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Symptom Map of Endocrine Therapy for Breast Cancer: A Scoping Review

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Breast cancer is the most commonly diagnosed cancer among women. It is estimated that there will be 252,710 new breast cancer diagnoses and 40,610 deaths in 2017 in the United States.[1] In China, 15% of all new cancer diagnoses in women are breast cancer, and the disease is the leading cause of cancer deaths in women younger than 45 years of age.[2] Globally, with the application of tamoxifen, the breast cancer recurrence and mortality rates were decreased by 41% and 34% respectively.[3] Third-generation aromatase inhibitors (AIs), including anastrozole, letrozole, and exemestane, are associated with significant improvement in disease-free and overall survival for post-menopausal women with breast cancer.[4,5] Therefore, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines of Breast Cancer (version 2.2017) recommend that women with early stage, hormone receptor positive breast cancer receive at least 5 years of endocrine therapy generally consisting of tamoxifen for pre-menopausal women and an aromatase inhibitor (AI) for post-menopausal women.[6] Additionally, except for immediately life-threatening cases, endocrine therapy alone or in combination has been recommended as an initial treatment for women with hormone receptor positive metastatic breast cancer by the American Society of Clinical Oncology.[7]

While endocrine therapy significantly improves the overall and disease-free survival in women with breast cancer, this treatment is associated with multiple symptoms that may have a detrimental impact on medication adherence, functional status and quality of life.[8–10] Co-occurring symptoms associated with endocrine therapy were reported as one of the most common reasons for treatment discontinuation (66.7% of AI discontinuers and 59.1% of tamoxifen discontinuers).[8] Moreover, endocrine therapy-related symptoms are more likely to be neglected by both health care providers and patients due to less frequent follow-up visits, compared to follow-ups for other forms of adjuvant therapy, such as chemotherapy and radiation therapy.[11]

Although assessment of adverse events is essential in clinical trials of endocrine therapy development mainly for the purpose of safety, evidence now suggests that endocrine therapy associated symptoms were underestimated. Ruhstaller et al. reported that hot flashes/sweats (70% vs. 38–40% in clinical trials), low energy (45% vs. 9–15% in clinical trials), fluid retention (22% vs. 7% in clinical trials), and vaginal dryness (30% vs. 3% in clinical trials)

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were significantly underrated in clinical trials of endocrine therapy.[12] Therefore, having a comprehensive understanding of the symptom experience associated with endocrine therapy is urgently needed, as it will serve as the bases for development of interventions to manage those symptoms. The purpose of this scoping review is to map the occurrence (frequency), intensity, and distress of symptoms during endocrine therapy for breast cancer.

Methods

This scoping review was conducted under the framework proposed by Khalil et al. and the Joanna Briggs Institute methods of evidence synthesis as detailed bellow.[13]

Step 1 Identify the Research Question

The research question for this scoping review was: what is the symptom(s) experience during endocrine therapy for breast cancer that has been reported? The Joanna Briggs Institute suggests using PCC (population, concept, and context) to construct a clear and meaningful scoping review. Therefore, we further defined the PCC of this scoping review as follows.

- Population

Participants in the included studies in this scoping review are adult females (18 years or older), who were diagnosed with breast cancer and receiving oral endocrine therapy. Both observational studies describing the symptom(s) experience and experimental studies comparing the symptom experience among different types of endocrine therapies were eligible. Studies with samples that were undividable from other types of cancer or other types of treatment were excluded from this review because they precluded the ability to discern symptoms specifically related to endocrine therapy.

- Concept

Endocrine therapy and symptom experience are two key concepts in this scoping review. Endocrine therapy refers to oral adjuvant endocrine therapy currently recommended by the NCCN Guideline for Breast Cancer, including selective estrogen receptor modulators (SERMS) such as Tamoxifen (Nolvadex and Soltamox), and aromatase inhibitors including Anastrozole (Arimidex), Letrozole (Femara), and Exemestane (Aromasin). Symptom experience is defined as the “perception of the frequency, intensity, distress, and meaning of symptoms as they are produced and expressed” in accordance with the Symptom Experience Model (SEM).[14]

- Context

In this scoping review, the symptom(s) experience is determined within the context of endocrine therapy for breast cancer in clinical studies. Excluded are clinical trials or studies using endocrine therapy to prevent breast cancer or chemoprevention.

Step 2 Identify Relevant Studies

Studies published in English and Chinese language before February 2017 were comprehensively searched. A three-step search strategy was utilized. An initial scoping

search was conducted in PubMed and China Science Periodical Databases (CSPD) to identify key terms. Then, comprehensive searches were performed in the following databases: PubMed, CINAHL®, and CSPD. The following search terms were combined: breast, neoplasm, endocrine therapy, hormonal therapy, antineoplastic agents, aromatase inhibitor, tamoxifen, symptom, and adverse effects. The search string in PubMed is: ((((“Antineoplastic Agents, Hormonal/adverse effects”[Majr]) OR “Aromatase Inhibitors/adverse effects”[Majr]) OR “Tamoxifen/adverse effects”[Majr])) AND “Breast Neoplasms”[Mesh:NoExp]. Lastly, additional pertinent studies were identified by reviewing the bibliographies of included studies.

Step 3 Study Selection

The initial search revealed 2,551 references (PubMed=1,489, CINAL=822, CSPD=236, other recourses=4). After removal of 70 duplicated references, 2,481 (2,245 English and 236 Chinese) were screened by title and abstract for eligibility. Figure 1 summarizes the details of study selection. Studies were reviewed by two researchers for determination of eligibility. A third researcher adjudicated situations in which there was a disagreement. Eventually, 53 clinical studies were identified from 57 articles (54 in English, 3 in Chinese) and were included in this scoping review (Table 1)

Step 4 Charting the Data

Data charting includes the process of data extraction and describing the data both narratively and in tabular form. The SEM model was used to guide the data charting, the process of data extraction. We synthesized the symptom experience based on each domain (frequency, intensity, distress). Since most studies reported symptom occurrence (a dichotomized variable of frequency), we integrated occurrence into a frequency domain. Due to the heterogeneity of study design (e.g., cross-sectional or longitudinal) and characteristics of participant across studies (e.g., tamoxifen or aromatase inhibitor users, Caucasian or African American), data on each characteristic at every time point were charted as an independent report if they were available in the original articles, to facilitate comparison across studies. For example, a 6-month longitudinal study on the occurrence of joint pain could have 12 occurrence reports based on the combination of time point (0, 3, 6 months), agent (tamoxifen or aromatase inhibitor) and ethnicity (Caucasian or African American). In terms of intensity and distress, some studies reported the percentage of people who experience different levels of symptoms among the entire sample, while some reported the percentage of participants who developed symptoms. To make the data comparable, we recalculated the percentage for the latter situation so that the percentages were referring to proportion among the all participants. For example, when a study reported 30% of 50 patients out of 100 research participants had severe pain, we recalculated the percentage of patients who had severe pain as 50*30%/100=15%.

Step 5 Collating, Summarizing and Reporting the Results

Symptom data from individual studies were collated after being extracted. Summary and interpretation of data were demonstrated in the results session. The implications of the findings for clinical practice and future research were further detailed in the discussion session.

Results

Since 2006, the number of studies on symptoms associated with endocrine therapy fluctuated with an increasing trend, reaching its peak in 2013 (n=11), and dropped dramatically in 2015 and 2016 (Figure 2). More studies focused on aromatase inhibitors than tamoxifen (34 vs 7). The sample sizes varied considerably ranging from 17 to 3000. Most of the studies used a cross-sectional design (n=33). The longest follow-up period for symptom assessment in the longitudinal studies was 24 months (see Table 1).

Most studies assessed symptoms by using self-report questionnaires or symptom checklists. Retrospective medical record reviews or telephone interviews was adopted in 8 studies.[15, 35, 36, 44, 47, 58, 67, 69] Two studies conducted retrospective semi-structured interviews[54] and patient interviews[27]. The recall period ranged from 24 hours to 12 months, with recall for the past 7 days and 4 weeks most commonly adopted. Twenty-three studies did not report recall period (see Table 1).

The mostly used symptom assessments used were the Breast Cancer Prevention Trial (BCPT) Symptom Checklist, Functional Assessment of Cancer Therapy (FACT-ES), and the M.D. Anderson Symptom Inventory (MDASI). Symptom intensity and distress were quantified using Likert scales. Investigator-developed symptom questionnaires and checklists adapted from Visual Analog Scales (VAS) were commonly used as well (see Table 1).

In this scoping review, individual symptoms identified were categorized into cognitive, musculoskeletal, vasomotor, gastrointestinal, urogenital, mood-related, sleep-related, and sexual symptoms, adapted from the subscales of BCPT Symptom Checklist. Symptoms which did not fall into these categories were grouped into a separate category labeled “others”. Symptom occurrence, intensity, and distress reported by each study are exhibited in the Supplemental Table 1.

Mostly Studied Symptoms

Based on the numbers of studies which reports of symptom occurrence, the 16 mostly studied symptoms were joint/muscle pain, hot flashes, vaginal dryness/insufficient lubrication, sleep disorder/insomnia, fatigue/lack of energy, nausea, vaginal bleeding or spotting, headaches/migraines, irritability, joint/muscle stiffness, weight gain, vaginal discharge, depression/depressive mood, low sexual interest/desire, difficulty breathing/short of breath, and dizziness/faintness (see Figure 3). Far fewer studies reported symptom intensity and distress. In the 16 mostly reported symptoms, results related to the occurrence, intensity, and distress domains were only reported for eight symptoms including joint/muscle pain, hot flashes, vaginal dryness/insufficient lubrication, sleep disorder/insomnia, fatigue/lack of energy, irritability, joint/muscle stiffness, and depression/depressive mood. Intensity was reported from more than one study on only 10 symptoms: joint/muscle pain (10), hot flashes (4), vaginal dryness/insufficient lubrication (4), vaginal discharge (3), joint/muscle stiffness (2), genital itching/irritation (2), vaginal bleeding/spotting (2), incontinence (2), sleep disorder/insomnia (2), and fatigue/lack of energy (2). Distress was reported from more than one study on only 10 symptoms: joint/muscle pain (5), hot flashes (3), pain with

intercourse (3), forgetfulness (2), general aches and pains (2), joint/muscle stiffness (2), unhappy with the appearance of body (2), irritability (2), headaches/migraines (2), and loss of hair/hair thinning (2).

Symptoms with Highest Occurrence, Intensity, and Distress

After extracting the symptom occurrences (the percentage of people who reported the symptom) from included studies (see Supplemental Table 1), we sorted the occurrences from low to high for each symptom and identified the median occurrence for each symptom. Based on the median of occurrence of individual symptom, we identified 15 symptoms with highest occurrence (most prevalent symptoms). From high to low, these 15 most prevalent symptoms include cramps, hot flashes, fatigue/lack of energy, eye irritation, heart discomfort, joint/muscle pain, night sweats, sexual arousal problem/orgasmic dysfunction, anxiety, dyspareunia, low sexual interest/desire, joint/muscle stiffness, urinary urgency, numbness or tingling, and dry eye syndrome (see Figure 4). Notably, 6 of these 15 symptoms (including cramps, eye irritation, heart discomfort, anxiety, dyspareunia, urinary urgency, numbness and tingling, and dry eye syndrome) were reported by only one study. Sexual arousal problem/orgasmic dysfunction were reported by only two studies.

Five out of the 15 most prevalent symptoms overlapped with the most studied symptoms, including joint/muscle pain, hot flashes, low sexual interest/desire, joint/muscle stiffness, and fatigue/lack of energy (see Figures 3 and 4). Interestingly, these five symptoms had the top 5 highest maximum symptom occurrences, suggesting that these five symptoms are particularly relevant to women receiving endocrine therapy for breast cancer.

Intensity and distress were assessed using visual analog scales (VAS) in several studies. The proportion of participants who rated symptoms as mild, moderate, severe or extremely severe and distressful was also reported (see Supplemental Table 1). Intensity of only four symptoms (joint/muscle pain, hot flashes, vaginal dryness/insufficient lubrication, and vaginal discharge) were reported by more than two studies. Moderate to severe joint/muscle pain was reported by 31.5% to 46% of participants.[23, 25, 45, 54] The range of mean intensity scores for joint/muscle pain was 4.9 to 5.4 out of 10.[20, 40, 61] Reports ranging from 19.7% to 53% of participants reported moderate to severe hot flashes.[16, 18, 40, 63] There were 20.6% to 32.8% of participants reported moderate to severe vaginal dryness/insufficient lubrication.[16, 24, 40] Moderate to severe vaginal discharge was reported by 4% to 17.6% of participants across studies.[16, 24] Only 3 symptoms have more than two studies reporting distress including joint/muscle pain, hot flashes, and pain with intercourse. Moderate or greater distress associated with joint/muscle pain was reported by 36% of participants.[28] The mean distress with joint/muscle pain was 3.29 out of 10.[61] The mean distress of hot flashes was 1.41 out of 4 and of pain with intercourse was 1.17 out of 4.[52]

Discussion

Symptoms are increasingly important self-reported outcomes during cancer treatment. Symptom science and self-management are listed as research priorities of both the National Institutes of Health (NIH) and National Institute of Nursing Research (NINR). However, the science of the symptom experience during endocrine therapy remains underdeveloped.

Heterogeneity across symptom assessment instruments and methodological limitations across completed studies underscore the inability to integrate the evidence and better understand the phenomenon of symptom experience during endocrine therapy for breast cancer.

Instrumentations for Symptoms during Endocrine Therapy

In this scoping review, considerable methodological heterogeneity was identified across the included 57 articles, including variance in study design, symptom assessment instruments, symptom measurement recall period, data collection procedures and sample characteristics (e.g., ethnicity, menopause status, previous treatments, cancer stage, etc.). The biggest barrier to the comparison of results across studies is the heterogeneity of symptom assessment instruments. Given the consensus related to the experience of multiple co-occurring symptoms, a self-reported symptom questionnaire/checklist is a plausible approach to efficient assessment of concurrent symptoms. Unfortunately, although the three most commonly used self-reported symptom questionnaires/checklists (BCPT, FACT-ES, and MDASI) have been reported to be reliable and valid,[70–72] none of them assesses symptoms associated with endocrine therapy comprehensively in terms of the types of symptoms experienced and the occurrence, intensity and distress associated with those symptoms. Table 2 shows the coverage of the 16 most commonly studied symptoms among these three commonly used symptoms questionnaires/checklists. The FACT-ES covers 14/16 symptoms, the BCPT symptom checklist covers 12/16 symptoms and the MDASI covers 5/16 symptoms. Table 3 shows the coverage of the 15 symptoms with the highest occurrences among the three symptom checklists. The BCPT and FACT-ES both cover 6/15 symptoms. The MDASI covers 2/15 symptoms. Compared to the BCPT and FACT-ES, the MDASI covers far fewer symptoms as illustrated in Tables 3 and 4. This is most probably due to the fact that the MADSI is not an endocrine therapy specific symptom assessment. However, only the MDASI comprehensively assesses the three domains of symptoms. The BCPT assesses symptom distress, the FACT-ES assesses occurrence and intensity, and the MDASI assesses occurrence, intensity and distress. In addition, (Table 3) six symptoms with high occurrence rates in women receiving endocrine therapy are not included in any of the three instruments, including eye irritation,[19] heart discomfort,[40] sexual arousal problem/orgasmic dysfunction,[17, 29] dyspareunia,[17] urinary urgency,[24] and dry eye syndrome.[38] Interestingly, each of these six non-included symptoms were reported by only one or two studies. Given the high occurrence rates, future studies should insure the inclusion of these six symptoms. In addition, more studies are needed to confirm the robustness of the high occurrence of these six symptoms.

Methodological Limitations in the Current Studies

In this scoping review, we identified several methodological issues that preclude comprehensively understanding of symptoms during endocrine therapy for breast cancer.

Firstly, most of the current studies used cross-sectional designs. Cross-sectional design precludes the possibility of examining causal relationships related to factors that may be associated with symptoms during endocrine therapy. Moreover, the onset time and shape of trajectories of symptoms remained understudied due to the lack of longitudinal studies. In

addition, the few longitudinal studies that have been reported only included follow-up periods up to 24 months,[40] a relatively short time frame relative to the 5–10 years of endocrine therapy typically recommended by the NCCN Guideline. Due to the relative short follow-up time, the trajectories of symptoms during the course of endocrine therapy are not fully described.

Secondly, there is a considerable variance in recall period. The recall period can affect the accuracy and comparability of symptom outcomes. However, the optimal recall period of symptoms is still under controversy; a shorter recall period (e.g., 3 days in children and 4 days in adults) may help assess symptoms occurrence accurately[73] but may underestimate symptoms distress when symptoms have diurnal fluctuation.[74]

Thirdly, there is a lack of definitions of symptoms in the current studies. The wording of one symptom vary among different studies. For example, lack of energy, low energy, feeling tired, physical and mental exhaustion, and fatigue are used by different studies.[8, 18, 34, 37, 40, 44, 51, 55, 56] Without a clear definition, it is not rigorous to treat them as one symptom. Moreover, it also remains arguable that whether or not the outcomes from one item of a symptom checklist and a series of items of a questionnaire for one symptom are equivalent. In addition, the definitions of the extents of intensity/distress (e.g., mild, moderate, severe, very severe) are not defined in most of the current studies, especially in the studies using symptoms checklist to assess multiple concurrent symptoms.

Lastly, there is a lack of theoretical guidance for the symptom related studies during endocrine therapy. Theoretical frameworks established for examining symptoms (e.g., the UCSF Symptom Management Theory (SMT), Symptom Experience Model (SEM), NIH Symptoms Science Model, etc.) should be encouraged in future studies.[14, 75, 76]

Other Gaps of Current Studies

None of the included studies adopted common data elements (CDE). The National Institute of Nursing Research (NINR) recommended six symptoms (pain, fatigue, sleep disturbance, mood, anxiety, and cognitive disturbance) as common data elements for symptoms studies.[77] However, these symptoms were not well assessed and reported in the studies on symptoms during endocrine therapy. This impedes further comparison of symptoms results both among studies for endocrine therapy, but also among different types of cancer treatments.

Symptom cluster and trajectory patterns are understudied in symptoms during endocrine therapy for breast cancer. The numbers of research on symptom clusters in cancer patients are exponentially increasing.[78] However, the symptom cluster in endocrine therapy for breast cancer is poorly studied. None of the identified studies in this scoping review is aiming to identify symptom clusters. The vast majority of current studies on symptom clusters are focusing on cancer patients in the period of surgery, chemotherapy and radiation therapy. Patients under endocrine therapy are rarely included. It is the same situation in the research focusing on trajectory patterns and high-risk subgroup membership. With an insufficient understanding of phenotypic characteristics of symptoms during endocrine therapy, there is a lack of studies further exploring underlying mechanisms of symptom clusters and phenotypic variant associated with endocrine therapy.

Strengths and Limitations—To the authors' knowledge, this is the first scoping review to map the multiple symptoms experienced during endocrine therapy for breast cancer. Furthermore, the methodology and data charting process were both framework-guided, which assured the rigorousness of this scoping review. In addition, including both English and Chinese language published articles facilitates broadening the scope of the results of related studies.

However, this review should be taken within the context of several limitations. The limitations include: 1) studies published in languages other than English and Chinese and unpublished studies were not included; 2) by only focusing on quantitative research, the meaning domain of the symptom experience was not included and discussed in this scoping review.

Implication for Clinical Practice and Future Research—For the implications for clinical practice, this scoping review identified 5 well-studied and highly prevalent symptoms which should be assessed in women with breast cancer receiving endocrine therapy. These five symptoms are joint/muscle pain, hot flashes, low sexual interest/desire, joint/muscle stiffness, and fatigue/lack of energy. Moreover, some rarely studied but highly prevalent symptoms should also be assessed, including cramps, eye irritation, heart discomfort, anxiety, dyspareunia, urinary urgency, numbness and tingling, and dry eye syndrome. When assessing symptoms, nurses should evaluate the frequency of occurrence, intensity, and distress of key symptoms to have a clear and comprehensive understanding of the symptom experience during endocrine therapy in women with breast cancer. Nurses should also assess the influence of symptoms experienced on the quality of life and functional ability of women receiving endocrine therapy.

Given the state of the science related to symptoms experienced by women with breast cancer receiving endocrine therapy, there are several implications for future research. Firstly, compared to the occurrence domain, there is a dearth of research addressing the intensity and distress domains of symptoms. There is a considerable need for studies to comprehensively determine the frequency of occurrence, intensity of symptoms, symptom distress and the impact of symptoms on functional ability and quality of life. Secondly, since the heterogeneity of instruments significantly affects the comparison of results across studies, a symptoms questionnaire/checklist encompassing multiple domains of endocrine therapy specific symptoms is urgently needed. Meanwhile, use of common data elements should be encouraged in future studies on symptoms during endocrine therapy. An optimal recall period and clear definitions of symptoms should be studied and standardized in the future studies. Thirdly, this scoping review indicates that more research is needed investigating rarely studied but highly prevalent symptoms, such as cramps, eye irritation, heart discomfort, anxiety, dyspareunia, urinary urgency, numbness and tingling, and dry eye syndrome, to confirm the robustness of the current evidence. Lastly, more studies are needed to determine the symptoms clusters that occur in women receiving endocrine therapy and the trajectory patterns of symptoms (such as joint pain) during endocrine therapy. In addition, more studies to determine the mechanisms underlying the symptoms/symptom clusters, and phenotypic variance should be conducted to gain a deeper understanding of symptoms

during endocrine therapy as the basis for the development of symptom management interventions.

Conclusions

In this scoping review, five key symptoms associated with endocrine therapy were identified, including joint/muscle pain, hot flashes, low sexual interest/desire, joint/muscle stiffness, and fatigue/lack of energy. These symptoms should be included in clinical practice and future studies of endocrine therapy for breast cancer. There remain substantial gaps in the science related to the symptom experience during endocrine therapy for breast cancer, especially for the domains of symptom intensity and distress, specific understudied symptoms and for symptom clusters. Investigations examining rarely studied but highly prevalent symptoms (e.g., cramps, eye irritation, heart discomfort, anxiety, dyspareunia, urinary urgency, numbness and tingling, and dry eye syndrome) are needed. Future studies on symptom clusters, individual variants of certain symptoms, and focused symptom assessment instruments are urgently needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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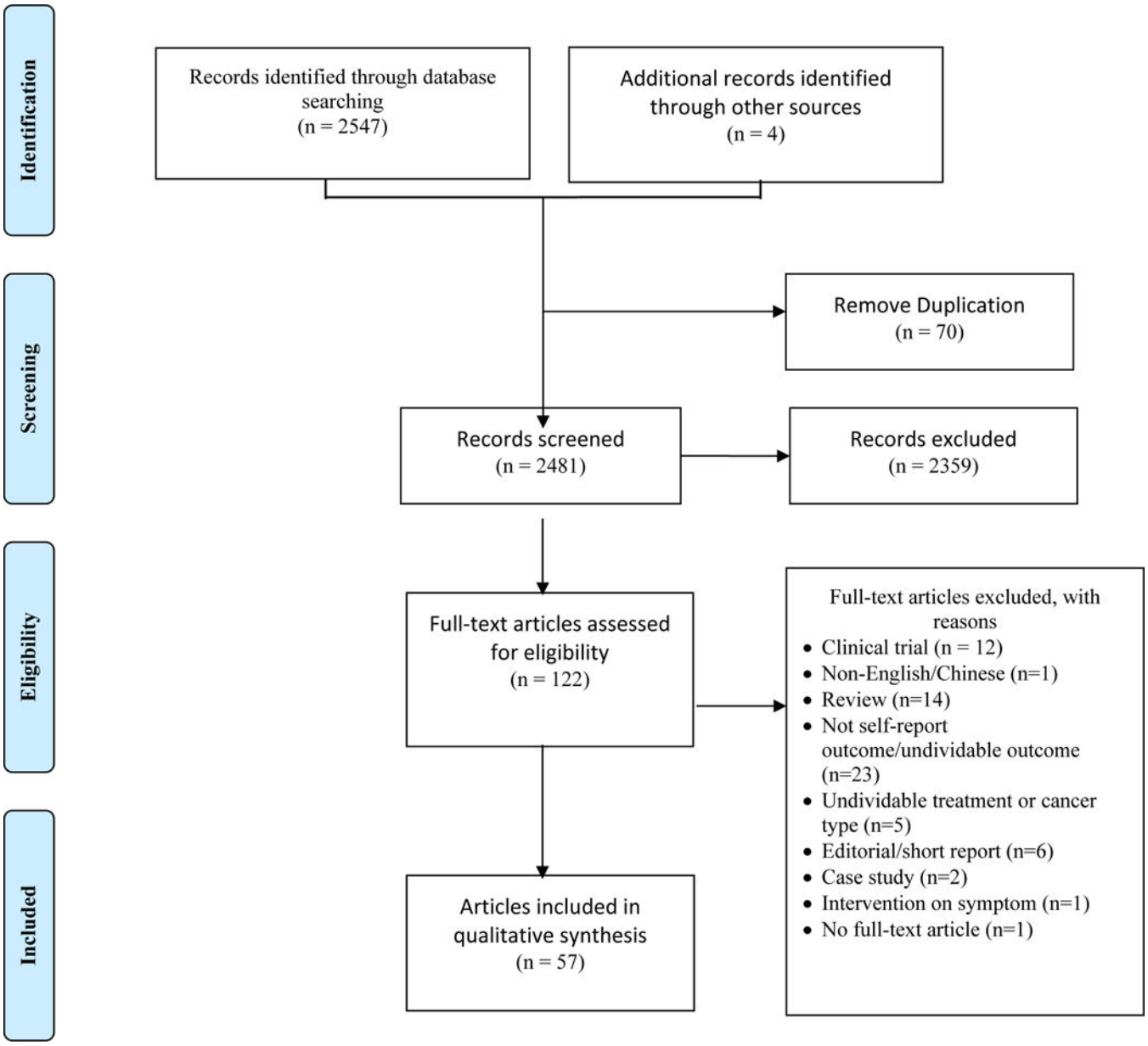

Figure 1.
The Process of Selecting Studies

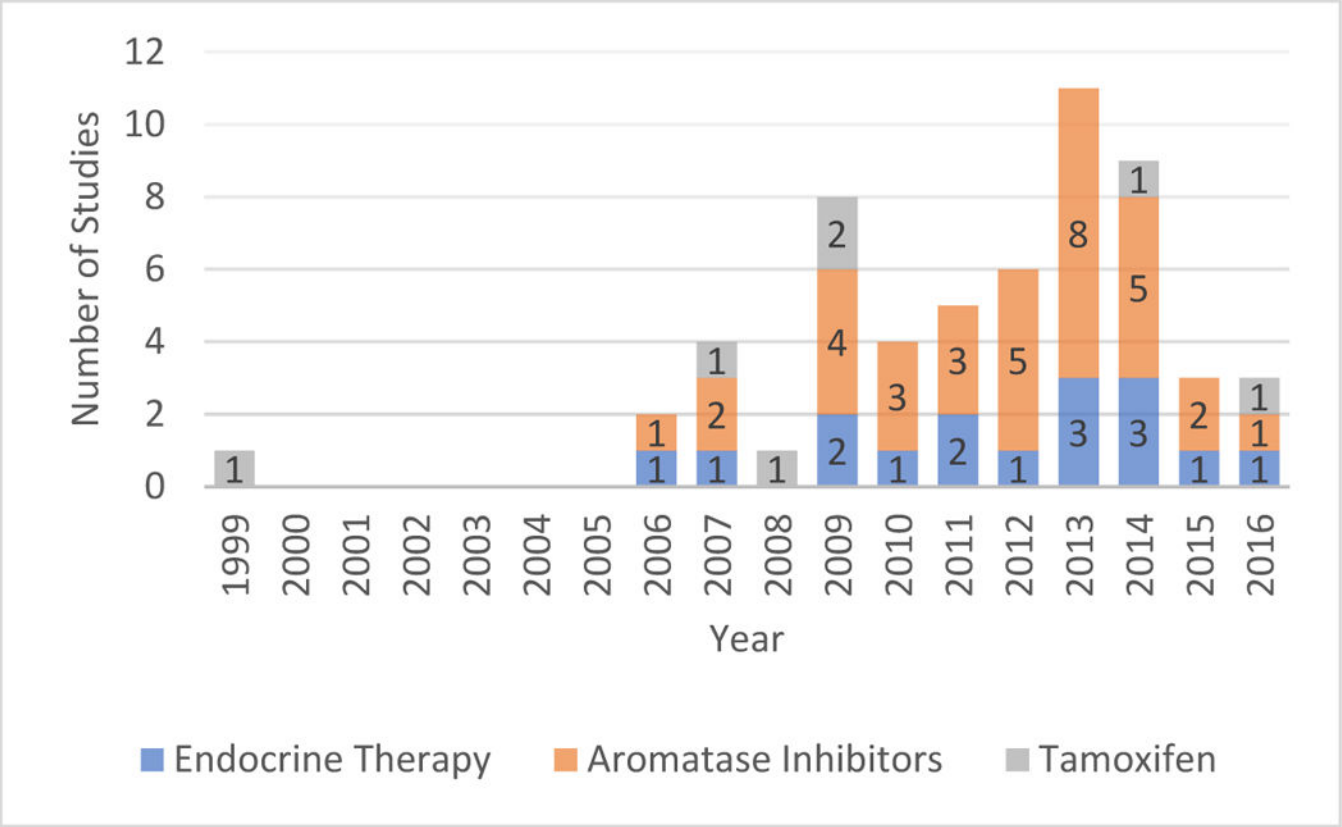

Figure 2.
Number of studies on endocrine therapy for breast cancer over time

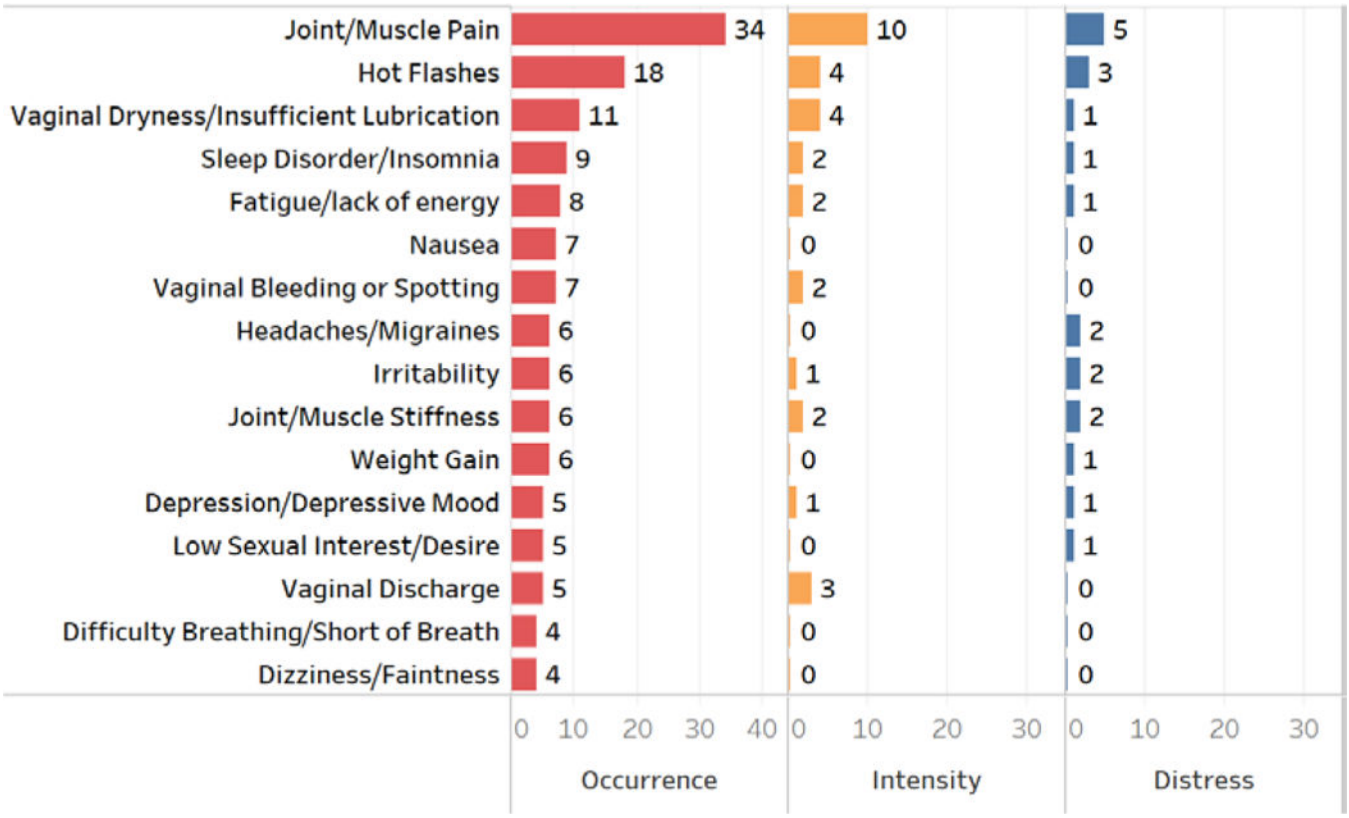

Figure 3.
Number of studies on the occurrence, intensity, distress of symptoms during endocrine therapy

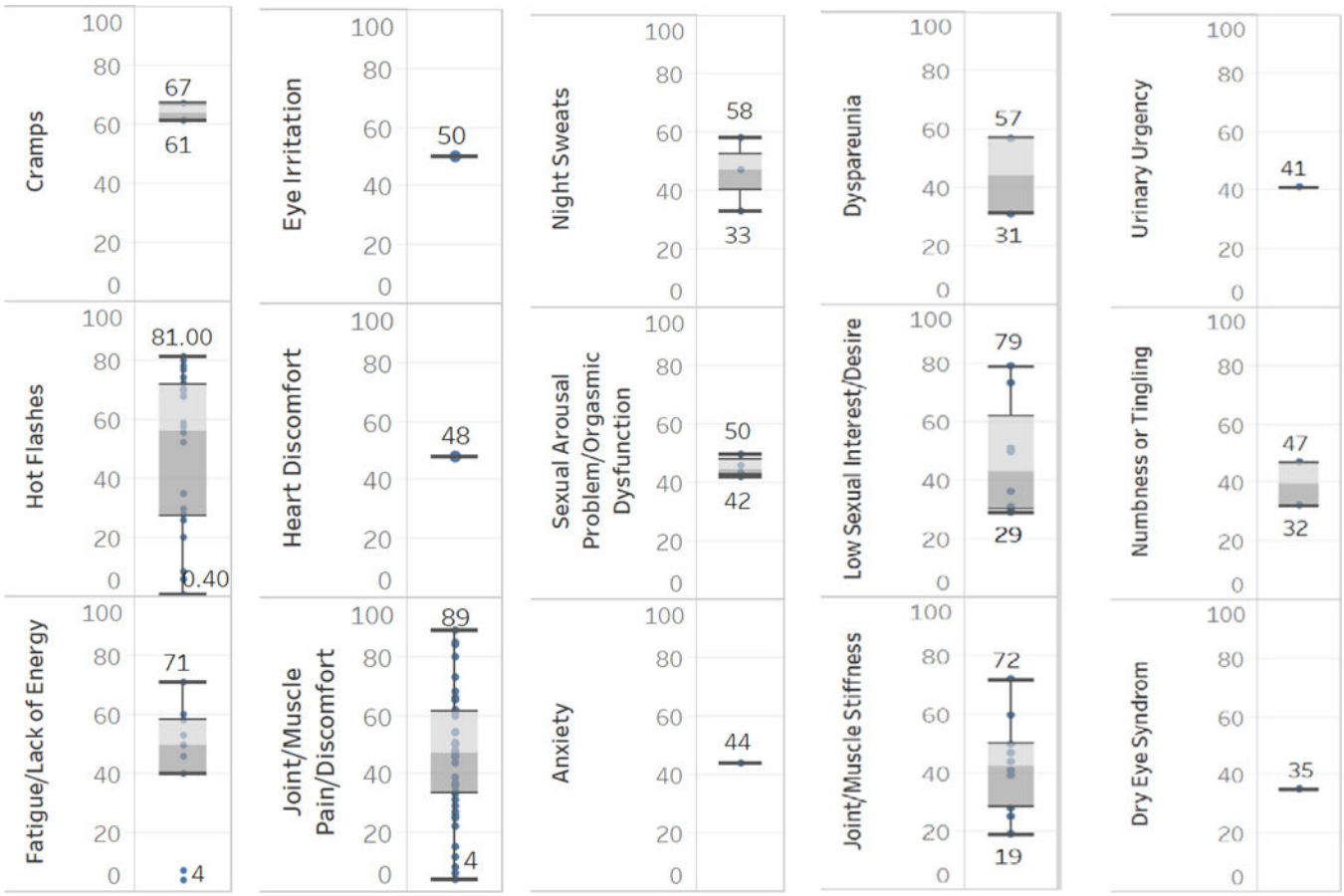

Figure 4.

Top 15 Prevalent Symptoms (based on median) Reported by Current Studies on Endocrine Therapy for Breast Cancer

Table 1

Studies Included in This Scoping Review

Author, Year	Country	Agent	Design	Instrument	Recall period	Domain	Symptoms
Ashraf 2009[15]	India	TAM	Retrospective review of case records (n=3000)	Medical records	-	Occurrence Intensity	TAM-related side effects
Baumgart 2011[16]	Sweden	ET	Cross-sectional (n=97)	FACT-ES IIQ-7 UDI-6	-	Occurrence Intensity	Urogenital symptoms ET related symptoms
Baumgart 2013[17]	Sweden	ET	Cross-sectional (n=97)	Standardized questionnaire	Past 12 months	Occurrence Frequency Distress	Sexual dysfunction symptoms
Baxter 2014[18]	Canada	TAM	Cross-sectional (n=132)	Survey	Past 7 days	Occurrence Frequency Intensity	Hot flashes and TAM-related symptoms
Boehm 2009[19]	Germany	TAM	Cross-sectional (n=136)	Questionnaire	Past 7 days	Occurrence Frequency	AI related symptoms
Boonstra 2013[20]	Netherlands	AI	Cross-sectional (n=57)	Rheumatoid Arthritis Disease Activity Index, FACT-ES	Past 7 days	Occurrence Intensity	Arthralgia/stiffness/AI related symptoms
Bowles 2012[8]	USA	ET	Cross-sectional (n=538)	Survey	At any point in ET	Occurrence	Adverse effects of ET
Brown 2014[21]	USA	AI	Cross-sectional (n=300)	WOMAC M-SACRAH Quick DASH	-	Occurrence Intensity	Musculoskeletal symptoms
Castel 2013[22]	USA	AI	Longitudinal (pre- and 2, 4, 6, 8, 12, 52 weeks post-AI, n=91)	FACT-ES PRAI	-	Occurrence Intensity	Arthralgia ET related symptoms
Chim 2013[23]	USA	AI	Cross-sectional (n=437)	BPI	Past 24 hours	Occurrence Intensity Distress	Joint Pain
Chin 2009[24]	Canada	ET	Cross-sectional (n=251)	FACT-ES Sexual activity questionnaire	Past 7 days	Occurrence Intensity	Vulvovaginal and urinary symptoms ET related symptoms
Crew 2007[25]	USA	AI	Cross-sectional (n=200)	Questionnaire adapted from BPI-SF	Past 7 days	Occurrence, Intensity	Joint symptoms
Desai 2013[26]	USA	AI	Cross-sectional (n=413)	Insomnia severity index (ISI)	Current	Occurrence Intensity Distress	Insomnia
Dizdar 2009[27]	Turkey	AI	Cross-sectional (n=92)	Patient Interview	Recently	Occurrence	Arthralgia

Author, Year	Country	Agent	Design	Instrument	Recall period	Domain	Symptoms
Egawa 2016[28]	Japan	AI	Longitudinal (pre- and 3, 6, 9, 12 months post-AI, n=391)	Questionnaire	-	Frequency Distress	Joint Symptoms
Frechette 2013[29]	Canada	ET	Longitudinal (pre- and 6 months post-ET, n=66)	Female sexual function index, FSDS-R, FACT-ES	Past 30 days (FSDS-R)/7 days (FACT-ES)	Occurrence Intensity Distress	Sexual dysfunction, ET related symptoms
Gallicchio 2012[30, 31]	USA	AI	Longitudinal (pre- and 3, 6 months post-AI, n=95)	VAS Symptom checklist of 20 menopausal-type symptoms	Past 4 weeks	Occurrence Intensity Distress	Musculoskeletal pain Menopausal-type symptoms
Gallicchio 2013[32]	USA	ET	Survey (n=851)	Hospital registry-based survey	Past 4 weeks	Distress	Hair loss & hair thinning
Garreau 2006[33]	USA	ET	Cross-sectional (n=452)	Questionnaire	-	Occurrence	ET related symptoms
Hadji 2014[34]	Germany	AI	Longitudinal (pre- and 3, 6, 9 months post-study n=1916)	RASQ	-	Occurrence Intensity	Arthralgia
Horimoto 2009[35]	Japan	AI	Retrospective (n=329)	Chart Review	-	Occurrence	Arthralgia
Hu 2016[36]	China	ET	Retrospective review of case records (n=160)	Chart review	-	Occurrence	ET-related symptoms
Huang 2010[37]	China	ET	Cross-sectional (n=315)	VAS	-	Occurrence Intensity	Cancer related fatigue
Inglis 2015[38]	Australia	AI	Cross-sectional (n=93)	OSDI FACT-ES	Past 2 weeks	Occurrence Intensity Distress	Dry eye syndrome ET related symptoms
Kanti 2016[39]	Germany	TAM	Longitudinal (1 day pre-therapy to up to 28 weeks post-therapy) (n=17)	Diary, questionnaire modified of the hairdex and the SF-MPQ	Past day	Occurrence Distress	Trichodynia (hair pain)
Kyvernitakis 2014[40]	Germany	AI	Longitudinal (pre- and 12, 24 months post-AI, n=174)	MRS	-	Occurrence Intensity	Menopausal symptoms
Laroche 2014[41]	France	AI	Longitudinal (pre- and 1, 3, 6, 12 months post-AI, n=135)	VAS, McGill Pain Questionnaire, BPI	-	Occurrence, Intensity, Distress	Pain
Lintermans 2014[42, 43]	Belgium	ET	Longitudinal (pre- and 3, 6, 12 months post-ET, n=292)	NSABP symptom checklist VAS Musculoskeletal questionnaire	Past 7 days	Occurrence intensity	Musculoskeletal pain
Lu 2011[44]	China	AI	Retrospective review of case records (n=271)	Telephone interview	-	Occurrence	ET-related symptoms
Mao 2009[45]	USA	AI	Cross-sectional (n=300)	Questionnaire	Past 7 days	Occurrence Intensity	Arthralgia

Author, Year	Country	Agent	Design	Instrument	Recall period	Domain	Symptoms
Mao 2011[46]	USA	AI	Cross-sectional (n=390)	Self-reported Arthralgia	-	Occurrence	Arthralgia
Menas 2012[47]	USA	AI	Cross-sectional (n=206)	Retrospective chart review	-	Occurrence	Arthralgia
Mortimer 1999[48]	USA	TAM	Cross-sectional (n=57)	BCPT Symptom Checklist	Past 4 weeks	Occurrence Distress	ET related symptoms
Mortimer 2008[49]	USA	TAM	Baseline data of RCT (n=864)	"Thoughts and Feelings" questionnaire	Past 4 weeks	Occurrence Intensity	Physical/psychological symptoms
Napoli 2010[50]	USA	AI	Cross-sectional (n=145)	Modified Leuven questionnaire	-	Occurrence Intensity	Musculoskeletal symptoms
Oberguggenberger 2011[51]	Australia	AI	Cross-sectional (n=280)	FACT-ES	Past 7 days	Occurrence Intensity	ET related symptoms
Ochayon 2014[52]	Israel	ET	Cross-sectional (n=210)	MDASI BCPT Symptom Checklist	Past 24 hours Past 4 weeks	Occurrence Intensity Distress	ET related symptoms
Ohsako 2006[54]	Japan	ANA	Longitudinal (n=53)	CTCAEver3.0	-	Occurrence Intensity	Musculoskeletal symptom
Olufade 2015[10]	USA	AI	Cross-sectional (n=68)	VAS	Past 4 weeks	Occurrence Intensity	Musculoskeletal pain
Presant 2007[54]	USA	AI	Semi-structured interview (n=56)	A linear analogue pain scale, location, character and treatment	-	Occurrence Intensity	Arthralgia
Ribi 2007[55] Ruhstaller 2009[56]	Switzerland	ET	Cross-sectional (n=373)	Checklist for Patients with Endocrine Therapy (C-PET)	-	Occurrence Frequency	ET-related symptoms
Rosenberg 2015[57]	USA	ET	Cross-sectional (n=2086)	BCPT Symptom Checklist	Past 4 weeks	Occurrence Distress	ET related symptoms
Sagara 2010[58]	Japan	AI	Longitudinal (n=656)	Symptom were collected retrospectively (no detail mentioned)	-	Occurrence	ANA related adverse events
Schover 2014[59]	USA	AI	Cross-sectional (n=129)	FSFI, MSIQ, FSDS-R, BESS	Past 4 weeks	Occurrence Distress	Sexual Function
Servitja 2012[60]	Spain	AI	Longitudina (pre- and 3 months post-AI, n=343)	VAS	-	Occurrence Intensity	Arthralgia
Shi 2013[61]	USA	AI	Longitudinal (pre- and biweekly for 1 year, n=47)	BPI MDASI Joint Pain Assessment (JPA)	Past 24 hours Past 7 days	Occurrence Intensity Distress	Arthralgia ET related symptoms

Author, Year	Country	Agent	Design	Instrument	Recall period	Domain	Symptoms
Singer 2012[62]	USA	AI	Longitudinal (pre- and 3, 6 months post-AI, n=52)	FACT-ES Global pain AUSCAN	Past 7 days	Occurrence Intensity	Arthralgia ET related symptoms
Su 2010[63]	USA	AI	Cross-sectional (n=300)	Questionnaire	Past 7 days	Occurrence Frequency Intensity	Hot flashes Weight Gain
Swenson 2013[64]	USA	AI	Longitudinal (pre- and 1, 3, 6 months post-AI, n=122)	BCPT Symptom Checklist AUSCAN WOMAC BPI QuickDASH	Past 24 hours Past 4 weeks	Occurrence Intensity Distress	Musculoskeletal symptoms
Waltman 2009[65]	USA	AI	Cross-sectional (n=29)	The Aromatase Inhibitor Questionnaire	Past 7 days	Occurrence Intensity Distress	Musculoskeletal symptoms
Wang 2013[66]	China	AI	Cross-sectional (n=436)	CTCAEver 3.0 WOMAC M-SACRAH BPI-SF	Past 7 days	Occurrence Intensity Distress	Musculoskeletal symptoms
Xu 2014[67]	China	ET	Cross-sectional (n=122)	Retrospective telephone interview	-	Occurrence	Musculoskeletal symptoms
Zhan 2007[68]	USA	TAM	Cross-sectional (n=138)	Symptom checklist	-	Occurrence	TAM-related side effects
Zhou 2011[69]	China	ET	Retrospective review of case records (n= 50)	CTCAEver3.0	-	Occurrence	ET-related symptoms

Abbreviations: AI, Aromatase Inhibitor; AUSCAN, Australian/Canadian Hand Osteoarthritis Index; ANA, Anastrozole; BCPT Symptom Checklist, Breast Cancer Prevention Trial Symptom Checklist; BESS, Breast Cancer Prevention Trial Eight Symptoms Scale; BPI, Brief Pain Inventory; CTCAEver3.0, Common Terminology Criteria for Adverse Events v3.0; ET, Endocrine Therapy; FACT-ES, Functional Assessment of Cancer; Therapy-Endocrine Symptom; FSDS-R, Female Sexual Distress S-Revised; FSFI, Female Sexual Function Index; IIQ-7, Incontinence Impact Questionnaire; MDASI, The M. D. Anderson Symptom Inventory; MRS, Menopause Rating Scale; M-SACRAH, Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands; MSIQ, Menopausal Sexual Interest Questionnaire; NSABP symptom checklist, National Surgical Adjuvant Breast and Bowel Project Symptom Checklist; OSDI, Ocular Surface Disease Index; PRAI, Patient-reported Arthralgia Inventory; Quick DASH, Quick Disabilities of the Arm, Shoulder and Hand Questionnaire; SF-MPQ, Short Form of the McGill Pain Questionnaire; TAM, Tamoxifen; UDI-6, Urogenital Distress Inventory-6; VAS, Visual Analog Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2.

Coverage of 16 Mostly Studied Symptoms in BCPT Symptom Checklist, FACT-ES, and MDASI

	BCPT	FACT-ES	MDASI
1. Joint/Muscle Pain	√	√	-
2. Hot Flashes	√	√	-
3. Vaginal Dryness/Insufficient Lubrication	√	√	-
4. Sleep Disorder/Insomnia	-	√	√
5. Fatigue/Lack of Energy	-	√	√
6. Nausea	√	√	√
7. Vaginal Bleeding or Spotting	√	√	-
8. Headaches/Migraines	√	√	-
9. Irritability	√	√	-
10. Joint/Muscle Stiffness	√	-	-
11. Weight Gain	√	√	-
12. Vaginal Discharge	√	√	-
13. Depression/Depressive Mood	-	√	√
14. Low Sexual Interest/Desire	-	√	-
15. Difficulty Breathing/Short of Breath	√	-	√
16. Dizziness/Faintness	√	√	-

√ Included in the instrumentation

- Not included in the instrumentation

Abbreviations: BCPT Symptom Checklist, Breast Cancer Prevention Trial Symptom Checklist; FACT-ES, Functional Assessment of Cancer; MDASI, The M. D. Anderson Symptom Inventory.

Table 3.

Coverage of 15 Most Prevalent Symptoms in BCPT Symptom Checklist, FACT-ES, and MDASI

	BCPT	FACT-ES	MDASI
1. Cramps	√	-	-
2. Hot Flashes	√	√	-
3. Fatigue/Lack of Energy	-	√	√
4. Eye Irritation	-	-	-
5. Heart Discomfort	-	-	-
6. Joint/Muscle Pain	√	√	-
7. Night Sweats	√	√	-
8. Sexual Arousal Problem/Orgasmic Dysfunction	-	-	-
9. Anxiety	-	√	-
10. Dyspareunia	-	-	-
11. Low Sexual Interest/Desire	-	√	-
12. Joint/Muscle Stiffness	√	-	-
13. Urinary Urgency	-	-	-
14. Numbness or Tingling	√	-	√
15. Dry Eye Syndrome	-	-	-

√ Included in the instrumentation

- Not included in the instrumentation

Abbreviations: BCPT Symptom Checklist, Breast Cancer Prevention Trial Symptom Checklist; FACT-ES, Functional Assessment of Cancer; MDASI, The M. D. Anderson Symptom Inventory.