#CO126

A Targeted Literature Review to Identify Patient-Reported Symptoms Associated With Breast Cancer Disease Progression

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BACKGROUND AND OBJECTIVES

- As more treatments for advanced BC continue to emerge, leading to longer survival, earlier patient-relevant endpoints are needed to evaluate clinical benefits and support regulatory and health technology assessment submissions
- Living with progressive disease is the reality for patients with advanced BC[1]; therefore, achieving better symptom management can be critical for maintaining patient quality of life
  - However, symptom interpretation is complex, with worsening or new symptoms potentially reflecting disease progression, treatment-related side effects, or comorbidities[2]
  - Uncertainty around symptom interpretation complicates clinical decision-making and underscores an urgent need to identify the symptoms that reliably indicate disease progression
- Symptomatic progression does not always occur in parallel with radiographic progression; in patients with BC, symptom deterioration can precede imaging confirmed disease progression[3]
- Due to such heterogeneity, patient perspectives are increasingly shaping trial design, with some health technology assessment bodies prioritizing patient-relevant intermediate endpoints, such as symptomatic progression and quality of life, over measures such as imaging-based progression[4,5]
- The objective of this targeted literature review was to identify and synthesize qualitative evidence on patient-reported signs and symptoms associated with BC progression across all BC stages
  - These insights will help with the development of robust symptom-based endpoints that could be used in advanced BC clinical trials

METHODS

- The PubMed, ESMO, Embase, and ASCO databases were searched for publications reporting signs and symptoms associated with BC progression across 15 years until December 2025 (**Figure 1**)
- The Patient, Intervention, Comparison, Outcome, Study Design (PICOS) framework was used to identify patient-reported symptoms across all BC stages with the goal of identifying symptoms associated with disease progression
- Insights were qualitatively assessed to better understand symptom severity and their association with progressive disease
- Data were extracted by one experienced researcher, with quality checks performed on a sample of 20% by a second researcher

Figure 1. Targeted Literature Search

Target search		PICOS	Search strategy
Objective	• To understand signs and symptoms reported by patients with advanced BC from published literature across 15 years until December 2025	*Population*	• Adult female patients with BC[a]
		Intervention/ comparison	• N/A
Databases	• PubMed, ESMO, Embase, ASCO	*Outcomes of interest*	• Concepts (ie, signs and symptoms of BC progression)
Output	• Patient experience of living with advanced BC • Symptoms related to disease progression in BC		• Patient interview studies • Noninterventional studies • Observational studies • Systematic reviews • Targeted reviews • Retrospective studies • Patient surveys

[a]Including patients with all BC subtypes.

RESULTS

- Ten of 723 articles met the full extraction criteria (patient-reported data from BC populations), including 8 primary research and 2 review articles (**Figure 2**)
- The 10 selected articles included studies in patients with advanced or metastatic BC across various countries (**Table 1**)

Figure 2. Literature Search PRISMA Flowchart

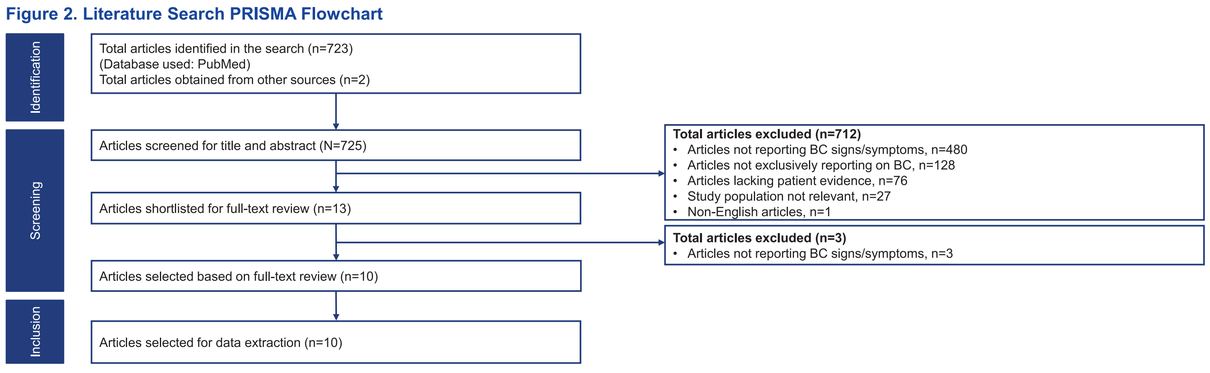


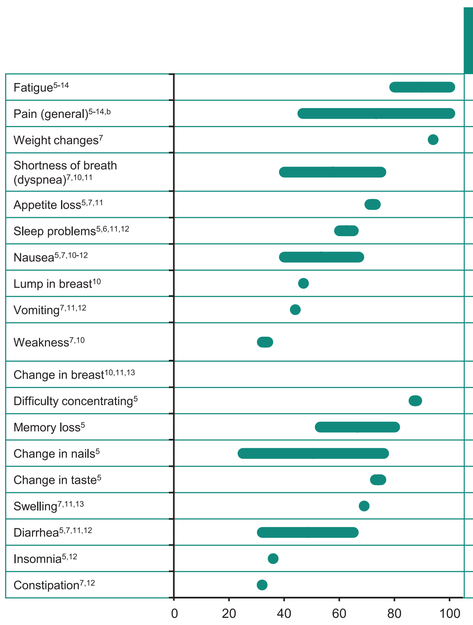
Table 1. Selected Articles

Ref no.	PMID	Title	Journal	Year of Publication	Study Type	Country
6	21689425	**Walker et al.** Retrospective study of the effect of disease progression on patient reported outcomes in HER-2 negative metastatic breast cancer patients	*Health and Quality of Life Outcomes*	2011	Semi-structured concept elicitation patient interviews	USA
7	28432593	**Niklasson et al.** Talking about breast cancer: which symptoms and treatment side effects are important to patients with advanced disease?	*Patient*	2017	Semi-structured concept elicitation patient interviews	USA
8	29597131	**Wang et al.** Health-related quality of life and utility scores of patients with breast neoplasms in China: a multicenter cross-sectional survey	*Breast*	2018	Cross-sectional concept elicitation patient interviews and survey	China
9	30584354	**Cherny et al.** Palliative care: needs of advanced breast cancer patients	*Breast Cancer* (Dove Medical Press)	2018	Review article	No country was reported; authors based in Israel
10	30734110	**Galipeau et al.** Understanding key symptoms, side effects, and impacts of HR+/HER2− advanced breast cancer: qualitative study findings	*Journal of Patient-Reported Outcomes*	2019	Qualitative concept elicitation patient and HCP interviews	USA
11	30937601	**Whisenant et al.** What symptoms are important to patients? Developing a symptom burden measure for women with breast cancer	*Support Care in Cancer*	2019	Semi-structured concept elicitation patient interviews	USA
12	32555955	**Lima and Silva.** Quality of life of women with locally advanced or metastatic breast cancer	*Revista Gaucha de Enfermagem*	2020	Cross-sectional quantitative patient interviews	Brazil
13	33167930	**Ng et al.** Presentation of breast cancer, help seeking behaviour and experience of patients in their cancer journey in Singapore: a qualitative study	*BMC Cancer*	2020	Semi-structured and open-ended concept elicitation patient interviews	Singapore
14	33749151	**So et al.** Symptom clusters experienced by breast cancer patients at various treatment stages: a systematic review	*Cancer Medicine*	2021	Review article	No country was reported; authors based in China and Australia
5	36649275	**Flood et al.** Using qualitative interviews to identify patient-reported clinical trial endpoints and analyses that are the most meaningful to patients with advanced breast cancer	*PLoS One*	2023	Cross-sectional, semi-structured concept elicitation patient interviews	USA and UK

- A broad range of symptoms were reported across BC stages, with fatigue and pain consistently among the most common disease-related symptoms (**Figure 3**)
  - A high prevalence of weight changes, shortness of breath (dyspnea), appetite loss, sleep problems, and cognitive functioning–related symptoms has also been reported

Figure 3. Prevalence and Clinical Characteristics of Reported Symptoms in BC

	Publications that provide symptom prevalence data	Disease-related symptoms[a]	Treatment-related symptoms[a]	Related metastatic site	BC subtype of studied population	Reported BC stage
Fatigue[5-14]	5, 10	Yes	Yes	Not reported	TNBC and HR+/HER2−	III/IV
Pain (general)[5-14,b]	5, 7, 10	Yes	Yes	Bone, liver, spinal cord	TNBC and HR+/HER2−	III/IV
Weight changes[7]	7	Yes	Yes	Not reported	Locally advanced/metastatic	III/IV
Shortness of breath (dyspnea)[7-10,11]	7, 10	Yes	Yes	Lung	TNBC, HR+/HER2−, and locally advanced/metastatic	III/IV
Appetite loss[5,7,11]	5	Yes	Yes	Not reported	Locally advanced/metastatic	III/IV
Sleep problems[5,6,11,12]	5	Yes	Yes	Not reported	TNBC and HR+/HER2−	III/IV
Nausea[5,7,10-12]	5, 7, 10	Yes	Yes	Not reported	TNBC and HR+/HER2−	III/IV
Lump in breast[10]	10	Yes	No	Not reported	TNBC and HR+/HER2−	I/II
Vomiting[7,11,12]	7	Yes	Yes	Not reported	Locally advanced/metastatic	III/IV
Weakness[7,10]	7, 10	Yes	Yes	Spinal cord	TNBC, HR+/HER2−, and locally advanced/metastatic	III/IV
Change in breast[10,11,13]	–	Yes	Yes	Not reported	Not reported	II-IV
Difficulty concentrating[5]	5	Not reported	Not reported	Not reported	TNBC and HR+/HER2−	III/IV
Memory loss[5]	5	Not reported	Not reported	Not reported	TNBC and HR+/HER2−	III/IV
Change in nails[5]	5	No	Yes	Not reported	TNBC and HR+/HER2−	III/IV
Change in taste[5]	5	No	Yes	Not reported	TNBC and HR+/HER2−	III/IV
Swelling[7,11,13]	7	No	Yes	Not reported	Locally advanced/metastatic	III/IV
Diarrhea[5,7,11,12]	5, 7	No	Yes	Not reported	Locally advanced/metastatic	III/IV
Insomnia[5,12]	5	No	Yes	Not reported	TNBC and HR+/HER2−	III/IV
Constipation[7,12]	7	No	Yes	Not reported	Locally advanced/metastatic	III/IV



[a]Symptoms were classified as disease related or treatment related based on clinician and patient reports during interviews. [b]Refers to general pain or nonspecific pain. [c]Prevalence ranges are presented where available. Circles represent the prevalence from single studies when no range is available.

- In patients with triple-negative or HR+/HER2− BC, fatigue and pain were the most prevalent and bothersome symptoms associated with advanced disease (**Table 2**)
- Patient quotes demonstrate the lived impact of pain, fatigue, swelling, and nausea and vomiting across BC stages (**Figure 4**)

CONCLUSIONS

- The current literature provides key insights on symptoms related to BC, demonstrating a higher burden in patients with advanced BC
  - Across studies, fatigue and pain consistently emerged as the most prevalent and burdensome symptoms, including in patients with TNBC and HR+/HER2− disease
  - The insights collected from this study will be invaluable to support future development of symptom-based endpoints for patients with advanced BC
- Although the current evidence provides limited insight into the evolution of symptoms at progression, the literature consistently demonstrates higher symptom burden and greater unmet medical need with advancing BC
  - An evidence gap remains regarding symptom evolution with disease progression, especially in subpopulations such as HR+/HER2− BC, and across treatment lines for advanced BC
- Given the clinical and patient-centered relevance of symptomatic disease progression, further research is needed to inform clinical practice and trial endpoints
  - The lack of patient-reported symptoms specifically related to disease progression was identified as an important evidence gap
- Investigating patient-reported symptoms around the time of progression may identify symptoms that are associated with disease progression and which were not identified in the current targeted literature review
  - The next phase of this project will directly address this evidence gap by qualitatively capturing patient-reported symptoms around the time of progression, generating insights that were limited in the current literature

RESULTS (continued)

Table 2. Symptoms Reported in Patients With TNBC or HR+/HER2− BC

Symptom	Prevalence in TNBC, %[5]	Prevalence in HR+/HER2− BC prevalence, %[5]	Average bothersome rating[5,a]	Mentioned as most bothersome, %[10]	Disease related, %[10]	Treatment related, %[10]
Lump in breast	—	46.7[10]	—	0	46.7	0
Fatigue/tiredness	94	80-100[5,10]	8	13.3	46.7	46.7
Pain[b]	59	46.7-87[5,10]	8	13.3	26.7	26.7
Difficulty concentrating	88	87	7	—	—	—
Memory loss	53	80	7	—	—	—
Sleep problems	65	60	7	—	—	—
Shortness of breath (dyspnea)	—	40[10]	—	20	20.0	13.3
Weakness	—	33.3[10]	—	6.7	6.7	26.7
Nausea	59	40-67[5,10]	7	0	6.7	40
Hair loss[c]	88	66.7-80[5,10]	6	6.7	0	66.7
Hot flashes	47	87	7	—	—	—
Diarrhea	53	73	6	—	—	—
Change in nails	76	73	5	—	—	—
Loss of appetite	71	73	5	—	—	—
Change in taste	75	73	5	—	—	—

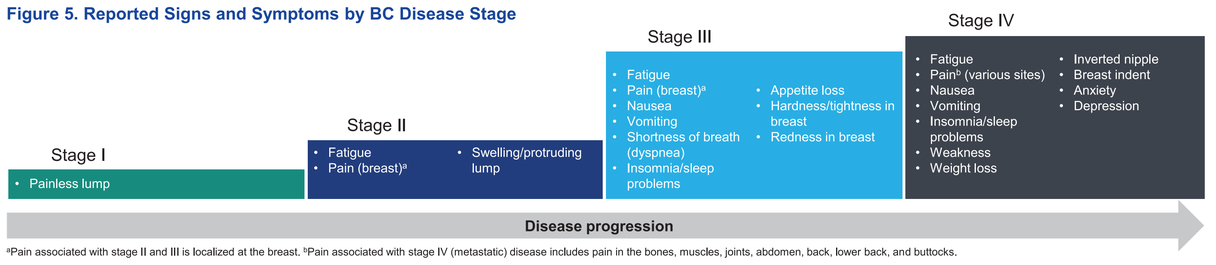
Data for HER2+ BC were not available.
[a]Average bothersome rating: 0 = not bothersome; 10 = extremely bothersome. [b]Pain was defined differently across studies: Flood et al. (2023)[5] reported metastatic site-specific pain, whereas Galipeau et al. (2019)[10] reported general/nonspecific pain. [c]Flood et al. (2023)[5] reported hair loss but did not explicitly identify it as a treatment-related side effect; Galipeau et al. (2019)[10] reported hair loss as treatment related.

Figure 4. Patient Experiences of Pain, Fatigue, Swelling, and Nausea and Vomiting

	BC (stages I-III)[11]	TNBC and HR+/HER2− (stage I/II)[10]
Pain	"I didn't have use of my arm very much at all **because I would have a sharp, shooting pain** that would go up, **and it was stopping me from doing anything.**"	"I say bad, you know, just—well, the only thing that really, **really hurt me a lot was my legs**. My legs were just—it, it felt to where **I could barely walk sometimes**. …Towards the end of the treatment it would get a little better. But **even after the treatment stopped**, um, **the pain in my legs were so bad** I had to end up going back to the doctor to see maybe it was something else."
Fatigue	"**The fatigue was pretty strong**… At lunch I would close my door **and lay my head down and take a nap**. Not that that does not sound good every day, but I typically do not have to do that every day."	"Now there are days when **you're really tired or you wake up and you feel weak**. But it's not every day. It's just some days that you're, you're tired and you're weak."
Lump and swelling	"A barely perceptible **swelling** in my **left breast**, and it was not something that one would ordinarily notice with normal breast self-examination because **it was not palpable** when lying down. Only when standing up, **I perceived somewhat more heaviness on one side than the other.**"	"**I found the lump myself** and, um, putting on my deodorant and I saw **an inversion in my breast** and I knew that was a sign of BC. …the first one **I felt was like hard as a rock**…I could see them. They were out. They weren't in, you know, where you could just feel it. They were out. **They were popping out.**"
Nausea and vomiting	"Just **extreme nausea**. I'd get in the car and it was like, oh, my God! I do not think I am going to make it home."	

- Eighteen symptoms were identified in patients with all types of stage II-IV mBC, with increasing burden associated with advanced BC; however, the studies did not indicate any association with disease progression (**Figure 5**)
- Four studies provided metastatic site–specific symptoms, including brain (headache/focal seizure), lung (cough/shortness of breath [dyspnea]), and liver (abdominal pain) (**Table 3**)
  - Several site-specific symptoms, including pain, shortness of breath (dyspnea), and weakness, overlapped with symptoms reported more broadly across BC populations

Figure 5. Reported Signs and Symptoms by BC Disease Stage



[a]Pain associated with stage II and III is localized at the breast. [b]Pain associated with stage IV (metastatic) disease includes pain in the bones, muscles, joints, abdomen, back, lower back, and buttocks.

Table 3. Reported Signs and Symptoms by Site of Metastases

Metastatic site[a]	Reported signs or symptoms
Bone	Bone pain, general pain
Brain	Headache, confusion, focal seizures
Leptomeningeal	Headache, cranial nerve palsies, radicular pain in lower back and buttocks, double vision, hearing loss, facial numbness, decreased vision
Liver	Abdominal pain
Lung	Cough, shortness of breath (dyspnea)
Lymph node	Lymphedema, lymph node inflammation
Spinal cord	Progressive back pain, weakness, sensory loss, autonomic dysfunction, reflex abnormalities

[a]Symptoms for skin and peritoneum metastasis were not reported.

DISCUSSION

- The current targeted literature review consistently indicates increasing symptom burden with advancing disease stage; however, limited insights were available on the evolution of symptoms with disease progression, specifically whether symptoms worsen, new symptoms emerge, or other symptomatic changes reflect disease progression vs treatment-related toxicities
- Fatigue and pain were consistently the most commonly reported and burdensome symptoms in patients with advanced BC, including those with TNBC and HR+/HER2− disease
- Evidence from real-world studies and clinical trials demonstrated that disease progression is associated with deterioration in symptoms and HRQOL, captured through validated PRO instruments[6,15,16]
- Walker et al (2011)[6] performed a retrospective analysis linking disease progression events documented in medical records with longitudinal symptom assessments collected during routine clinical care from patients with HER2− metastatic BC
  - Fatigue, pain, and trouble sleeping were identified as patient-reported measures that worsened with disease progression, along with worsening of general physical symptoms
- As patient perspectives increasingly shape trial designs and some health technology assessment bodies prioritize patient-relevant endpoints over measures such as imaging-based progression, it becomes increasingly important to better characterize how patient-experienced symptoms evolve with disease progression, particularly across treatment lines in advanced BC

LIMITATIONS

- Targeted literature reviews use predefined, narrower search strategies, which are less exhaustive and may omit relevant studies that a full systematic review would capture
- Non–English language publications, and gray literature were excluded, which may have omitted important relevant evidence
- Conference abstracts were excluded due to a lack of methodological and qualitative detail (such as patient quotes and concept elicitation methods) which are needed to extract patient-reported symptom data; however, this could have led to the exclusion of relevant data
- Despite the limitations, the findings of this targeted literature review provide insight into where evidence is sparse and where further research is needed to understand symptoms associated with disease progression in patients with BC

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ABBREVIATIONS

ASCO, American Society of Clinical Oncology; BC, breast cancer; HCP, healthcare professional; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRQOL, health-related quality of life; mBC, metastatic breast cancer; N/A, not applicable; PICOS, Patient, Intervention, Comparison, Outcome, Study Design; PMID, PubMed Identifier; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRO, patient-reported outcome; TNBC, triple-negative breast cancer.

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