweats, hot flashes, problems with sexual interest or activity, pain Respiratory cluster: difficulty breathing, shortness of breath, cough	

			Psychological/GI cluster: abdominal cramps, feeling sad, feeling bloated, worrying, feeling nervous, diarrhea, problems with sexual interest or activity, difficulty concentrating, feeling drowsy, constipation, feeling irritable, itching GI/epithelial cluster: lack of appetite, change in the way food tastes, changes in skin, nausea, dizziness, itching, "I don't look like myself", hair loss, dry mouth, feeling irritable Weight change cluster: weight gain, increased appetite, lack of appetite, weight loss, feeling bloated Additional outcomes: N/A	

Ren et al., 2017 Purpose(s): Describe symptom experiences and explore whether symptoms were clustered Explore the potential predictors of each symptom cluster Analyze the correlations between symptom clusters and QOL in bladder cancer patients three months after radical cystectomy with an ileal conduit or orthotopic neobladder reconstruction Design: cross-sectional Location: China	*n* = 99 Mean age: 61.9 (±9.6). Range: NR Female: 6.1% Ethnicity: NR Race: NR Employment status: NR Inpatients: NR Outpatients: NR Diagnosis: Histologically confirmed bladder cancer 100% Treatment: Adjuvant CTX 45.5% Time of symptom assessment: 3 months post radical cystectomy with an ileal conduit or orthotopic neobladder reconstruction	Instrument(s): Chinese - MDASI (modified): 15 symptoms Criteria used to exclude symptoms: No Analysis: EFA Dimension(s): severity Symptoms allowed to load on more than one factor: NR Minimum factor loadings required to include symptom within cluster: NR Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: N/A Analysis of secondary outcomes: Accordion Severity Grading System of surgical complications ASA score FACT-General	3 symptom clusters identified: Fatigue-malaise cluster: fatigue, drowsiness, pain, memory problems, loss of appetite GI cluster: Nausea, vomiting Psycho-urinary cluster: sleep disturbance, body image impairment, urinary dysfunction, sadness, distress Additional outcomes: Age, complication severity, plasma albumin level, orthotopic neobladder reconstruction, adjuvant CTX and ASA score significantly predicted fatigue-malaise distress CTX, orthotopic neobladder reconstruction, female gender, ASA	Strengths: Evaluated symptom clusters in patients with bladder cancer Utilized a valid and reliable symptom inventory Correlated symptom cluster factor scores with other patient outcomes Limitations: Cross-sectional design Small sample size Recruited patients from a single medical center Used only a single dimension to evaluate for symptom clusters

			score and albumin significantly predicted gastrointestinal distress Being unmarried, having a higher level of education, and higher complication severity level significantly predicted psycho-urinary distress Negative correlations were found between QOL and each symptom cluster factor score	
Sezgin & Bektas, 2020 Purpose(s): Determine the symptoms experienced by lymphoma patients Determine the symptom clusters of lymphoma patients Determine the functional status of lymphoma patients	*n* = 109 Mean age: NR Range: 19-84 years Female: 41.3% Ethnicity: NR Race: NR Employment status: Unemployed 74.3% Employed part-time 14.7% Employed full-time 11.0% Inpatients: *n* = 0	Instrument(s): Turkish MSAS: 32 symptoms Criteria used to exclude symptoms: No Analysis: HCA Dimension(s): frequency, severity, distress Symptoms allowed to load on more than one factor: No	3 symptom clusters identified across each symptom dimension: *Frequency symptom clusters* Main cluster I: nausea, vomiting, loss of appetite, dry mouth, fatigue or energy loss, pain Main cluster II: diarrhea, being/feeling sensitive, dizziness,	Strengths: Symptom clusters were created using multiple dimensions of the symptom experience Utilized a valid and reliable symptom inventory Evaluated symptom clusters in patients with lymphoma Limitations:

Determine the effect of symptoms on the functional status of lymphoma patients Design: cross-sectional Location: Turkey	Outpatients: *n* = 109 Diagnosis: Non-Hodgkin's lymphoma 73.4% Hodgkin's lymphoma 26.6% Treatment: CTX 100.0% Time of symptom assessment: NR	Minimum factor loadings required to include symptom within cluster: NR Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: NR Analysis of additional outcomes: N/A	difficulty in swallowing, difficulty in concentrating, difficulty in urinating, feeling swelled, feeling angry, problems with sexual desire and activity Main cluster III: feeling sad, worrying difficulty in sleeping, cough, shortness of breath, feeling sleepy or dizzy, sweating, numbness/tingling in hands or feet, itching *Severity symptom clusters* Main cluster I: mouth sores, changes in tasting foods, nausea, vomiting, weight loss, pain, fatigue or energy loss, sweating Main cluster II: constipation, swelling of arms or legs, changes in skin, dry mouth, feeling sad, worrying, feeling sleepy or dizzy,	Cross-sectional design Timing of symptom assessment was not reported Clusters were not named Did not use a method to assess for stability of symptom clusters across symptom dimensions

			difficulty in sleeping, itching <u>Main cluster III</u>: cough, shortness of breath, numbness/tingling in the hands or feet, difficulty in swallowing, swelling of arms or legs, dizziness, swelling feeling, difficulty in urinating, difficulty in concentrating, feeling angry, diarrhea, I don't like myself, feeling/being sensitive, problems with sexual desire and activity *Distress symptom clusters* <u>Main cluster I</u>: dizziness, difficulty in swallowing, feeling sleepy or dizzy, cough <u>Main cluster II</u>: shortness of breath, swelling of arms or legs, changes on skin, itching, difficulty in concentrating,	

			feeling angry, feeling swelled, difficulty in urinating, diarrhea, feeling/being sensitive, I don't like myself, numbness/tingling in hands or feet, problems with sexual desire and activity Main cluster III: feeling sad, worrying, difficulty in sleeping, sweating, nausea, loss of appetite, mouth sores, change in taste of food, weight loss, pain, fatigue or energy loss, dry mouth, vomiting, hair loss, constipation Additional outcomes: N/A	
Sullivan et al., 2017 Purpose(s): Identify whether the number and types of symptom clusters differed based on symptom occurrence rates or severity ratings were	*n* = 515 Mean age: 53.3 (±11.6) years Range: 21-90 years Female: 99.2% Ethnicity and Race: White 66.9% Black 6.9%	Instrument(s): MSAS (modified): 38 symptoms Criteria used to exclude symptoms: Yes Analysis: EFA	5 symptom clusters identified using symptom occurrence: Psychological cluster: feeling nervous, feeling sad, worrying, feeling irritable, "I don't look like myself"	Strengths: Symptom clusters were created using two dimensions of the symptom experience Utilized a valid and reliable symptom inventory

used to create the symptom clusters Design: cross-sectional Location: United States	Asian or Pacific Islander 15.3% Hispanic, Mixed, or other 10.9% Employment status: Working 41.0% Not working 59.0% Inpatients: *n* = 0 Outpatients: *n* = 515 Diagnosis: Breast Cancer 100.0% Treatment: Adjuvant CTX 74.0% Neoadjuvant CTX 26.0% Time of symptom assessment: 7 days after the administration of the 2nd or 3rd cycle of CTX	Dimension(s): occurrence, severity Symptoms allowed to load on more than one factor: Yes Minimum factor loadings required to include symptom within cluster: 0.40 Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: Kirkova and Walsh, 2007 Analysis of additional outcomes: N/A	Hormonal cluster: hot flashes, difficulty sleeping, sweats, problems with sexual interest or activity Nutritional cluster: dry mouth, nausea, lack of appetite, change in the way food tastes, weight loss, abdominal cramps, diarrhea GI cluster: weight loss, feeling bloated, weight gain Epithelial cluster: “I don’t look like myself”, change in the way food tastes, hair loss, mouth sores 6 symptom clusters identified using symptom severity: Hormonal cluster: hot flashes, sweats Psychological cluster: feeling sad, feeling nervous, worrying, feeling irritable	Limitations: Cross-sectional design

			CTX neuropathy cluster: feeling drowsy, numbness or tingling in hands/feet, pain GI cluster: feeling bloated, abdominal cramps, weight gain Nutritional cluster: weight gain, weight loss, nausea, lack of appetite Epithelial cluster: hair loss, changes in the way food tastes, "I don't look like myself", changes in skin, mouth sores Additional outcomes: N/A	
Vuttanon et al., 2019 Purpose(s): Identify symptom clusters in Thai patients with breast cancer who are undergoing CTX	*n* = 96 Mean age: Experimental group: 50.7 (±9.1) years Control group: 52.4 (±10.0) Female: NR Ethnicity: Thai 100.0%	Instrument(s): ESAS – Thai version: 9 symptoms Criteria used to exclude symptoms: No Analysis: EFA Dimension(s): severity	4 symptom clusters identified: Cluster 1: anxiety, emotional distress Cluster 2: nausea, pain Cluster 3: drowsiness, fatigue	Strengths: Utilized a valid and reliable symptom inventory Limitations: Cross-sectional design

Examine the effect of PMR on symptom clusters Design: cross-sectional Location: Thailand	Race: NR Employment status: NR Inpatients: NR Outpatients: NR Diagnosis: Breast cancer 100.0% Treatment: Taxane 87.5% Herceptin 12.5% Time of symptom assessment: After completion of CTX	Symptoms allowed to load on more than one factor: No Minimum cluster value required to include symptom within cluster: NR Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: N/A Analysis of secondary outcomes: N/A	Cluster4: depression, lack of appetite Additional outcomes: N/A	Small sample size Used 9 symptoms to evaluate for symptom clusters Unclear when the symptoms were assessed in relation to the completion of CTX Used only a single dimension to evaluate for symptom clusters Symptom clusters were not named
Wong et al., 2017 Purpose(s): Compare the number and types of symptom clusters identified using ratings of symptom occurrence vs. severity in a homogeneous sample of lung cancer patients one week after CTX administration Design: cross-sectional	*n* = 157 Mean age: 64.0 (±11.1) years Range: NR Female: 56.6% Ethnicity and Race: White 71.8% Black 9.9% Asian or Pacific Islander 9.9% Hispanic, Mixed, or other 8.5% Employment status: Working 24.8% Not working 75.2% Inpatients: *n* = 0	Instrument(s): MSAS (modified): 38 symptoms Criteria used to exclude symptoms: Yes Analysis: EFA Dimension(s): occurrence, severity Symptoms allowed to load on more than one factor: Yes	5 symptom clusters identified across each symptom dimension: *Occurrence symptom clusters* Sickness behavior cluster: abdominal cramps, constipation, difficulty concentrating, feeling drowsy, lack of energy, nausea, sweats, vomiting Lung cancer-specific cluster: chest	Strengths: Symptom clusters were created using two dimensions of the symptom experience Evaluated symptom clusters in patients with lung cancers Used a valid and reliable symptom inventory Limitations:

Location: United States	Outpatients: *n* = 157 Diagnosis: Non-small cell lung cancer 88.1% Small cell lung cancer 11.9% Treatment: Platinum-doublet CTX 77.9% Single agent CTX 20.0% Monoclonal antibody alone 2.1% Time of symptom assessment: 7 days after the administration of the 2nd or 3rd cycle of CTX	Minimum factor loadings required to include symptom within cluster: 0.40 Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: Kirkova and Walsh, 2007 Analysis of additional outcomes: N/A	tightness, cough, difficulty breathing, shortness of breath Psychological cluster: difficulty concentrating, feeling bloated, feeling irritable, feeling nervous, feeling sad, problems with sexual interest or activity, worrying Nutritional cluster: increased appetite, lack of appetite, weight gain, weight loss Epithelial cluster: changes in skin, har loss, “I don’t look like myself,” mouth sores *Severity symptom clusters* Sickness behavior cluster: abdominal cramps, constipation, difficulty concentrating, feeling drowsy, lack of energy, nausea, sweats, vomiting, feeling bloated,	Cross-sectional design

			feeling nervous, feeling sad, problems with sexual interest or activity, worrying, dizziness, dry mouth, pain, swelling of arms or legs Lung cancer-specific cluster: chest tightness, cough, difficulty breathing, shortness of breath, swelling of arms or legs Nutritional cluster: increased appetite, lack of appetite, weight gain, weight loss Psychological cluster: feeling irritable, feeling nervous, feeling sad, worrying Epithelial cluster: changes in skin, “I don’t look like myself,” mouth sores, swelling of arms or legs Additional outcomes: N/A	

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; ASA = American Society of Anesthesiologists; CTX = chemotherapy; CIPN = chemotherapy-induced peripheral neuropathy; EFA = exploratory factor analysis; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; FACT = Functional Assessment of Cancer Therapy; FSIS = Female Sexual Function Index; GI = gastrointestinal; HADS = Hospital Anxiety and Depression Scale; MDASI = M.D. Anderson Symptom Instrument; MSAS = Memorial Symptom Assessment Scale; NA = not applicable; NR = not reported; NRS = Numeric Rating Scale; PCA = principle component analysis; PSQI = Pittsburgh Sleep Quality Index; QOL = quality of life; TSO = Treatment-Specific Optimism

Supplemental Table 2. Longitudinal studies of symptom clusters in samples of patients who received chemotherapy

Author, year, purpose and design	Sample size, patient characteristics, time of symptom assessment	Symptom assessment instrument(s), number of symptoms on instrument; statistical analysis method, symptom dimension(s) used to create symptom clusters; analysis of secondary outcomes	Number of symptom clusters, specific symptoms within each cluster, change in symptom clusters over time Evaluation of additional outcomes	Strengths and Limitations
Albusoul et al., 2017 Purpose(s): Identify symptom clusters and their change over time from baseline to after completion of adjuvant breast cancer CTX Design: longitudinal Location: United States	*n* = 219 Mean age: 52.2 (±10.0) years Range: 29-83 years Female: 100.0% Ethnicity: Hispanic 3.7% Non-Hispanic 96.3% Race: White 95.4% Non-White 4.6% Employment status: Employed 75.3% Non-employed 24.7% Inpatients: NR Outpatients: NR Diagnosis: Breast cancer 100.0% Treatment: Adjuvant CTX 100.0% Time of symptom assessment: T1: 2 days prior to first CTX (baseline) T2: first 7 days after cycle 3 CTX T3: first 7 days after cycle 4 CTX T4: 30 days after the last CTX	Instrument(s): HADS – 14 items SES – 24 items Medical Outcomes Study Short-Form Survey v2 – 36 items Criteria used to exclude symptoms: Yes Analysis: EFA Dimension(s): severity Symptoms allowed to load on more than one factor: NR Minimum factor loadings required to include symptom within cluster: 0.30 Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: Investigator appraisal Analysis of secondary outcomes: None	2 symptom clusters identified at each timepoint: **T1** Treatment-related symptom cluster: sleep disturbance, concentration, anxiety, appearance GI symptom cluster: nausea, appetite, bowel pattern, pain, fatigue **T2** Treatment-related symptom cluster: sleep disturbance, pain, fatigue, bowel pattern, concentration, appearance, anxiety, depression GI symptom cluster: nausea, appetite **T3** Treatment-related symptom cluster: fatigue, appetite, concentration,	Strengths: Evaluated for symptom clusters across multiple timepoints Utilized valid and reliable symptom measures Limitations: Evaluated for symptom clusters with only 10 symptoms Used a single dimension to evaluate for symptom clusters Removed symptom clusters that were not reliable Primarily a non-Hispanic, Caucasian sample

			appearance, anxiety, depression GI symptom cluster: nausea, bowel pattern, sleep disturbance, pain **T4** Treatment-related symptom cluster 1: fatigue, sleep disturbance, pain Treatment-related symptom cluster 2: concentration, appearance, anxiety Changes in symptom clusters over time: T2 and T3 were assessed to evaluate stability of symptom clusters. Symptom clusters appear to be dynamic and change over time GI symptom cluster disappeared at T4. However, a second treatment-related symptom cluster emerged Additional outcomes: N/A	
Berger et al., 2020 Purpose(s): Identify the prevalence and severity of individual symptoms, symptom clusters, and QOL in women receiving adjuvant breast cancer	*n* = 219 Mean age: 52.2 (±10) years Range: 29-83 years Female: 100.0% Ethnicity: Hispanic 3.7% Non-Hispanic 96.3%	Instrument(s): HADS – 14 items SES – 24 items Medical Outcomes Study Short-Form Survey v2 – 36 items Criteria used to exclude symptoms: Yes	2 symptom clusters identified at each timepoint: **T1** Treatment-related symptom cluster: sleep disturbance, concentration, anxiety	Strengths: Evaluated for symptom clusters across multiple timepoints Utilized valid and reliable symptom measures Limitations:

CTX from baseline over 1 year Design: longitudinal Location: United States	Race: White 95.4% Non-White 4.6% Employment status: Employed 75.3% Non-employed 24.7% Inpatients: NR Outpatients: NR Diagnosis: Breast Cancer 100.0% Treatment: Adjuvant CTX 100.0% Time of symptom assessment: T1: 2 days prior to first CTX (baseline) T2: 6 months after baseline (1 month after last CTX) T3: 1 year after baseline (~6 months after last CTX)	Analysis: EFA Dimension(s): severity Symptoms allowed to load on more than one factor: Yes Minimum factor loadings required to include symptom within cluster: 0.30 Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: Investigator appraisal Analysis of secondary outcomes: QOL	GI symptom cluster: fatigue, pain, bowel pattern, nausea **T2** Treatment-related symptom cluster: fatigue, sleep disturbance, pain, concentration GI symptom cluster: concentration, appearance, anxiety **T3** Treatment-related symptom cluster: fatigue, sleep disturbance, pain, concentration, anxiety GI symptom cluster: pain, bowel pattern Changes in symptom clusters over time: Treatment-related symptom cluster was identified across all timepoints with a basis of two core symptom. However, the number of symptoms increased across timepoints Additional outcomes: At all timepoints, physical component scores were the lowest and were lower than the population norms (≤50)	Evaluated for symptom clusters with only 10 symptoms Used a single dimension to evaluate for symptom clusters Did not relate changes in QOL to the dynamic nature of symptom clusters Primarily a non-Hispanic, Caucasian sample

			QOL scores significantly improved over time	
Browall et al., 2017 Purpose(s): Describe symptom clusters at four points in time during CTX treatment in patients with stage I to IIIa breast cancer Design: longitudinal Location: Sweden	*n* = 124 Mean age: 59 years Range: 34-79 years Female: 100.0% Ethnicity: NR Race: NR Employment status: NR Inpatients: NR Outpatients: NR Diagnosis: Breast cancer 100.0% Treatment: Adjuvant CTX 100% Timepoints of symptom assessment: T1: Enrollment (baseline) T2: Day 12 post cycle 1 FEC T3: Day 12 post cycle 3 FEC T4: Day 12 post final cycle of docetaxel	Instrument(s): MSAS: 32 symptoms Criteria used to exclude symptoms: Yes Analysis: PCA Dimension(s): symptom burden summary score (calculated as the average of the frequency, severity, and distress scores for each symptom) Symptoms allowed to load on more than one factor: NR Minimum factor loadings required to include symptom within cluster: NR Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: NR Analysis of secondary outcomes: N/A	3 symptom clusters identified across all timepoints: **T1** Emotional cluster: worrying, difficulty concentrating, feeling sad Gastro cluster: taste change, constipation, diarrhea Physical cluster: breathlessness, dizziness, dry mouth, nausea **T2** Emotional cluster: feeling sad, worrying, difficulty concentrating Gastro cluster: lack of appetite, taste change, constipation, diarrhea Physical cluster: hair loss, breathlessness, dizziness, dry mouth, nausea **T3** Physical cluster: lack of appetite, breathlessness, feeling nervous, lack of energy, feeling irritable, dizziness, nausea Emotional cluster: worrying, feeling sad, difficulty concentrating Gastro cluster: mouth sores, dry mouth, lack of	Strengths: Evaluated for symptom clusters across multiple timepoints Symptom clusters were created using multiple dimensions of the symptom experience Utilized a valid and reliable symptom assessment inventory Limitations: Relatively small sample size Did not use a method to assess for stability of symptoms across timepoints Did not define time of enrollment in relationship to the administration of CTX

			appetite, taste change, constipation, diarrhea **T4** Emotional cluster: feeling nervous, worrying, feeling sad, difficulty concentrating Gastro cluster: lack of appetite, taste change, constipation, diarrhea Physical cluster: sexual relations, sweats, difficulty sleeping, lack of appetite, breathlessness, feeling nervous, lack of energy, feeling irritable, dizziness, nausea Changes in symptom clusters over time: Symptom clusters at the first treatment cycle were quite stable and similar to baseline Order of symptoms changed at cycle 3 Symptom clusters remained relatively stable across time with a basis of core symptoms Additional outcomes: N/A	
Han et al., 2019 Purpose(s): Evaluated the occurrence, severity, and distress of 38 symptoms prior to patients' second	*n* = 399 Mean age: 57.9 (±11.8) years Range: NR Female: 45.1%	Instrument(s): MSAS (modified): 38 symptoms Criteria used to exclude symptoms: Yes Analysis: EFA	4 symptom clusters identified across the symptom dimensions and timepoints: *Occurrence symptom clusters*	Strengths: Evaluated for symptom clusters across multiple timepoints

or third cycle of CTX (time 1), approximately one week after CTX (time 2), and approximately two weeks after CTX (time 3) Evaluated for differences in the number and types of symptom clusters at each of these assessments using ratings of occurrence, severity, and distress Evaluated for changes in the symptom clusters over time Design: longitudinal Location: United States	Ethnicity and Race: White 68.7% Black 9.0% Asian or Pacific Islander 11.5% Hispanic, Mixed, or Other 10.8% Employment status: Working 33.3% Not working 66.7% Inpatients: *n* = 0 Outpatients: *n* = 399 Diagnosis: Colon 46.4% Rectal 20.1% Pancreatic 18.5% Esophageal 5.3% Gastric 4.8% Gallbladder/bile duct 2.5% Liver 1.5% Small intestine 1.5% Anal 1.3% Other 6.3% Treatment: CTX 100.0% Timepoints of symptom assessment: T1: prior to second or third cycle of CTX T2: approximately 1 week after CTX T3: approximately 2 weeks after CTX	Dimension(s): occurrence, severity, distress Symptoms allowed to load on more than one factor: Yes Minimum factor loadings required to include symptom within cluster: 0.40 Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: Kirkova and Walsh, 2007 Analysis of secondary outcomes: N/A	**T1** Psychological cluster: lack of energy, difficulty concentrating, feeling nervous, feeling drowsy, feeling sad, worrying, feeling irritable, changes in skin CTX-related cluster: dry mouth, nausea, itching, lack of appetite, weight loss, change in the way food tastes, changes in skin, dizziness GI cluster: feeling bloated, abdominal cramps, constipation Weight change cluster: increased appetite, weight gain **T2** Psychological cluster: lack of energy, difficulty concentrating, feeling nervous, feeling sad, worrying, feeling irritable, problems with sexual interest or activity, “I don’t look like myself” CTX-related cluster: dry mouth, nausea, lack of appetite, weight loss, change in the way food tastes, cough, lack of energy, abdominal cramps, feeling bloated, diarrhea, feeling drowsy, numbness/tingling in hands/feet	Symptom clusters were created using multiple dimensions of the symptom experience Evaluated symptom clusters in patients with gastrointestinal cancers Utilized a valid and reliable symptom inventory Limitations: Heterogeneity in types of GI cancers

			Weight change cluster: increased appetite, weight gain, lack of appetite Epithelial cluster: hair loss, change in the way food tastes, changes in skin **T3** Psychological cluster: lack of energy, difficulty concentrating, feeling nervous, feeling sad, worrying, feeling irritable, problems with sexual interest or activity, difficulty sleeping CTX-related cluster: dry mouth, nausea, lack of appetite, weight loss, change in the way food tastes, cough, lack of energy, abdominal cramps, diarrhea, feeling drowsy Weight change cluster: increased appetite, weight gain, lack of appetite, weight loss Epithelial cluster: changes in skin, itching, “I don’t look like myself” *Severity symptom clusters* **T1** Psychological cluster: lack of energy, difficulty concentrating, feeling nervous, feeling drowsy, feeling sad, worrying, feeling irritable, problems	

			with sexual interest or activity CTX-related cluster: itching, lack of appetite, weight loss, change in the way food tastes, changes in skin, dizziness, hair loss, "I don't look like myself" GI cluster: feeling bloated, abdominal cramps, nausea, diarrhea Weight change cluster: increased appetite, weight gain **T2** Psychological cluster: lack of energy, difficulty concentrating, feeling nervous, feeling sad, worrying, feeling irritable, problems with sexual interest or activity CTX-related cluster: dry mouth, nausea, lack of appetite, weight loss, change in the way food tastes, cough, lack of energy, abdominal cramps, feeling bloated, diarrhea, feeling drowsy, numbness/tingling in hands/feet, sweats Weight change cluster: increased appetite, weight gain, lack of appetite, weight loss	

			Epithelial cluster: hair loss, changes in skin, itching, “I don’t look like myself” **T3** Psychological cluster: lack of energy, difficulty concentrating, feeling nervous, feeling sad, worrying, feeling irritable, constipation CTX-related cluster: dry mouth, nausea, lack of appetite, weight loss, change in the way food tastes, dizziness, cough, lack of energy, abdominal cramps, diarrhea, feeling drowsy, numbness/tingling in hands/feet Weight change cluster: increased appetite, weight gain, lack of appetite, weight loss Epithelial cluster: changes in skin, itching, “I don’t look like myself” *Distress symptom clusters* **T1** Psychological cluster: lack of energy, difficulty concentrating, feeling nervous, feeling drowsy, feeling sad, worrying, feeling irritable, difficulty sleeping, pain, sweats CTX-related cluster: itching, lack of appetite, weight loss, change in the	

			way food tastes, changes in skin, dizziness, hair loss, “I don’t look like myself” Weight change cluster: increased appetite, weight gain GI cluster: abdominal cramps, diarrhea **T2** Psychological cluster: lack of energy, difficulty concentrating, feeling nervous, feeling sad, worrying, feeling irritable, problems with sexual interest or activity, difficulty sleeping CTX-related cluster: dry mouth, nausea, lack of appetite, weight loss, change in the way food tastes, cough, abdominal cramps, diarrhea, feeling drowsy, sweats Weight change cluster: increased appetite, weight gain Epithelial cluster: hair loss, changes in skin, itching, “I don’t look like myself” **T3** Psychological cluster: lack of energy, difficulty concentrating, feeling nervous, feeling sad, worrying, feeling irritable,	

			changes in skin, problems with sexual interest or activity, constipation <u>CTX-related cluster</u>: dry mouth, nausea, lack of appetite, weight loss, change in the way food tastes, cough, abdominal cramps, diarrhea, feeling drowsy <u>Weight change cluster</u>: increased appetite, weight gain, lack of appetite, weight loss <u>Epithelial cluster</u>: changes in skin, itching, "I don't look like myself" <u>Changes in symptom clusters over time</u>: Three symptom clusters (i.e., psychological, CTX-related, weight change) were identified across all three symptom dimensions and timepoints For the psychological symptom cluster, six symptoms of 14 remained stable across all three symptom dimensions and timepoints For the CTX-related symptom cluster, five of 18 symptoms remained stable across all symptom dimensions and timepoints. The symptoms	

			measured at T1 were relatively consistent across all three dimensions. At T2, the symptoms changed and remained relatively stable across each symptom dimension and through T3 GI symptom cluster was identified across all three dimensions at T1 only. The symptoms within this cluster varied across each dimension Weight change cluster was present at each timepoint with two core symptoms present throughout Epithelial symptom cluster was identified across all three dimensions and the symptoms within this cluster remained relatively stable across each symptom dimension. However, this cluster was present at T2 and T3 only Additional outcomes: N/A	
Kim, S., 2018 Purpose(s): Identify the changes and relationship between symptom clusters and the level of lipid peroxidation in patients with primary malignant brain cancer during concurrent chemoradiotherapy	*n* = 51 Mean age: 53.1 (±9.6) years Range: NR Female: 41.7% Ethnicity: NR Race: NR Employment status: NR	Instrument(s): MSAS: 32 symptoms Analysis: EFA Dimension(s): severity Symptoms allowed to load on more than one factor: No	2 symptom clusters identified at each timepoint: **T1** Negative emotion cluster: feeling sad, worrying, lack of energy Neurocognitive cluster: dizziness, difficulty in	Strengths: Evaluated for symptom clusters in patients with a type of brain cancer Evaluated for symptom clusters across multiple timepoints

Design: longitudinal Location: South Korea	Inpatients: NR Outpatients: NR Diagnosis: Anaplastic astrocytoma 37.5% Glioblastoma multiforme 62.5% Treatment: Chemoradiotherapy 100% Timepoints of symptom assessment: T1: prior to initiation of chemoradiotherapy T2: 2 to 3 weeks after initiation of chemoradiotherapy T3: 4 to 6 weeks after initiation of chemoradiotherapy	Minimum factor loadings required to include symptom within cluster: NR Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: Investigator appraisal Analysis of secondary outcomes: serum lipid profile ratios	sleeping, difficulty in concentrating **T2** Negative emotion and decreased vitality cluster: feeling sad, worrying, lack of energy, feeling irritable, difficulty in concentrating GI cluster: dry mouth, change in the way food tastes, difficulty in swallowing, weight loss, nausea **T3** Body image and decreased vitality cluster: lack of energy, difficulty in concentrating, “I don’t look like myself”, problems with sexual interest or activity, hair loss Decreased sensory cluster: feeling irritable, swelling of arms or legs, problems with urination, numbness/tingling in the hands/feet Changes in symptom clusters over time: The negative emotion symptom clusters were relatively stable from T1 to T2 with a basis of three core symptoms A GI symptom cluster emerged at T2 following the initiation of	Utilized a valid and reliable symptom assessment instrument Evaluated for a secondary outcome associated with symptom clusters Limitations: Recruited patients from a single hospital Very small sample size Used a single dimension to evaluate for symptom clusters Not clear how the relationships between symptom clusters and serum lipid profile ratios were evaluated

			chemoradiation therapy and disappeared at T3 A decreased sensory cluster emerged at T3 Additional outcomes: Three lipid profile ratios (i.e., TC/HDL-c, LDL-cHDL-c, TG/HDL-c) were positively associated with the two symptom clusters at T2	
Li et al., 2020 Purpose(s): Identify symptom clusters experienced by women with breast cancer treated with AI therapy from pre-adjuvant therapy up to 18 months of adjuvant therapy Design: longitudinal Location: United States	*n* = 354 Mean age: 61.2 (±6.2) years Range: NR Female: 100.0% Ethnicity: NR Race: White 96.3% African American 3.7% Employment status: Working 70.7% Not working 29.3% Inpatients: NR Outpatients: NR Diagnosis: Breast cancer 100.0% Treatment: Adjuvant CTX with AI 35.9% AI only 64.1% Timepoints of symptom assessment: T0: pre-adjuvant therapy (baseline) T1: six months into adjuvant therapy T2: 12 months into adjuvant therapy T3: 18 months into adjuvant therapy	Instrument(s): Breast Cancer Prevention Trial Symptom Checklist: 42 symptoms Profile of Mood States: 2 symptoms (i.e., fatigue, anxiety) Beck Depression Inventory II: 2 symptoms (i.e., depression, changes in sleep pattern) Patient's Assessment of Own Functioning: 1 symptom (i.e., perceived cognitive ability) Criteria used to exclude symptoms: Yes Analysis: EFA Dimension(s): severity Symptoms allowed to load on more than one factor: No Minimum factor loadings required to include symptom within cluster: 0.40 Method of evaluating for stability of symptoms across	8 symptom clusters identified across the timepoints: **T0** Psychological cluster: depression, anxiety, changes in sleep patterns, avoid of social affairs, fatigue Neurocognitive cluster: difficulty concentrating, easily distracted, forgetfulness, perceived cognitive disturbance Musculoskeletal cluster: joint pain, general aches and pain, muscle stiffness Vasomotor cluster: night sweats, hot flashes Urinary cluster: difficulty with bladder control when laughing or crying, difficulty with bladder control at other times	Strengths: Evaluated for symptom clusters across multiple timepoints Utilized valid and reliable symptom assessment instruments Limitations: Primarily a Caucasian sample Used a single dimension to evaluate for symptom clusters

		symptom dimensions and/or timepoints: Kirkova and Walsh, 2007 Analysis of secondary outcomes: N/A	Sexual cluster: vaginal dryness, pain with intercourse Weight cluster: decreased appetite, weight loss **T1** Psychological cluster: anxiety, depression, fatigue, avoid of social affairs Neurocognitive cluster: difficulty concentrating, forgetfulness, easily distracted, perceived cognitive disturbance, dry mouth Musculoskeletal cluster: general aches and pain, joint pain, muscle stiffness Vasomotor cluster: night sweats, hot flashes Urinary cluster: difficulty with bladder control at other times, difficulty with bladder control when laughing or crying Sexual cluster: vaginal dryness, pain with intercourse Weight cluster: unhappy with the appearance of my body, weight gain GI cluster: diarrhea, nausea **T2**	

			Psychological cluster: fatigue, depression, changes in sleep patterns Neurocognitive cluster: easily distracted, difficulty concentrating, perceived cognitive disturbance, forgetfulness, excitability, tendency toward accidents, short temper, anxiety Musculoskeletal cluster: joint pain, general aches and pain, muscle stiffness Vasomotor cluster: night sweats, hot flashes Urinary cluster: difficulty with bladder control at other times, difficulty with bladder control when laughing or crying Sexual cluster: vaginal dryness, pain with intercourse Weight cluster: weight gain, unhappy with the appearance of my body **T3** Psychoneurocognitive cluster: perceived cognitive disturbance, excitability, forgetfulness, anxiety, difficulty concentrating, easily distracted, depression, fatigue	

			Musculoskeletal cluster: joint pain, muscle stiffness, general aches and pain Vasomotor cluster: night sweats, hot flashes Urinary cluster: difficulty with bladder control when laughing or crying, difficulty with bladder control at other times Sexual cluster: vaginal dryness, pain with intercourse Weight cluster: weight gain, unhappy with the appearance of my body Changes in symptom clusters over time: The psychological and neurocognitive symptom clusters were present at T0, T1, and T2, and the symptoms within the clusters remained relatively stable across timepoints. However, these clusters merged at T3 Weight symptom cluster was present at all four timepoints. However, the symptoms within the cluster changed from T0 to T1. Symptoms from T1-T3 were stable	

			GI symptom cluster was only present at T1 The musculoskeletal, vasomotor, urinary, and sexual symptom clusters remained stable across time with a basis of core symptoms Additional outcomes: N/A	
Lin et al., 2019 Purpose(s): Identify symptom clusters using the ratings of occurrence, severity, and distress in newly diagnosed patients with AML at three stages of their induction therapy Evaluated for consensus among the numbers and types of symptoms in each symptom cluster identified by multiple dimensions over time Design: longitudinal Location: China	*n* = 126 Mean age: 35.4 (±11.6) years Range: NR Female: 56.3% Ethnicity: NR Race: NR Employment status: NR Inpatients: *n* = 126 Outpatients: *n* = 0 Diagnosis: AML 100.0% Treatment: Induction CTX 100.0% Timepoints of symptom assessment: T1: within the six days prior to induction CTX T2: 1 to 7 days during induction CTX T3: 1 to 7 days after induction CTX	Instrument(s): MSAS-Chinese version: 32 symptoms Criteria used to exclude symptoms: Yes Analysis: EFA Dimension(s): occurrence, severity, distress Symptoms allowed to load on more than one factor: Yes Minimum factor loadings required to include symptom within cluster: 0.40 Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: Kirkova and Walsh, 2007 Analysis of secondary outcomes: N/A	6 symptom clusters identified across the symptom dimensions and timepoints: *Occurrence symptom clusters* **T1** Nutritional cluster: cough, dry mouth, sweats, lack of appetite, change in the way food tastes Sickness behavior cluster: difficulty sleeping, shortness of breath, feeling sad, dizziness, changes in skin Neuropathy cluster: difficulty concentrating, feeling drowsy **T2** GI cluster: difficulty concentrating, nausea, vomiting Psychological cluster: feeling nervous, difficulty sleeping, shortness of breath, feeling sad **T3**	Strengths: Evaluated for symptom clusters across multiple timepoints Symptom clusters were created using multiple dimensions of the symptom experience Evaluated symptom clusters in patients with AML Utilized a valid and reliable symptom inventory Limitations: Recruited patients from a single hospital Names of symptom clusters are not consistent with symptoms within the cluster (e.g., neuropathy cluster) Relatively small sample size

			Nutritional cluster: dry mouth, mouth sores, constipation GI cluster: difficulty concentrating, nausea, vomiting, feeling drowsy, "I don't like myself" Psychological cluster: feeling nervous, feeling sad Body image cluster: itching, changes in skin *Severity symptom clusters* **T1** Nutritional cluster: cough, dry mouth, sweats Sickness behavior cluster: difficulty sleeping, shortness of breath, feeling sad Neuropathy cluster: difficulty concentrating, feeling drowsy Body image cluster: itching, mouth sores **T2** Sickness behavior cluster: difficulty concentrating, change in the way food tastes, "I don't look myself" GI cluster: difficulty concentrating, nausea, vomiting, change in the way food tastes	

			Psychological cluster: feeling nervous, difficulty sleeping, feeling sad **T3** Nutritional cluster: dry mouth, change in the way food tastes, mouth sores, weight loss, constipation, "I don't like myself" GI cluster: difficulty concentrating, nausea, vomiting, feeling drowsy Psychological cluster: feeling nervous, difficulty sleeping, feeling sad, feeling irritable Body image cluster: itching, changes in skin *Distress symptom clusters* **T1** Nutritional cluster: cough, dry mouth, sweats Sickness behavior cluster: shortness of breath, feeling sad, changes in skin Neuropathy cluster: difficulty concentrating, feeling drowsy, feeling irritable Body image cluster: itching, mouth sores **T2** Sickness behavior cluster: difficulty concentrating, change in the way food	

			tastes, “I don’t look myself” GI cluster: difficulty concentrating, nausea, vomiting, change in the way food tastes Psychological cluster: feeling nervous, feeling sad **T3** Nutritional cluster: dry mouth, change in the way food tastes, difficulty concentrating, constipation, “I don’t like myself GI cluster: difficulty concentrating, nausea, vomiting, sweats Psychological cluster: feeling nervous, feeling sad Body image cluster: itching, changes in skin Changes in symptom clusters over time: The number and agreement of symptoms within each symptom cluster varied across dimensions and over time GI symptom cluster emerged at T2 and remained present at T3. Three core symptoms were present across each	

			dimension and both time points (i.e., difficulty concentrating, nausea, vomiting) Psychological symptom cluster emerged at T2 and persisted into T3. However, only two core symptoms remained consistent across each timepoint and dimension (i.e., feeling nervous, feeling sad Additional outcomes: N/A	
Russell et al., 2019 Purpose(s): Evaluate for differences in the number and types of symptom clusters at three time points using ratings of symptom occurrence and severity Evaluate for changes in these symptom clusters over time Design: longitudinal Location: United States	*n* = 145 Mean age: 64.0 (±11.1) years Range: NR Female: 56.6% Ethnicity and Race: White 71.8% Black 9.9% Asian or Pacific Islander 9.9% Hispanic, Mixed, or Other 8.5% Employment status: Working 24.8% Not working 75.2% Inpatients: *n* = 0 Outpatients: *n* = 145 Diagnosis: Non-small cell lung cancer 88.1% Small cell lung cancer 11.9% Treatment: Platinum-doublet CTX 77.9% Single agent CTX 20.0% Monoclonal antibody only 2.1%	Instrument(s): MSAS (modified): 38 symptoms Criteria used to exclude symptoms: Yes Analysis: EFA Dimension(s): occurrence, severity Symptoms allowed to load on more than one factor: Yes Minimum factor loadings required to include symptom within cluster: 0.40 Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: Kirkova and Walsh, 2007 Analysis of secondary outcomes: N/A	6 symptom clusters identified across the symptom dimensions and timepoints: *Occurrence symptom clusters* **T1** Sickness behavior cluster: feeling drowsy, lack of energy, problems with sexual interest, hair loss, dizziness, pain Lung cancer-specific cluster: cough, difficulty breathing, shortness of breath, dry mouth, swelling of arms or legs Psychological cluster: difficulty concentrating, difficulty breathing, feeling bloated, feeling irritable, feeling nervous, feeling sad, worrying, weight loss Epithelial/GI cluster: abdominal cramps,	Strengths: Evaluated for symptom clusters across multiple timepoints Symptom clusters were created using multiple dimensions of the symptom experience Evaluated symptom clusters in patients with lung cancers Utilized a valid and reliable symptom inventory Limitations:

	Timepoints of symptom assessment: T1: prior to second or third cycle of CTX T2: approximately 1 week after CTX T3: approximately 2 weeks after CTX		constipation, nausea, sweats, lack of appetite, weight loss, changes in skin, I don't look like myself, change in the way food tastes Nutritional cluster: increased appetite, lack of appetite, weight gain **T2** Sickness behavior cluster: abdominal cramps, constipation, difficulty concentrating, feeling drowsy, lack of energy, nausea, sweats, vomiting Lung cancer-specific cluster: chest tightness, cough, difficulty breathing, shortness of breath Psychological cluster: difficulty concentrating, feeling bloated, feeling irritable, feeling nervous, feeling sad, problems with sexual interest or activity, worrying Nutritional cluster: increased appetite, lack of appetite, weight gain, weight loss Epithelial cluster: changes in skin, hair loss, "I do not look like myself", mouth sores **T3** Sickness behavior cluster: difficulty concentrating,	

			feeling drowsy, lack of energy, cough Lung cancer-specific cluster: chest tightness, cough, difficulty breathing, shortness of breath, weight loss, dizziness, pain Epithelial/GI cluster: abdominal cramps, feeling drowsy, sweats, feeling bloated, problems with sexual interest or activity, lack of appetite, weight gain, changes in skin, hair loss, “I do not look like myself”, mouth sores, dizziness, change in the way food tastes Psychological cluster: nausea, vomiting, feeling irritable, feeling nervous, feeling sad, worrying Nutritional cluster: increased appetite, lack of appetite, weight gain *Severity symptom clusters* **T1** Lung cancer-specific cluster: feeling drowsy, lack of energy, chest tightness, cough, difficulty breathing, shortness of breath, dizziness, pain Epithelial/GI cluster: constipation, nausea, sweats, lack of appetite, weight loss, changes in skin, “I do not look like	

			myself", change in the way food tastes Psychological cluster: feeling bloated, feeling irritable, feeling nervous, feeling sad, worrying, weight loss, difficulty sleeping Nutritional cluster: sweats, increased appetite, lack of appetite, weight gain **T2** Sickness behavior cluster: abdominal cramps, constipation, difficulty concentrating, feeling drowsy, lack of energy, nausea, sweats, vomiting, feeling bloated, feeling nervous, feeling sad, problems with sexual interest or activity, worrying, dizziness, dry mouth, pain, swelling of arms or legs Lung cancer-specific cluster: chest tightness, cough, difficulty breathing, dry mouth, shortness of breath Nutritional cluster: increased appetite, lack of appetite, weight gain, weight loss Psychological cluster: feeling irritable, feeling nervous, feeling sad, worrying	

			Epithelial cluster: changes in skin, “I do not look like myself”, mouth sores, swelling of arms or legs **T3** Sickness behavior cluster: difficulty concentrating, chest tightness, feeling irritable, feeling nervous, dizziness Lung cancer-specific cluster: difficulty concentrating, feeling drowsy, lack of energy, chest tightness, cough, difficulty breathing, shortness of breath, dry mouth, pain Epithelial/GI cluster: abdominal cramps, constipation, sweats, feeling bloated, problems with sexual interest or activity, lack of appetite, weight loss, changes in skin, hair loss, “I do not look like myself”, mouth sores, dizziness, change in the way food tastes Psychological cluster: nausea, vomiting, feeling nervous, feeling sad, worrying Nutritional cluster: increased appetite, weight gain, weight loss Changes in symptom clusters over time:	

			Three symptom clusters (i.e., lung-cancer specific, psychological, nutritional) were relatively stable across both symptom dimensions and across all six timepoints Two symptom clusters (i.e., epithelial/GI, epithelial) varied by time but not symptom dimension Sickness behavior symptom cluster was present across both symptom dimensions at T2 and T3, but was not present at T1 in the severity dimension Additional outcomes: N/A	
Sullivan et al., 2018 Purpose(s): Determine the occurrence rates and severity ratings for 38 common symptoms Evaluate for differences in the number and types of symptom clusters Evaluate for changes over time in these symptom clusters Design: longitudinal Location: United States	*n* = 540 Mean age: 53.3 (±11.6) years Range: NR Female: 99.1% Ethnicity and Race: White 67.0% Black 6.7% Asian or Pacific Islander 14.9% Hispanic, Mixed, or Other 11.4% Employment status: Working 41.0% Not working 59.0% Inpatients: *n* = 0 Outpatients: *n* = 540 Diagnosis: Breast cancer 100.0%	Instrument(s): MSAS (modified): 38 symptoms Criteria used to exclude symptoms: Yes Analysis: EFA Dimension(s): occurrence, severity Symptoms allowed to load on more than one factor: Yes Minimum factor loadings required to include symptom within cluster: 0.40 Method of evaluating for stability of symptoms across symptom dimensions and/or	8 symptom clusters identified across the symptom dimensions and timepoints: *Occurrence symptom clusters* **T1** Sickness behavior cluster: pain, dry mouth, nausea, feeling drowsy, numbness and/or tingling in hands and/or feet, lack of appetite, dizziness Psychological cluster: difficulty concentrating, feeling nervous, feeling sad, worrying, feeling irritable, “I don’t look like myself”	Strengths: Large sample size Evaluated for symptom clusters across multiple timepoints Symptom clusters were created using multiple dimensions of the symptom experience Utilized a valid and reliable symptom inventory Limitations:

	Treatment: Adjuvant CTX 74.0% Neoadjuvant CTX 26.0% Timepoints of symptom assessment: T1: prior to second or third cycle of CTX T2: approximately 1 week after CTX T3: approximately 2 weeks after CTX	timepoints: Kirkova and Walsh, 2007 Analysis of secondary outcomes: N/A	Hormonal cluster: hot flashes, sweats GI cluster: difficulty sleeping, abdominal cramps, shortness of breath, weight loss Weight change cluster: weight gain, weight loss Epithelial cluster: weight gain, mouth sores, hair loss, change in the way food tastes, changes in skin **T2** Psychological cluster: feeling nervous, feeling sad, worrying, feeling irritable, “I don’t look like myself” Hormonal cluster: hot flashes, difficulty sleeping, sweats, problems with sexual interest or activity Nutritional cluster: dry mouth, nausea, lack of appetite, change in the way food tastes, weight loss, abdominal cramps, diarrhea GI cluster: weight loss, feeling bloated, weight gain Epithelial cluster: “I do not look like myself”, change in the way food tastes, hair loss, mouth sores	

			T3 Hormonal cluster: hot flashes, sweats Psychological cluster: worrying, feeling irritable, difficulty concentrating, feeling nervous, feeling drowsy, feeling sad GI cluster: abdominal cramps, difficulty sleeping, feeling bloated, weight gain, nausea Nutritional cluster: weight gain, nausea, lack of appetite, weight loss, change in the way food tastes Epithelial cluster: change in the way food tastes, changes in skin, mouth sores, “I do not look like myself”, itching *Severity symptom clusters* **T1** Psychological cluster: difficulty concentrating, feeling nervous, feeling sad, worrying, feeling irritable, “I don’t look like myself” Sickness behavior cluster: pain, dry mouth, nausea, feeling drowsy, dizziness Hormonal cluster: sweats, hot flashes	

			GI cluster: feeling bloated, diarrhea, abdominal cramps Weight change cluster: lack of appetite, weight gain, weight loss Epithelial cluster: “I do not look like myself”, weight gain, change in the way food tastes, changes in skin, hair loss **T2** Hormonal cluster: hot flashes, sweats Psychological cluster: feeling sad, feeling nervous, worrying, feeling irritable CTX-neuropathy cluster: feeling drowsy, numbness in hands and/or feet, pain GI cluster: feeling bloated, abdominal cramps, weight gain Nutritional cluster: weight gain, weight loss, nausea, lack of appetite Epithelial cluster: hair loss, change in the way food tastes, “I do not look like myself”, changes in skin, mouth sores **T3** Hormonal cluster: hot flashes, sweats	

			Psychological cluster: difficulty concentrating, feeling nervous, feeling sad, feeling drowsy, worrying, feeling irritable GI cluster: feeling bloated, abdominal cramps, weight gain Nutritional cluster: weight gain, nausea, lack of appetite, weight loss, change in the way food tastes Epithelial cluster: change in the way food tastes, mouth sores, hair loss, "I don't look like myself", changes in skin Changes in symptom clusters over time: Five symptom clusters (i.e., psychological, hormonal, nutritional, GI, epithelial) were relatively stable across both symptom dimensions and across all six timepoints Two symptom clusters (i.e., sickness behavior, weight change) varied by time but not symptom dimension Additional outcomes: N/A	
Wiggenraad et al., 2020 Purpose(s): Evaluate for longitudinal changes in symptom	*n* = 60 (total sample n=206) Mean age: 53.3 (±10.0) years Range: NR	Instrument(s): MSAS: 32 symptoms Criteria used to exclude symptoms: Yes	3 symptom clusters identified across each timepoint for the control group:	Strengths: Evaluated for symptom clusters across multiple timepoints

clusters and core burdensome symptoms in breast cancer patients Design: longitudinal Location: Sweden	Female: 100.0% Ethnicity: NR Race: NR Employment status: Employed 80.3% Not employed 19.7% Inpatients: NR Outpatients: NR Diagnosis: Breast cancer 100.0% Treatment: Adjuvant CTX 100.0% Timepoints of symptom assessment: T1: 1 week prior to 2nd CTX treatment (baseline) T2: 16 weeks post-T1 T3: 12-months post-T1	Analysis: PCA Dimension(s): symptom burden (calculated as the average of the frequency, severity, and distress scores of each symptom) Symptoms allowed to load on more than one factor: No Minimum factor loadings required to include symptom within cluster: 0.50 Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints: NR Analysis of secondary outcomes: N/A	**T1** Emotional cluster: feeling nervous, lack of appetite, feeling sad, feeling irritable, pain, difficulty sleeping, shortness of breath, "I don't look like myself" Treatment-related toxicity cluster: lack of energy, difficulty concentrating, feeling bloated, diarrhea, worrying, feeling drowsy, nausea Physical cluster: hair loss, changes in the way food tastes, sweats **T2** Emotional cluster: feeling irritable, swelling of arms or legs, problems with sexual interest or activity, sweats, feeling bloated, feeling sad, worrying, numbness Treatment-related toxicity cluster: lack of appetite, dry mouth, changes in the way food tastes, changes in skin Physical cluster: difficulty sleeping, feeling drowsy, "I don't look like myself", difficulty concentrating, lack of energy **T3** Emotional cluster: lack of energy, feeling nervous, feeling sad, difficulty	Symptom clusters were created using symptom burden Used a valid and reliable symptom measure Limitations: Patients were recruited from a single hospital Small sample size Did not use a method to assess for stability of symptoms across timepoints

			concentrating, feeling irritable, pain Treatment-related toxicity cluster: numbness, sweats Physical cluster: dry mouth, difficulty sleeping Changes in symptom clusters over time: Three symptom clusters were discovered at each timepoint However, the symptoms within two of the symptom clusters (i.e., treatment-related, physical) were not stable Symptoms within only one cluster (i.e., emotional) remained relatively stable across timepoints Additional outcomes: N/A	

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; ASA = American Society of Anesthesiologists; CTX = chemotherapy; CIPN = chemotherapy-induced peripheral neuropathy; EFA = exploratory factor analysis; FACIT-F = Functional assessment of Chronic Illness Therapy-Fatigue; FACT = Functional Assessment of Cancer Therapy; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; FSIS = Female Sexual Function Index; GI = gastrointestinal; HADS = Hospital Anxiety and Depression Scale; MDASI = M.D. Anderson Symptom Instrument; MSAS = Memorial Symptom Assessment Scale; NR = not reported; NRS = Numeric Rating Scale; PCA = principle component analysis; PSQI = Pittsburgh Sleep Quality Index; QOL = quality of life; SES = Symptom Experience Scale; TSO = Treatment-Specific Optimism