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” <u>GI cluster</u>: difficulty concentrating, nausea, vomiting, change in the way food tastes <u>Psychological cluster</u>: feeling nervous, feeling sad **T3** <u>Nutritional cluster</u>: dry mouth, change in the way food tastes, difficulty concentrating, constipation, “I don’t like myself <u>GI cluster</u>: difficulty concentrating, nausea, vomiting, sweats <u>Psychological cluster</u>: feeling nervous, feeling sad <u>Body image cluster</u>: itching, changes in skin <u>Changes in symptom clusters over time</u>: 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 <u>Lung cancer-specific cluster</u>: chest tightness, cough, difficulty breathing, shortness of breath, weight loss, dizziness, pain <u>Epithelial/GI cluster</u>: 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 <u>Psychological cluster</u>: nausea, vomiting, feeling irritable, feeling nervous, feeling sad, worrying <u>Nutritional cluster</u>: increased appetite, lack of appetite, weight gain *Severity symptom clusters* **T1** <u>Lung cancer-specific cluster</u>: feeling drowsy, lack of energy, chest tightness, cough, difficulty breathing, shortness of breath, dizziness, pain <u>Epithelial/GI cluster</u>: 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