



What symptoms are important to patients? Developing a symptom burden measure for women with breast cancer

Meagan S. Whisenant¹ · Faith A. Strunk² · Debasish Tripathy³ · Loretta A. Williams¹

Received: 5 November 2018 / Accepted: 21 March 2019 / Published online: 2 April 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Purpose The American Cancer Society predicted that 266,120 women would be diagnosed with breast cancer in 2018. Women experience significant symptom burden in response to tumor and treatment-related adverse effects, particularly in advanced disease. Use of valid and reliable patient-reported outcomes (PRO) symptom measures may assist clinicians in systematically monitoring and managing symptoms. The MD Anderson Symptom Inventory (MDASI) is a brief PRO measure of cancer symptom burden; specific symptoms can be added to the core symptoms to produce disease- and treatment-specific modules. The purpose of this study was to describe the patient symptom experience, define the content domain, and generate items for a breast cancer-specific MDASI module for measuring symptom burden in women with breast cancer.

Methods Women with breast cancer were qualitatively interviewed about their experiences of disease and treatment. Descriptive exploratory analysis identified symptoms and symptom interference to define the symptom burden of breast cancer. An expert panel rated the relevance of the identified symptoms to patients with breast cancer.

Results A conceptual model of breast cancer symptom burden was developed from interviews with 36 women (mean age of 57.9 years, 86.1% had stages I–III, and 52.8% were on chemotherapy and/or radiation therapy) across the breast cancer disease and treatment trajectory. Thirty-six symptoms and 6 interference categories were identified. Symptoms specific to treatment modalities and breast cancer met the criteria for inclusion in the provisional instrument for psychometric testing.

Conclusions We generated an instrument with content validity for measuring symptom burden specific to women with breast cancer.

Keywords Oncology · Symptoms · Patient-reported outcomes · Breast cancer · Chemotherapy · Endocrine therapy · Hormonal therapy

✉ Meagan S. Whisenant
mswhisenant@mdanderson.org

Faith A. Strunk
Faith.A.Strunk@uth.tmc.edu

Debasish Tripathy
DTripathy@mdanderson.org

Loretta A. Williams
loriwilliams@mdanderson.org

¹ Department of Symptom Research, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1450, Houston, TX 77030, USA

² Department of Acute and Continuing Care, The University of Texas Health Science Center at Houston School of Nursing, 6901 Bertner Avenue, SON-686, Houston, TX 77030, USA

³ Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1354, Houston, TX 77030, USA

Introduction

The American Cancer Society predicted that 266,120 women would be diagnosed with breast cancer in 2018, making breast cancer the most frequently diagnosed cancer for women [1]. Most patients present with early-stage breast cancer, which has an expected 5-year survival rate of 91% [1]. Of the estimated 3.5 million breast cancer survivors in the USA, a significant proportion will experience transient or permanent symptoms related to their treatment [2].

Symptoms are subjective phenomena reported by patients that indicate a change in normal functioning, sensation, or appearance due to disease [3]. Symptom burden is the combined impact of all disease- and therapy-related symptoms on the ability of persons to function as they did prior to onset of their disease and/or therapy [4]. Across the disease trajectory for breast cancer, women experience significant and variable

symptom burden that may be disease-related or that may occur in response to treatments, such as the acute and sometimes chronic effects of surgery, chemotherapy, radiation therapy, or hormonal therapies [5]. Although breast cancer may be associated with increased survival compared with other cancers, this prolonged survivorship can produce uncertainty due to fear of recurrence/progression, residual symptom burden, and functional limitations from treatment effects [5–8].

Optimal symptom management depends on frequent and accurate symptom assessment and communication between patients and clinicians [9]. Even though increased symptom communication between patients and clinicians reduces symptom distress and improves outcomes [10–16], best practices for symptom monitoring remain unknown [17, 18]. Use of valid and reliable patient-reported outcome (PRO) symptom measures may assist clinicians in systematically monitoring cancer symptoms, improving the ability of clinicians to improve symptom management [17]. While there are existing valid and reliable PRO measures specific to breast cancer, including the Functional Assessment of Cancer Therapy-Breast (FACT-B) and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Breast Cancer Module (QLQ-BR23), these measures assess health-related quality of life (HRQOL), which is often too general a concept to be sensitive to important changes caused by disease and treatment [19–25]. Symptom burden is a subset of HRQOL and refers the components most closely related to the physiological effects of disease and treatment, symptoms, and functioning [4, 24]. In contrast to existing measures of HRQOL, a measure of symptom burden allows a focus on the domains most related to a single disease and treatment, which allows judgements to be made about the disease and treatment impact on the patient [25]. A breast cancer-specific PRO measure of symptom burden is needed for use in clinical practice to facilitate assessment of breast cancer disease- and treatment-related symptoms and functioning, enhancing patient-clinician communication in clinical care.

The MD Anderson Symptom Inventory (MDASI) is a brief PRO measure of the severity of 13 symptoms and 6 areas of symptom interference with daily life that are common to all cancer types [4]. The core MDASI has been validated for use in multiple cancer diagnoses; in addition, symptoms that are unique to a particular population can be added to the core symptoms to produce disease- and treatment-specific modules [26–28]. Whereas the core MDASI is validated for use in patients with breast cancer and has been used in large studies that have included patients with breast cancer [28], it may not include some symptoms that are relevant to the breast cancer population, such as symptoms of lymphedema.

A disease-specific, symptom-specific tool for routine symptom monitoring and clinical research in breast cancer, developed using the current standard of practice for instrument

validation, is needed [19]. Instrument development involves several phases and should proceed from a conceptual model or framework that describes the theoretical relationships among concepts [29, 30]. Content domain specification, item generation, and subsequent psychometric testing are guided by this conceptual model. Thus, instrument development begins with obtaining the input of patients with the diagnosis of interest to ensure content validity [29]. After the content domain is specified, items are generated. This is followed by the judgment qualification stage, in which a panel of experts assesses the degree to which the items adequately represent the specified content domain [31, 32]. The concept of symptom burden, with its inclusion of both the severity of symptoms common to breast cancer and its treatment and the impact of those symptoms on daily living [4, 24], provides the framework for the development of a MDASI module specific to breast cancer.

The purpose of this paper is to describe the symptom burden of women with breast cancer and to delineate the content domain and generate items for a PRO measure of symptom burden specific to breast cancer, the MDASI for breast cancer (MDASI-Br). Within the symptom burden framework, we expected that women with breast cancer experience symptom burden common to all patients with cancer, but with additional symptoms related specifically to breast cancer and its treatment.

Methods

Women with breast cancer participated in single, semistructured qualitative interviews conducted by trained research staff to determine the aspects of the breast cancer disease and treatment experience that were most important to them. Eligibility criteria included having a diagnosis of breast cancer, being 18 years of age or older, being able to speak and read in English, and having no known brain metastasis or other malignancy besides breast cancer. Sampling was purposive, in that eligible women were approached for participation according to desired percentages of characteristics that have been previously shown to be related to differences in symptom burden, such as sex, age, race/ethnicity, and prior treatment [33]. The sample included women across all stages of the breast cancer trajectory, from early-stage newly diagnosed through survivorship. We purposively sampled for 5 informants in each clinical group: pretreatment, perioperative, receiving chemotherapy, receiving radiation therapy, with metastatic disease, with lymphedema, and survivors receiving endocrine therapy and not receiving endocrine therapy. We planned to recruit patients until saturation was reached, such that no new symptoms or functional interference information were identified in 3 consecutive interviews [33].

Women being seen in the Breast Center at The University of Texas MD Anderson Cancer Center were screened for eligibility from the medical record, and potential participants were approached by study staff, who explained the purpose

and procedures of the study. The study was approved by the MD Anderson Institutional Review Board, and all participants provided written informed consent. Demographic, disease, and treatment-related data were collected from the patient's medical record.

Qualitative interviews

Research staff trained in qualitative interviewing conducted the individual qualitative interviews using an interview guide with open-ended questions (Table 1) [33]. Interviews were conducted in a private room at MD Anderson with only the participant and the interviewer present. In-depth interviews began with a general question, such as “What is it like for you to have breast cancer?” Participants were encouraged to report their experiences at diagnosis, during different treatments, and when their disease progressed, using open-ended questions such as, “What other symptoms have you experienced that were related to breast cancer or any treatments you may have received for breast cancer?” Probe questions were asked to gain further insight into the patient's experience. Interviews were digitally recorded and transcribed verbatim.

Analysis

Descriptive statistics were used to present the sample's demographic, disease, and clinical characteristics. Three experienced qualitative researchers initially independently reviewed the interviews and identified symptom concepts, descriptions, and names using descriptive exploratory techniques [33]. Symptoms were divided into disease symptoms (those symptoms reported at diagnosis or after disease progression) and treatment symptoms (those symptoms reported to occur during treatment). Exact participant quotes describing each symptom were extracted. The researchers met to review, discuss, and resolve differences in symptom concepts, description,

names, and categorization. Decisions were made about the discrete nature of identified symptoms. The interview transcripts were reviewed by the team to ensure that the context of each symptom name was understood and that the name had been assigned correctly. Team decisions about inclusion and combining of symptom names were documented. The researchers compiled a single list capturing all symptoms; this list was agreed upon by all members of the analysis team jointly. The numbers and percentages of participants who mentioned each disease symptom and treatment symptom were determined to identify symptoms common to breast cancer and its treatment. A symptom was considered to be common if it was reported by 20% or more of participants interviewed.

Expert panel rating

The list of disease and treatment symptoms generated from the qualitative interviews was presented to a panel of experts, who were asked to rate the relevance of each symptom to patients with breast cancer. Potential expert panel participants were identified by staff in the MD Anderson Breast Center. Healthcare providers were recruited by email; patients and caregivers were approached during a follow-up visit in the Breast Center. The panel included 6 physicians (medical, surgical, and radiation oncologists) and 6 other healthcare providers (mid-level practitioners and clinical nurses) experienced in the care of patients with breast cancer, 6 women with breast cancer, and 6 family caregivers of women with breast cancer. The relevance of the symptoms on the list of symptoms generated from the qualitative interviews was rated on a scale of 1–4, with 1 meaning not relevant and 4 meaning very relevant.

Provisional MDASI-Br module

Symptoms were selected for inclusion in the provisional instrument for psychometric testing and cognitive debriefing if they met at least one of the following criteria: (1) the item received a mean relevance rating of ≥ 3 (3 = relevant) by the panel of breast cancer experts; (2) at least 20% of the sample mentioned the symptom as a disease or treatment symptom during qualitative interviews; or (3) the symptom was one of the 13 core MDASI items, which have been extensively psychometrically validated and used in a broad range of patients with cancer for many years.

Results

The experience of breast cancer was consistent across patients and saturation was easily reached, with no new information being found after 36 interviews were analyzed. Participant

Table 1 Interview guide for qualitative interviews

Semistructured interview questions (follow-up probe questions as needed)
What is it like for you to have breast cancer?
Have all the important aspects of experiencing breast cancer been described?
What was it like for you when you first had breast cancer?
Have all the important aspects of experiencing breast cancer been described?
What do you see happening in the future with your breast cancer?
Are there any other aspects of experiencing breast cancer that you would like to tell me about?
Is there anything else important about having breast cancer that you would like to tell me?

Table 2 Sample characteristics for participants diagnosed with breast cancer ($n = 36$)

	Mean	SD
Age (years)	57.9	12.1
	Frequency	Percentage
Sex		
Female	36	100.0
Race		
White	28	77.8
Asian	1	2.8
African American	7	19.4
Ethnicity		
Hispanic	6	16.7
Non-Hispanic	30	83.3
Cancer stage at diagnosis		
I	6	16.7
II	15	41.7
III	9	25.0
IV	5	13.9
Treatment status at time of interview		
Active treatment (chemotherapy and/or radiation therapy)	19	52.8
Survivorship	17	47.2

SD standard deviation

demographic and clinical characteristics are summarized in Table 2. The sample had a mean age of 57.9 (standard deviation = 12.1), 86.1% had stage I–III diseases, 13.9% had stage IV disease, and 52.8% were on chemotherapy and/or radiation therapy at the time of the interview.

Patient quotes exemplifying the most common symptoms reported in the interviews are detailed in Table 3. The main symptom-related themes found in the analysis were symptom occurrence, symptom severity, symptom interference with activities, and symptom management. A total of 36 symptoms were identified, with 4 reported by $\geq 20\%$ of participants. Symptoms varied among participants by disease stage and treatment modalities received. One uniquely disease-related symptom, coughing, was identified; 11 other disease symptoms were also reported by patients as being treatment-related symptoms. In addition, 24 symptoms were identified as being solely treatment-related.

The identified disease and treatment symptoms and the mean ratings of each symptom item by the expert panel were calculated and are shown in Table 4, which presents how each symptom met the criteria for inclusion in the final MDASI-Br module. The common disease symptoms identified by patients in the qualitative interviews as occurring at diagnosis or at disease recurrence included distress (86.1%) and breast changes (22.2%). The common treatment symptoms identified by patients as occurring during treatment included pain

(69.4%), fatigue (tiredness) (58.3%), distress (58.3%), skin changes (50.0%), nausea (33.3%), numbness/tingling (30.6%), disturbed sleep (27.8%), arm swelling (27.8%), hot flashes (22.2%), fingernail/toenail changes (22.2%), and constipation (22.2%). Fatigue and distress were described by most women regardless of treatment: numbness/tingling and fingernail/toenail changes were described by women who had received chemotherapy; arm swelling was described by women postsurgery; skin changes were described by women receiving radiation therapy; and menopausal symptoms, including hot flashes, vaginal dryness, and decrease in sexual interest or activity, were described by women receiving endocrine therapies. The final list of symptoms to be included in the provisional MDASI-Br is presented in Table 5.

The qualitative analysis also confirmed that symptoms interfered with patients' daily activities, work, walking, relationships with others, and mood. Figure 1 illustrates the final content domain of the provisional MDASI-Br, including all symptom and interference items.

Discussion

The content domain for a PRO measure of breast cancer symptom burden encompasses the severity of common symptoms of breast cancer and its treatment and the interference of those symptoms with daily functioning. In the current study, women with breast cancer described numerous symptoms related to their disease and treatment, with various treatment modalities resulting in unique symptom burden. Participants described the 13 core MDASI symptoms of pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, problems remembering things, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness/tingling, which are common to all patients with cancer. Additional symptoms specific to breast cancer and its treatment also were described. On the basis of these findings, we developed a provisional version of the MDASI-Br, a breast cancer-specific module of the MDASI, to measure the symptom burden experienced by women with breast cancer. The provisional MDASI-Br includes the 13 core MDASI symptom items plus 8 breast cancer-specific items identified through qualitative interviews with women with breast cancer and an expert panel review: hot flashes, breast changes, constipation, arm swelling, fingernail or toenail changes, skin changes, decrease in sexual interest or activity, and vaginal dryness.

Importantly, women with breast cancer described symptoms unique to various treatment modalities, either currently or previously received. For example, only women who had a history of surgery described arm swelling and only women who had received chemotherapy described numbness/tingling. This is consistent with the symptom experience described by Boehmke and Dickerson, who found that the

Table 3 Quotes from qualitative interviews illustrating symptom findings

Breast cancer disease symptoms	
Breast changes	“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.” – 68-year-old female
Distress	“I was like nervous. I was scared. I do not know whether to come here, go somewhere else. I did not know what to do. I was lost. It was like a total complete change. It changed everything. It was horrible.” – 51-year-old female
Breast cancer treatment symptoms	
Pain	“After the surgery – the breast area was just so tender that any time we were driving, and you hit a bump – just pretty much having to hold onto your breast.” – 51-year-old female
Fatigue (tiredness)	“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.” – 47-year-old female
Distress	“So there’s anxiety. I think most of my anxiety is about my family, what they’ll go through... how are my daughters and my son going to deal with it? What are they going to go through?” – 65-year-old female
Skin changes	“As the radiation proceeded, then you find out that spots hurt because it’s sunburned. Radiation burned.” – 64-year-old female
Nausea	“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.” – 67-year-old female
Numbness or tingling	“It’s either numb or tingly. The tingling is better for me than the numb, because it’s really kind of hard to walk when your feet are numb.” – 50-year-old female
Disturbed sleep	“The lack of sleep and the interruption at night when you are going through treatment – how many times you get up to go to the bathroom.” – 58-year-old female
Arm swelling	“I started noticing the swelling. And at first, I did not know what it was...it feels like your skin is stretching. It feels tight...it does hurt.” – 44-year-old female
Hot flashes	“The hot flashes...are horrible. It happens mainly at night, and that’s when I wake up and I cannot sleep.” – 36-year-old female
Fingernail or toenail changes	“My toenails turned black. When I had the skin toxicity, my toenails, my fingernails, all turned black. I mean black to the core. And they just looked horrible. My toenails have not grown out yet.” – 51-year-old female
Constipation	“I had severe, severe constipation. It was another fallback when you do the medication, because I already had problems with constipation. And then taking the opiates and all of those drugs... you have little to no bowel movement.” – 60-year-old female

symptom experience is congruent with the type of treatment received [5], and the treatment-attributed symptoms described by Niklasson, Paty, and Ryden [34]. Given that item selection may vary by current and/or previous treatment modality as well as by disease stage, researchers developing PRO measures of symptom burden unique to breast cancer must take care to include the disease symptoms as well as the most important symptoms associated with a particular treatment modality, while reducing participant burden by not including symptoms of treatments a patient has not received.

Women described interference of symptoms with daily activities, work, walking, relationships with others, and mood. Boehmke and Dickerson describe this as how “life had changed,” suggesting that the diagnosis of cancer and subsequent symptom experiences affect a woman’s daily life and

functioning [5]. Others have described the impact of pain and distress on daily life in patients with breast cancer [34–36]. Women in our sample described a similar experience, with specific symptoms affecting various domains of functioning. For example, women who reported numbness/tingling described interference with walking and daily activities, such as getting dressed or cooking. Women who reported vaginal dryness or decrease in sexual interest or activity also reported interference with relationships with others, as has been described in other samples [37, 38]. Women with children described the impact of their symptoms on their ability to care for their children and expressed distress about how their disease and treatment would affect their children, similar to findings reported by Tavares, Brandao, and Matos [39]. Symptoms were described as interfering with work and employment, consistent with

Table 4 MDASI-Br development summary of the 36 symptoms that were identified from the qualitative interviews

	Qualitative interview N	Qualitative interview %	Expert panel mean	Core
Breast cancer disease symptoms				
Distress ^a	31	86.1	3.04	X
Breast changes ^a	8	22.2	3.04	
Sadness ^a	7	19.4	2.96	X
Pain ^a	5	13.8	3.25	X
Fatigue (tiredness) ^a	2	5.6	3.38	X
Lack of appetite ^a	2	5.6	2.13	X
Shortness of breath ^a	2	5.6	2.58	X
Coughing	1	2.7	2.04	
Lightheadedness	1	2.7	2.13	
Nausea ^a	1	2.7	2.58	X
Disturbed sleep ^a	1	2.7	3.25	X
Vomiting ^a	1	2.7	2.13	X
Breast cancer treatment symptoms				
Pain ^a	25	69.4	3.25	X
Fatigue (tiredness) ^a	21	58.3	3.38	X
Distress ^a	21	58.3	3.04	X
Skin changes ^a	18	50.0	2.46	
Nausea ^a	12	33.3	2.58	X
Numbness or tingling ^a	11	30.6	3.04	X
Disturbed sleep ^a	10	27.8	3.25	X
Arm swelling ^a	10	27.8	2.92	
Constipation ^a	8	22.2	2.29	
Hot flashes ^a	8	22.2	3.08	
Fingernail or toenail changes ^a	8	22.2	2.46	
Problem remembering things ^a	6	16.7	2.58	X
Lack of appetite ^a	6	16.7	2.13	X
Sadness ^a	6	16.7	2.96	X
Diarrhea	6	16.7	2.17	
Change in taste	5	13.8	2.33	
Regurgitation (acid reflux)	5	13.8	1.96	
Lightheadedness	5	13.8	2.13	
Swelling	5	13.8	2.67	
Vomiting ^a	4	11.1	2.13	X
Sore mouth	4	11.1	1.79	
Breast changes ^a	4	11.1	3.04	
Trouble moving my arm	4	11.1	2.67	
Decrease in sexual interest or activity	4	11.1	2.54	
Vaginal dryness	4	11.1	2.54	
Eye problems	3	8.3	2.04	
Shortness of breath ^a	3	8.3	2.58	X
Feeling drowsy (sleepy) ^a	2	5.6	2.42	X
Dry mouth ^a	2	5.6	1.83	X
Headache	2	5.6	2.54	
Chills/feeling cold	2	5.6	2.08	
Problem with paying attention (concentrating)	1	2.8	2.54	
Chest heaviness or tightness	1	2.8	2.42	
Feeling bloated	1	2.8	1.96	
Problem with racing heart (palpitation)	1	2.8	1.88	

^a Meets one or more criteria for inclusion in the provisional MDASI-Br module

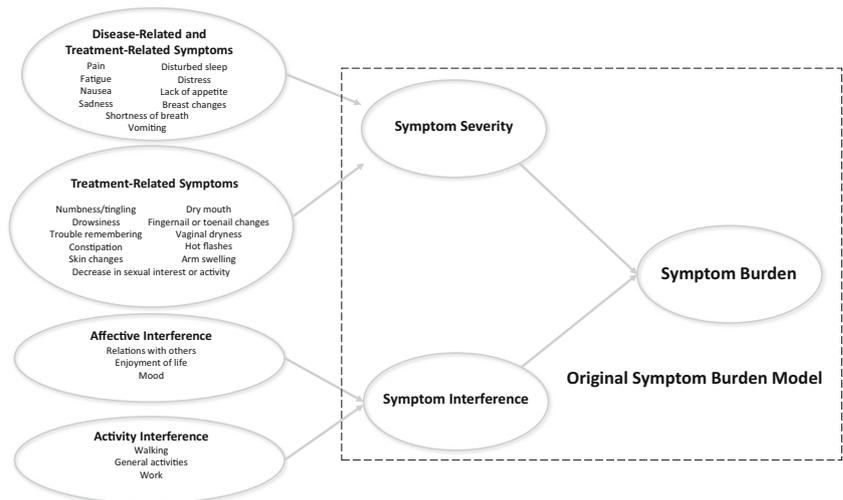
MDASI MD Anderson Symptom Inventory

Table 5 The 21 symptoms to be included in the provisional MDASI-Br

Reason for inclusion	Items selected
Item received a mean relevance rating from the expert panel of ≥ 3.0 (1–4 scale), meaning that the item was either relevant or very relevant	Your pain at its WORST?
	Your fatigue (tiredness) at its WORST?
	Your disturbed sleep at its WORST?
	Your feelings of being distressed (upset) at its WORST?
Item was endorsed in qualitative interviews by at least 20% of informants with breast cancer	Your numbness or tingling at its WORST?
	Your hot flashes at its WORST?
	Your breast changes at its WORST?
	Your nausea at its WORST?
Item was one of the 13 core MDASI symptom items, which have been tested in large samples of patients with cancer and are consistently found to be important	Your sadness at its WORST?
	Your constipation at its WORST?
	Your arm swelling at its WORST?
	Your fingernail or toenail changes at its WORST?
Item was related to a common breast cancer therapy (endocrine therapy)	Your skin changes at its WORST?
	Your problem with lack of appetite at its WORST?
	Your feeling shortness of breath at its WORST?
	Your feeling problem with remembering things at its WORST?
The final list of items to be included in the provisional MDASI-Br	Your feeling drowsy (sleepy) at its WORST?
	Your having a dry mouth at its WORST?
	Your vomiting at its WORST?
	Your decrease in sexual interest or activity at its WORST?
	Your vaginal dryness at its WORST?
	1. Your pain at its WORST?
	2. Your fatigue (tiredness) at its WORST?
	3. Your nausea at its WORST?
	4. Your disturbed sleep at its WORST?
	5. Your feelings of being distressed (upset) at its WORST?
	6. Your feeling shortness of breath at its WORST?
	7. Your feeling problem with remembering things at its WORST?
	8. Your problem with lack of appetite at its WORST?
	9. Your feeling drowsy (sleepy) at its WORST?
	10. Your having a dry mouth at its WORST?
	11. Your sadness at its WORST?
	12. Your vomiting at its WORST?
	13. Your numbness or tingling at its WORST?
	14. Your hot flashes at its WORST?
	15. Your breast changes at its WORST?
	16. Your constipation at its WORST?
	17. Your arm swelling at its WORST?
	18. Your fingernail or toenail changes at its WORST?
	19. Your skin changes at its WORST?
	20. Your decrease in sexual interest or activity at its WORST?
	21. Your vaginal dryness at its WORST?

MDASI MD Anderson Symptom Inventory

Fig. 1 Conceptual model including 21 symptom items and 6 interference items for the provisional MDASI-Br



others' findings that symptoms and physical limitations lead to the difficulty or impossibility of performing work tasks [40, 41].

We selected the MDASI as an existing measure of symptom burden that might be modified to measure the symptom burden unique to breast cancer. Although the MDASI has been validated for use in patients with breast cancer, several important symptoms specific to breast cancer are missing from the core MDASI items. These include symptoms related to hormonal therapies (such as hot flashes, vaginal dryness, and decrease in sexual interest or activity) and other treatment-related symptoms (such as arm swelling or fingernail or toenail changes) that may be specific to the therapies used for breast cancer management.

We used qualitative interviews and expert panel review to define the content domain for the MDASI-Br, ensuring that the instrument includes the symptom items that are most relevant to breast cancer. Defining symptom items using direct patient input through qualitative interviews, combined with clinician, patient, and caregiver expertise via the expert panel, ensures that the content validity of the final measure will be strong (Fig. 1). Unlike models of symptom burden in other patient populations, no solely disease-specific symptoms were included in our final model, with all disease-related symptoms also described as treatment-related symptoms by informants. This is not surprising, given that most breast cancers are asymptomatic at diagnosis, with the exception of breast changes and distress [42]. As shown in the model, both breast changes and distress are commonly described treatment-related symptoms as well.

Next steps in development of the MDASI-Br will include psychometric validation studies in multiple samples of women with breast cancer receiving various treatments at various disease stages, to establish the reliability and further validity of the items. Symptoms specific to different treatments and, possibly, to disease

stage will be identified to guide researchers and clinicians in selecting the group of symptoms most appropriate for such treatments and disease stages. Once initial validity and reliability have been established, one or more versions of the MDASI-Br will be ready for use in the clinical setting.

Limitations

Our sample of patients with breast cancer may have been limited in demographic characteristics, given that most of the participants were white and all participants were female. However, given known epidemiological and biological differences in breast cancer between men and women, study of the symptoms of breast cancer should be conducted separately based on sex [43, 44]. In addition, because patients in our sample were not receiving newer targeted therapies at the time of the interview, further work is needed to study treatment-related symptoms specific to these therapies. Given that instrument validation, including content validity, is an ongoing process, the content domain of the MDASI-Br should be assessed each time instrument is used, particularly given the rapidly changing nature of breast cancer clinical care.

Conclusion

Patients with breast cancer experience numerous symptoms related to their disease and treatment, and different treatments result in unique symptom burden. We generated a PRO instrument with content validity for measuring symptom burden specific to women with breast cancer. The content domain for a PRO symptom-burden measure of breast cancer encompasses the severity and activity interference of common symptoms of breast cancer and its treatment. Symptoms may result in interference with daily activities, relationships, life plans, treatment adherence, and mood. Well-designed PRO measures

are essential for accurate symptom assessment and management to maintain patient functioning and for use as tools linked to clinical research studies.

Acknowledgements Jeanie F. Woodruff, BS, ELS provided editorial support.

Funding information The study was sponsored by funding from the Houston Chapter of the Oncology Nursing Society, the Zeta Pi Chapter of Sigma Theta Tau International Honor Society of Nursing, and the Hawn Foundation Fund for Education Programs in Pain and Symptom Research.

Compliance with ethical standards

The study was approved by the MD Anderson Institutional Review Board, and all participants provided written informed consent.

Conflict of interest The authors declare that they have no conflicts of interest.

References

- American Cancer Society (2018) Cancer Facts & Figures 2018. Atlanta, Georgia
- Rhodes VA, Watson PM (1987) Symptom distress—the concept: past and present. *Semin Oncol Nurs* 3(4):242–247
- Miller KD, Siegler RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, Stein KD, Alteri R, Jemal A (2016) Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin* 66(4):271–289. <https://doi.org/10.3322/caac.21349>
- Cleeland CS (2007) Symptom burden: multiple symptoms and their impact as patient-reported outcomes. *J Natl Cancer Inst Monogr* 37:16–21. <https://doi.org/10.1093/jncimonographs/lgm005>
- Boehmke MM, Dickerson SS (2005) Symptom, symptom experiences, and symptom distress encountered by women with breast cancer undergoing current treatment modalities. *Cancer Nurs* 28(5):382–389
- Kayl AE, Meyers CA (2006) Side-effects of chemotherapy and quality of life in ovarian and breast cancer patients. *Curr Opin Obstet Gynecol* 18(1):24–28. <https://doi.org/10.1097/01.gco.0000192996.20040.24>
- Payne J, Piper B, Rabinowitz I, Zimmerman B (2006) Biomarkers, fatigue, sleep, and depressive symptoms in women with breast cancer: a pilot study. *Oncol Nurs Forum* 33(4):775–783. <https://doi.org/10.1188/06.onf.775-783>
- Dodd MJ, Cho MH, Cooper BA, Miaskowski C (2010) The effect of symptom clusters on functional status and quality of life in women with breast cancer. *Eur J Oncol Nurs* 14(2):101–110. <https://doi.org/10.1016/j.ejon.2009.09.005>
- Cleeland CS (2000) Cancer-related symptoms. *Semin Radiat Oncol* 10(3):75–90
- Mooney KH, Beck SL, Wong B, Duson W, Wujcik D, Whisenant M, Donaldson G (2017) Automated home monitoring and management of patient-reported symptoms during chemotherapy: results of the symptom care at home RCT. *Cancer Med* 6(3):537–546. <https://doi.org/10.1002/cam4.1002>
- Basch E, Am D, Kris MG et al (2016) Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. *J Clin Oncol* 34(6):557–565. <https://doi.org/10.1200/jco.2015.63.0830>
- Berry DL, Blumenstein BA, Halpenny B et al (2011) Enhancing patient-provider communication with the electronic self-report assessment for cancer: a randomized trial. *J Clin Oncol* 29(8):1029–1035. <https://doi.org/10.1200/jco.2010.30.3909>
- Berry DL, Hong F, Halpenny B et al (2014) Electronic self-report assessment for cancer and self-care support: results of a multicenter randomized trial. *J Clin Oncol* 32(3):199–205. <https://doi.org/10.1200/jco.2013.48.6662>
- Cleeland CS, Wang XS, Shi Q et al (2011) Automated symptom alerts reduce postoperative symptom severity after cancer surgery: a randomized controlled clinical trial. *J Clin Oncol* 29(8):994–1000. <https://doi.org/10.1200/jco.2010.29.8315>
- Berry DL, Hong F, Blonquist T, Halpenny B, Siefert ML, Partridge A (2013) Self report assessment and support for cancer symptoms: impact on hospital admissions and emergency department visits. *J Clin Oncol* 31(15 suppl):e20552
- Barbera L, Sutradhar R, Howell D et al (2015) Does routine symptom screening with ESAS decrease ED visits in breast cancer patients undergoing adjuvant chemotherapy? *Support Care Cancer* 23(10):3025–3032. <https://doi.org/10.1007/s00520-015-2671-3>
- Mooney K, Berry DL, Whisenant M, Sjoberg D (2017) Improving cancer care through the patient experience: how to use patient-reported outcomes in clinical practice. *Am Soc Clin Oncol Educ Book* 37:695–704. https://doi.org/10.14694/edbk_175418
- Kroenke K, Cheville AL (2016) Symptom improvement requires more than screening and feedback. *J Clin Oncol* 34(27):3351–3352. <https://doi.org/10.1200/jco.2016.67.7708>
- Patrick DL, Burke LB, Powers JH et al (2007) Patient-reported outcomes to support medical product labeling claims: FDA perspective. *Value Health* 10(Suppl 2):S125–S137. <https://doi.org/10.1111/j.1524-4733.2007.00275.x>
- Brady MJ, Cella DF, Mo F et al (1997) Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *J Clin Oncol* 15(3):974–986. <https://doi.org/10.1200/jco.1997.15.3.974>
- Maratia S, Cedillo S, Rejas J (2016) Assessing health-related quality of life in patients with breast cancer: a systematic and standardized comparison of available instruments using the EMPRO tool. *Qual Life Res* 25(10):2467–2480. <https://doi.org/10.1007/s11136-016-1284-8>
- Chopra I, Kamal KM (2012) A systematic review of quality of life instruments in long-term breast cancer survivors. *Health Qual Life Outcomes* 10:14. <https://doi.org/10.1186/1477-7525-10-14>
- Niu HY, Niu CY, Wang JH et al (2014) Health-related quality of life in women with breast cancer: a literature-based review of psychometric properties of breast cancer-specific measures. *Asian Pac J Cancer Prev* 15(8):3533–3536
- Cleeland CS, Reyes-Gibby CC (2002) When is it justified to treat symptoms? Measuring symptom burden. *Oncology (Williston Park)* 16(9 Suppl 10):64–70
- Williams LR, Yucel E, Cortes JE et al (2013) Measuring symptoms as a critical component of drug development and evaluation in hematological diseases. *Clin Invest* 3(12):1–2. <https://doi.org/10.4155/cli.13.108>
- Sailors MH, Bodurka DC, Gning I, Ramondetta LM, Williams LA, Mendoza TR, Agarwal S, Sun CC, Cleeland CS (2013) Validating the M. D. Anderson Symptom Inventory (MDASI) for use in patients with ovarian cancer. *Gynecol Oncol* 130(2):323–328. <https://doi.org/10.1016/j.ygyno.2013.05.009>
- Jones D, Zhao F, Fisch MJ, Wagner LI, Patrick-Miller LJ, Cleeland CS, Mendoza TR (2014) The validity and utility of the MD Anderson Symptom Inventory in patients with prostate cancer: evidence from the Symptom Outcomes and Practice Patterns (SOAPP) data from the Eastern Cooperative Oncology Group. *Clin Genitourin Cancer* 12(1):41–49. <https://doi.org/10.1016/j.clgc.2013.07.003>

28. Mendoza TR, Zhao F, Cleeland CS, Wagner LI, Patrick-Miller LJ, Fisch MJ (2013) The validity and utility of the M. D. Anderson Symptom Inventory in patients with breast cancer: evidence from the symptom outcomes and practice patterns data from the eastern cooperative oncology group. *Clin Breast Cancer* 13(5):325–334. <https://doi.org/10.1016/j.clbc.2013.02.014>
29. US Department of Health and Human Services Food and Drug Administration (2009) Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. Available from: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf. Accessed 1 Oct 2018
30. Turner RR, Quittner AL, Parasuraman BM, Kallich JD, Cleeland CS (2007) Patient-reported outcomes: instrument development and selection issues. *Value Health* 10(Suppl 2):S86–S93. <https://doi.org/10.1111/j.1524-4733.2007.00271.x>
31. Cleeland CS, Zhao F, Chang VT, Sloan JA, O'Mara AM, Gilman PB, Weiss M, Mendoza TR, Lee JW, Fisch MJ (2013) The symptom burden of cancer: evidence for a core set of cancer-related and treatment-related symptoms from the Eastern Cooperative Oncology Group Symptom Outcomes and Practice Patterns study. *Cancer* 119(24):4333–4340. <https://doi.org/10.1002/cncr.28376>
32. Williams LA, Agarwal S, Bodurka DC, Saleeba AK, Sun CC, Cleeland CS (2013) Capturing the patient's experience: using qualitative methods to develop a measure of patient-reported symptom burden: an example from ovarian cancer. *J Pain Symptom Manag* 46(6):837–845. <https://doi.org/10.1016/j.jpainsymman.2013.02.007>
33. Parse RR, Coyne AB, Smith MJ (1985) *Nursing research: qualitative methods*. Brady Communications, Bowie
34. Niklasson AJ, Paty J, Ryden A (2017) Talking about breast cancer: which symptoms and treatment side effects are important to patients with advanced disease? *Patient* 10(6):719–727. <https://doi.org/10.1007/s40271-017-0242-z>
35. Hellerstedt-Borjesson S, Nordin K, Fjallskog ML, Homstrom IK, Arving C (2015) Women with breast cancer: experience of chemotherapy-induced pain: triangulation of methods. *Cancer Nurs* 38(1):31–39. <https://doi.org/10.1097/ncc.000000000000124>
36. Mosher CE, Johnson C, Dickler M, Norton L, Massie MJ, DuHamel K (2013) Living with metastatic breast cancer: a qualitative analysis of physical, psychological, and social sequelae. *Breast J* 19(3):285–292. <https://doi.org/10.1111/tbj.12107>
37. Barthakur MS, Sharma MP, Chaturvedi SK, Manjunath SK (2017) Body image and sexuality in women survivors of breast cancer in India: qualitative findings. *Indian J Palliat Care* 23(1):13–17. <https://doi.org/10.4103/0973-1075.197954>
38. Wang F, Chen F, Hou X, Xu R, Wu L, Wang J, Lu C (2013) A neglected issue on sexual well-being following breast cancer diagnosis and treatment among Chinese women. *PLoS One* 8(9):e74473. <https://doi.org/10.1371/journal.pone.0074473>
39. Tavares R, Brandao T, Matos PM (2018) Mothers with breast cancer: a mixed-method systematic review on the impact on the parent-child relationship. *Psychooncology* 27(2):367–375. <https://doi.org/10.1002/pon.4451>
40. Zomkowski K, Cruz de Souza B, Pinheiro da Silva F, Moreira GM, de Souza Cunha N, Sperandio FF (2018) Physical symptoms and working performance in female breast cancer survivors: a systematic review. *Disabil Rehabil* 40(13):1485–1493. <https://doi.org/10.1080/09638288.2017.1300950>
41. Sun W, Chen K, Terhaar A, Wiegmann DA, Heidrich SM, Tavaarwerk AJ, Sesto ME (2016) Work-related barriers, facilitators, and strategies of breast cancer survivors working during curative treatment. *Work* 55(4):783–795. <https://doi.org/10.3233/wor-162449>
42. Koo MM, von Wagner C, Abel GA, McPhail S, Rubin GP, Lyratzopoulos G (2017) Typical and atypical presenting symptoms of breast cancer and their associations with diagnostic interval: evidence from a national audit of cancer diagnosis. *Cancer Epidemiol* 48:140–146. <https://doi.org/10.1016/j.canep.2017.04.010>
43. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN (2004) Breast carcinoma in men: a population-based study. *Cancer* 101(1):51–57. <https://doi.org/10.1002/cncr.20312>
44. Miao H, Verkooijen HM, Chia KS, Bouchardy C, Pukkala E, Larunningen S, Mellekjaer L, Czene K, Hartman M (2011) Incidence and outcome of male breast cancer: an international population-based study. *J Clin Oncol* 29(33):4381–4386. <https://doi.org/10.1200/jco.2011.36.8902>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.