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## **Urinary Symptoms in Breast Cancer: A Systematic Review**

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### Abstract

**Background**—A large body of research has documented the prevalence and severity of menopausal symptoms, especially vasomotor symptoms, in breast cancer survivors and their impact on quality of life. Urinary symptoms as part of the constellation of menopausal symptoms, however, have received relatively little attention. Thus, less is known about the prevalence and severity of urinary symptoms in breast cancer survivors.

**Methods**—We conducted a systematic review of studies published between 1990 and 2010 to describe the prevalence and severity of urinary symptoms in breast cancer survivors.

**Results**—We identified 16 eligible studies involving more than 2,500 women. Studies varied with respect to purpose, design, and nature of samples included; the majority used the same definition and assessment approach for urinary symptoms. Prevalence rates for symptoms ranged from 12% of women reporting burning or pain on micturition to 58% reporting difficulty with bladder control. Although in many studies the largest percentage of women rated symptoms as mild, as many as 23% reported severe symptoms.

**Conclusions**—Mild to moderate urinary symptoms are common in breast cancer survivors and some women report severe symptoms. Symptoms appear to adversely affect women's quality of life. There is a need for additional research assessing the natural history of urinary symptoms using consensus definitions and validated measures in diverse populations. Nevertheless, this review suggests that clinicians should screen for urinary symptoms in breast cancer survivors and offer treatment recommendations or make referrals as appropriate.

#### Keywords

breast cancer; menopause; urogenital system; survivorship

#### Introduction

Women with a history of breast cancer currently account for approximately 22% of cancer survivors in the United States, making them the largest group of cancer survivors today.<sup>1</sup> With ongoing advances in early detection and treatment, this trend is likely to continue.

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Nearly 90% of women diagnosed with invasive breast cancer are expected to survive five years or more following diagnosis.<sup>2, 3</sup> As a result, interest has shifted increasingly to include the prevention and treatment of long-term and late effects of breast cancer and its treatment. As well, national cancer research goals include a focus on survivorship issues to improve health-related outcomes and enhance quality of life in survivorship.<sup>4</sup> Consistent with this, the loss of menses due to chemotherapy and the menopausal transition have received considerable attention in breast cancer survivorship research.

Symptoms of menopause in women with breast cancer are typically the result of ovarian suppression and failure secondary to chemotherapy in premenopausal women and the use endocrine therapy in both premenopausal and postmenopausal women.<sup>5, 6</sup> These symptoms are often more severe than those experienced with natural menopause.<sup>7-9</sup> To date, a relatively large body of research has documented the prevalence and severity of menopausal symptoms, especially vasomotor symptoms such as hot flashes and night sweats and genital symptoms such as vaginal dryness, in breast cancer survivors, and their impact on quality of life in survivorship. Urinary symptoms are also commonly associated with menopause<sup>9-12</sup> and include urgency, urgency incontinence, stress incontinence, dysuria or burning, pelvic pressure and frequency, recurrent urinary tract infections and dryness.<sup>6</sup> Estrogen receptors have been identified in the structures of the lower urinary and genital tracts, including the uterus, vagina, ovaries, bladder, urethra, external genitalia and pelvic floor muscles. Thus, researchers have postulated that the development of urinary symptoms in menopause may be the result of lower urinary tract atrophy secondary to estrogen deficiency.<sup>10, 12-15</sup> Urinary symptoms may occur after other menopausal symptoms such as vasomotor symptom have abated.<sup>6</sup> And unlike menopausal vasomotor symptoms, if left untreated, urinary symptoms continue throughout life and may even worsen over time.<sup>16, 17</sup>

Research in women in the general population has consistently demonstrated that urinary symptoms adversely affect women's quality of life<sup>18-20</sup> and that the impact of these symptoms is determined by type and severity of symptoms.<sup>21, 22</sup> Treatment options for urinary symptoms associated with menopause depend on the symptom and its severity.<sup>17</sup> There are a number of non-invasive, behavioral interventions available to treat mild to moderate symptoms.<sup>17, 23-26</sup> Many women with urinary symptoms are a normal part of aging, uncertainty about available treatment options, or the belief that they can cope on their own.<sup>19, 27-30</sup>

Despite the attention to menopausal symptoms in breast cancer survivors, urinary symptoms as part of the constellation of menopausal symptoms appear to have received little attention. As a result, less is known about the prevalence and severity of urinary symptoms and their impact on quality of life in breast cancer survivors. We conducted a systematic literature review to identify studies that assessed urinary symptoms as part of the constellation of menopausal symptoms in women with a diagnosis of breast cancer. The aims of this paper are to review and characterize the available scientific literature with respect to urinary symptoms and breast cancer and to describe the prevalence and severity of urinary symptoms in breast cancer survivors.

#### Methods

#### Search and Selection Strategy

The identification of relevant studies began with electronic searches of English language journal articles in Medline, PsycINFO, and CINAHL from 1990 through June 2010. The MeSH search terms used were "breast neoplasms" and "menopause." The first two authors (K.A.D. and A.R.B.) separately screened study abstracts based on two eligibility criteria.

The first was that each study must have been published in a peer-reviewed English language journal. The second was that each study had to report on the quantitative assessment of any urinary symptom in the context of menopausal symptoms and breast cancer. Articles that reported menopausal symptoms but that did not include urinary symptoms as part of the constellation of symptoms were excluded. Similarly, articles involving qualitative assessments of menopausal symptoms in women with breast cancer and reviews of existing research that summarized results of published studies on menopause in women with breast cancer were excluded. Reference lists from studies retrieved also were reviewed to ensure all possible studies were identified.

#### **Review and Data Extraction**

The first two authors (K.A.D. and A.R.B.) separately reviewed the retrieved studies and extracted data from all of the studies that met eligibility criteria using a standardized form. Data extracted included basic descriptive information from each study about participants, including demographic and clinical characteristics, the purpose and design of the study, and the manner in which menopausal symptoms, including urinary symptoms were assessed. Extraction of results focused on published findings that provided information about urinary symptoms in women with a diagnosis of breast cancer. Any discrepancies in study eligibility criteria and data extraction were discussed and consensus was reached. Bias was reduced by conducting a comprehensive search of published studies in several electronic databases and searching reference lists of published reviews.

#### Results

#### Search Results and Nature of Selected Studies

Of 1266 abstracts screened, 1166 did not meet eligibility criteria (Figure 1). The complete texts of 100 published studies were retrieved and an additional 84 were excluded based on eligibility criteria. As a result, 16 publications were included in this review (Table 1).<sup>31-46</sup> Thirteen of the identified studies were conducted in the United States while the remaining three studies were conducted in Belgium,<sup>38</sup> Canada,<sup>46</sup> and the United Kingdom.<sup>43</sup> The nature and purpose of each study varied widely. Five studies focused specifically on the prevalence and severity of menopausal symptoms in women with breast cancer;<sup>31, 32, 43-45</sup> two of these five studies tested an intervention focused, at least in part, on relieving menopausal symptoms.<sup>32, 45</sup> Four studies focused on treatments for breast cancer and their relationship to menopausal symptoms.<sup>35, 37, 38, 46</sup> Two studies<sup>41, 42</sup> evaluated the psychometric properties of a modified version of the Breast Cancer Prevention Trial (BCPT) Symptom Checklist, a 43-item checklist from the National Surgical Adjuvant Breast and Bowel Project, a multi-center chemoprevention trial evaluating the efficacy of tamoxifen.<sup>47</sup> Another study used an early version of the BCPT Symptom Checklist to identify particular "problem areas" women experienced after breast cancer.<sup>36</sup> Three studies described quality of life.<sup>33, 34, 40</sup> including sexual function, after breast cancer, and included the assessment of menopausal symptoms in their assessment battery. Finally, one study assessed factors associated with hospitalization after breast cancer.<sup>39</sup> With respect to study design, the 16 studies identified included 10 cross-sectional studies, 4 longitudinal studies, and 2 randomized controlled intervention trials.

#### **Demographic and Clinical Characteristics of Study Participants**

All but one of the studies reported mean age of the sample which ranged from 36 to 62 years. Eight of these studies also reported age range; women as young as 27 years<sup>35, 36, 40, 41, 46</sup> and as old as 91 years were included. Three studies included only women who were 50 years of age or younger at diagnosis and one study<sup>44</sup> included only women who were 40 years of age or younger at diagnosis. Fourteen studies provided race

and/or ethnicity information for participants. Across these studies, a mean of 84% of women were classified as white (range = 60% to 96%) and a mean of 17% were classified as black or African American (range = 1% to 100%).

With respect to disease characteristics, 13 studies provided information about disease stage. Across studies, the majority of patients had stage I – III disease; some patients had stage 0 disease and some had recurrent disease. Ten studies reported mean time since diagnosis; this ranged from 7 months to 6.3 years. Five of these studies also reported the range of time since diagnosis; the shortest time since diagnosis was 1 month<sup>41</sup> while the longest was 11.7 years.<sup>41</sup> With respect to position in the treatment trajectory, one study<sup>37</sup> included only women in active treatment. Twelve studies included only women who had completed adjuvant therapy. Of these, 10 studies specified whether the women were receiving endocrine therapy for early stage or advanced breast cancer.<sup>38, 46</sup> And finally, two studies,<sup>36, 40</sup> drawn from the same sample of women, included both women who were post-treatment or in active treatment.

Thirteen studies provided detail about adjuvant therapies received by study participants. Each of these studies included women who had received some combination of surgery and chemotherapy; most studies also included women who had received radiotherapy. No samples were comprised exclusively of women who had undergone surgical resection and chemotherapy, with or without radiotherapy. For example, in the study by Alfano et al.,<sup>42</sup> 32.3% had undergone surgery only, 36.9% surgery plus radiotherapy, 9.2% surgery plus chemotherapy, and 21.7% surgery, radiotherapy, and chemotherapy; 45% were on tamoxifen. As noted previously, one study<sup>37</sup> involved women in active treatment with doxorubicin and cyclophosphamide (AC) with standard cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) and tamoxifen or placebo after surgical resection. As also noted previously, most studies included information about whether the women were currently receiving endocrine therapy, or radiotherapy, two studies<sup>38, 46</sup> limited participation to those women who were currently receiving endocrine therapy.

#### Assessment of Menopausal Symptoms

The assessment of menopausal symptoms varied minimally across studies (Table 2).<sup>31-46</sup> Twelve studies utilized a modified version of the 43-item BCPT Symptom Checklist. The checklist is a measure of common physical and psychological symptoms as well as symptoms associated with menopause and tamoxifen use. Respondents are asked to rate how bothered they were by each symptom during the past four weeks, using a 5-point Likert scale ranging from 0 = "not at all," 1 = "slightly," 2 = "moderately," 3 ="quite a bit," to 4 ="extremely." The versions used in the 12 studies included an early 50-item version that was later modified for use in the BCPT,<sup>39</sup> 42-item versions<sup>35</sup> 16-item versions,<sup>42, 44</sup> 15-item versions,<sup>36, 40</sup> and an "abbreviated" version with the number of items not specified.<sup>34</sup> One study<sup>37</sup> used a symptom checklist constructed from existing instruments including the BCPT Symptom Checklist. Four used the 7-item Menopausal Symptom Scale adapted from the 43item BCPT checklist. <sup>32, 33, 41, 45</sup> The study by Stanton et al.<sup>41</sup> used both the 42-item version of the checklist and the 7-item Menopausal Symptom Scale.

Among the four studies that did not use the BCPT Symptom Checklist, the approach to assessing menopausal symptoms included a study-specific 66-item survey that included vasomotor and gynecologic symptoms,<sup>31</sup> the Functional Assessment of Cancer Therapy-Endocrine Symptoms scale supplemented by study-specific questions about urinary symptoms,<sup>46</sup> the 10-item Menopause Rating Scale,<sup>43</sup> and the 20-item Leuven menopause form.<sup>38</sup>

#### **Assessment of Urinary Symptoms**

All of the studies assessed urinary symptoms as part of a constellation of menopausal or hormone-related symptoms. As noted, 12 studies utilized some version of the BCPT Symptom Checklist to assess the relevant symptoms. In 10 of these 12 studies, urinary symptoms were assessed with two items: "difficulty with bladder control when laughing or crying" and "difficulty with bladder control at other times." Respondents were asked to rate how bothered they were by each symptom during the past four weeks, using the 5-point Likert scale described above. The four-week time frame was used in each of the 10 studies with one exception; the study by Alfano et al.<sup>42</sup> used the past year as the time period of interest. The two (out of 12) remaining studies that used some version of the BCPT Symptom Checklist apparently did not include both bladder control items but reportedly used "difficulty in bladder control"<sup>39</sup> and "bladder problems"<sup>37</sup> to assess urinary symptoms, although this is not completely clear. Difficulty in bladder control was rated on a 4-point Likert scale ranging from 0 = not present to 3 = serious problem<sup>39</sup> in the past seven days while "bladder problems" was rated with respect to bother associated with the symptom on a 5-point Likert scale ranging from 0 =not at all to 4 =very much in the past seven days and since the beginning of the last chemotherapy cycle.<sup>37</sup>

Urinary symptoms were assessed in various ways in the remainder of the studies. For example, Morales et al.<sup>38</sup> defined "urinary problems" as "frequent urination (even at night) and urgency, urine loss when coughing, sneezing and laughing" and then asked respondents in a single question to rate the degree of inconvenience associated with these urinary problems during the past seven days. Chin et al.<sup>46</sup> used four questions specific to dysuria, urinary incontinence, urgency, and increased frequency of urinary tract infections. Respondents rated how true a statement about each of these symptoms had been for them in the past 7 days on a 5-point Likert scale.

#### Prevalence and Severity of Urinary Symptoms

Ten of the 16 studies reported data related to the prevalence of urinary symptoms. In general, the rate of women reporting any type of urinary symptom ranged from a low of 12% reporting burning or pain on micturition in a study of women receiving endocrine therapy for early stage or metastatic breast cancer<sup>46</sup> to a high of 58% reporting difficulty with bladder control at other times in a study of the psychometric properties of a BCPT-derived checklist for measuring hormone-related symptoms in breast cancer survivors.<sup>42</sup> Across those studies assessing bladder control using items from the BCPT Symptom Checklist,<sup>31, 32, 36, 39, 40, 42, 44</sup> a mean of 37% reported difficulty with bladder control either in general, when laughing or crying or at other times. In two studies,<sup>38, 43</sup> a mean of 34% reported "urinary problems."

Nine studies reported data related to the perceived severity of urinary symptoms. The method of reporting these data, and therefore, the information provided with respect to symptom severity was quite variable. In three of these studies<sup>41, 42, 45</sup> data were reported as mean scores on the BCPT 5-point Likert scale of bother associated with symptoms. For example, in the study by Alfano et al.,<sup>42</sup> that was designed to evaluate the psychometric properties of a 16-item version of the BCPT Symptom Checklist, the mean severity score for women reporting difficulty with bladder control while laughing or crying was 1.8 + 0.9. This score corresponds most closely to "somewhat" bothersome on the BCPT 5-point Likert scale of bother. In a study to identify particular problem areas for women with breast cancer, Avis et al.<sup>36</sup> reported the percent of women in every category of bother on the 5-point Likert scales for each bladder control question; 15.4% rated difficulty with bladder control while laughing or crying as at least somewhat bothersome. In five studies,<sup>31, 38, 39, 43, 46</sup>

perceived severity was reported as the percent of patients reporting some combination of no symptoms, mild, moderate, and severe symptoms. For example, in the study by Chin et al.,<sup>46</sup> to assess the prevalence and severity of symptoms of urogenital atrophy, 57% reported no urinary urgency, 27% reported mild urinary urgency, and 14% reported moderate/severe symptoms. In a similar study by Couzi et al.,<sup>31</sup> among those reporting difficulty with bladder control, 55% reported symptom severity as mild, 22% as moderate, and 23% as severe.

#### Relationship of Urinary Symptoms to Treatment and Quality of Life

Two studies examined the effects of adjuvant therapy with surgery, chemotherapy, and/or radiotherapy on urinary symptoms. In the study by Land et al.<sup>37</sup>women who received CMF were approximately four times more likely to be bothered by bladder problems during and immediately after treatment than women who received AC. Conversely, Alfano et al.<sup>42</sup> reported that neither receipt of chemotherapy nor type of surgery were predictive of bladder control problems in the post-treatment period. As noted previously, the primary aim of two studies<sup>38, 46</sup> was to examine the effects of endocrine therapy for breast cancer. In a longitudinal study of women with breast cancer about to start endocrine therapy. Morales et al.<sup>38</sup> found no significant changes in urinary problems from baseline to one and three months of therapy with first-line tamoxifen or non-steroidal aromatase inhibitors. The Chin et al.<sup>46</sup> study likewise included only women currently on endocrine therapy so no comparisons with a control group were possible, nor were comparisons made between types of endocrine therapy used. Four other studies<sup>41-44</sup> included an examination of the effect of endocrine treatment on urinary symptoms in their analyses with mixed results. In the study by Stanton et al.,<sup>41</sup> women currently taking tamoxifen reported significantly more bladder control problems than nonusers of tamoxifen. Conversely, three studies<sup>42-44</sup> found no difference in urinary symptoms between current tamoxifen users and nonusers. Taken together, these results suggest the effects of endocrine therapy on urinary symptoms are not vet known.

Finally, four studies<sup>32, 33, 41, 43</sup> examined the relationship of urinary symptoms to quality of life, including sexuality, <sup>33, 43</sup> after a breast cancer diagnosis. Less vitality, worse physical quality of life,<sup>41, 43</sup> worse social life,<sup>43</sup> and worse overall quality of life<sup>43</sup> were significantly associated with more urinary symptoms in the post-treatment period. With respect to sexuality, more urinary incontinence<sup>33</sup> and worse urinary problems<sup>43</sup> were significantly associated with adverse effects on sexuality in the post-treatment period.

#### Discussion

We identified 16 studies published between 1990 and June 2010 that examined urinary symptoms as part of the constellation of menopausal symptoms in women with breast cancer. Studies varied widely with respect to study purpose, design, and the nature and size of the samples included. There was less variation in terms of how urinary symptoms were defined and assessed. In general, this reflects the state of the science related to urinary symptom research in women in the general population wherein such variability makes evaluating existing findings and estimating prevalence more difficult.<sup>48, 49</sup> Nevertheless, most, but not all of the studies we identified report data on the prevalence of urinary symptoms. A high of 58% of women reported difficulty with bladder control. On average, using items from the BCPT Symptom Checklist,<sup>47</sup> a mean of 37% reported difficulty with bladder control when laughing or crying or other times. Similarly, 34% reported "urinary problems." More than half of the studies report data related to severity. All points along a continuum of mild, moderate and severe were represented. Although in many studies the largest percentage of women rated their symptoms as mild, as many as 23% of women rated their symptoms in

women with breast cancer include chemotherapy and endocrine therapy. In our review, relatively few studies examined the relationship of specific cancer treatments to urinary symptoms. Among these studies results are mixed. The relationship of urinary symptoms to quality of life was relatively clearer, with results suggesting that symptoms adversely affect the quality of life of women with a diagnosis of breast cancer.

#### Limitations of Existing Research

Several limitations of the existing literature should be acknowledged. As noted, relatively few studies have explored the relationship of various treatments for breast cancer to urinary symptoms as part of the constellation of menopausal symptoms. To our knowledge, no studies have made comparisons to a healthy, non-cancer control group of women; thus, it is not known whether urinary symptoms are more closely associated with breast cancer treatment. Further, only two studies have explored whether urinary symptoms may be more strongly associated with other factors such as age, obesity and race or ethnicity in women with breast cancer. Ganz et al.<sup>35</sup> found that among breast cancer survivors, urine loss with sneezing or coughing increased in frequency with age while Morales et al.<sup>38</sup> found that among women receiving endocrine therapy for early stage or advanced breast cancer, women with higher body mass index were more likely to report urinary problems. No studies have included a pre-treatment assessment of menopausal symptoms so it is not possible to know whether reported urinary symptoms predate a breast cancer diagnosis. There are limited data available about the course of symptoms and whether symptoms resolve or worsen over time. Only two studies<sup>34, 42</sup> of the 16 studies we identified are longitudinal in design and the results are mixed. Studies have been limited by either a single focus on a symptom of stress urinary incontinence or a lack of specificity. To date, no study has examined the full range of urinary symptoms, including urgency, urgency incontinence, stress incontinence, dysuria or burning, pelvic pressure and frequency, recurrent urinary tract infections and dryness. This is particularly significant because the appropriate course of treatment for urinary symptoms is determined by the type and severity of symptoms.<sup>21, 22</sup> The vast majority of studies used two questions related to bladder control from the BCPT Symptom Checklist<sup>47</sup> to assess the prevalence and severity of urinary symptoms. In the remainder of the studies, individual questions about select urinary symptoms were used or women were asked to reflect on a short list of urinary symptoms and respond to a single question related to severity or inconvenience. To date, no studies have used validated measures specifically designed to assess urinary symptoms or urologic condition-specific quality of life measures as recommended by the International Consultation on Incontinence.<sup>50</sup> Finally, although research in women in the general population has consistently demonstrated that urinary symptoms adversely affect women's quality of life,<sup>18-20</sup> there are limited data available about the effect of urinary symptoms on quality of life after breast cancer; existing data suggest that symptoms do have a negative effect on women's quality of life after breast cancer, however.

#### Conclusions

Our systematic review of the literature suggests that urinary symptoms are prevalent among women diagnosed and treated for breast cancer and that these symptoms tend to be mild to moderate in severity. In women in the general population, conservative first-line treatment of mild to moderate urinary symptoms includes behavioral strategies such as self-monitoring, lifestyle changes,<sup>24, 51</sup> and pelvic floor muscle exercises.<sup>52</sup> Such treatment typically results in significant improvement and minimal adverse outcomes. More severe symptoms may require more invasive interventions and pharmacologic management. Our findings support the notion that clinicians should screen for urinary symptoms in women with breast cancer and offer treatment recommendations or make referrals as appropriate. Our review also highlights the need for additional research assessing the natural history of

urinary symptoms using consensus definitions,<sup>53</sup> their relation to breast cancer treatments and their impact on women's quality of life using validated, recommended assessment approaches in diverse populations. Results of such studies would serve to inform the development of interventions to ameliorate the effects of urinary symptoms in survivorship.

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#### **Condensed Abstract**

A systematic review of studies published between 1990 and 2010 was conducted to describe the prevalence and severity of urinary symptoms in breast cancer survivors. Results show that urinary symptoms are prevalent among women diagnosed and treated for breast cancer and tend to be mild to moderate in severity.

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**Figure 1.** Study identification.

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Table 1

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Characteristics of studies included in the systematic review.

| Treatment Characteristics Menop   |
|---|
| Surgery only 32.3%;<br>surgery/radiotherapy<br>36.9%;<br>surgery/chemotherapy<br>9.2%;<br>surgery/radiation/<br>chemotherapy<br>21.7%                                       |
| No mastectomy 56.5%; No<br>mastectomy, no<br>reconstruction<br>20.0%; mastectomy,<br>reconstruction 23.5%;<br>initial<br>chemotherapy 74.9%;<br>initial<br>radiation 69.3%  |
| No mastectomy 56.6%; Not<br>mastectomy, no<br>reconstruction<br>19.7%; mastectomy,<br>reconstruction 23.7%;<br>initial<br>chemotherapy 75.1%;<br>initial<br>radiation 69.6% |
| Endocrine therapy for early Po<br>stage 84%; being treated for<br>metastatic disease 16%; on<br>atmoxifen 31%; on<br>aromatase<br>inhibitor 69%                             |
| Surgery only with or<br>without<br>radiation 37%; adjuvant<br>therapy, in form of<br>chemotherapy, tamoxifen or<br>both 63%; Tamoxifen at<br>time                           |

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| Time Since<br>Diagnosis /<br>Treatment           |   | 2.5 years (1.3)  | Mean 6.3 years<br>(range $= 5.0$ to<br>9.5)   | 5.9 (1.5) years   | 2.4 years,<br>range =<br>.8 - 5.6   | > 5 years =<br>8%, 3<br>- 5 years =<br>20%, 1<br>- 20%, 1<br>56%, <<br>1 year = 16%  |
|--|---|--|---|---|---|--|
| Position in Disease /<br>Treatment Trajectory    |   | Between 8 months and 5<br>years after diagnosis;<br>completed treatment at<br>least 4 months prior   | Between 1 and 5 years<br>post<br>diagnosis at first<br>assessment. Between 5<br>and 10 years post<br>diagnosis at follow-up                 | Disease free between 2<br>and 10 years without<br>recurrence / post treatment   | At least 8 months but not<br>more than 5 years post<br>diagnosis; completed<br>chemotherapy or<br>radiotherapy at least 4<br>months before enrollment | Received treatment within<br>last 5 years  |
| Menopausal Status                                |   | Mean of 6.9 (7.3)<br>years<br>postmenopausal   | Not reported  | Premenopausal 16%,<br>perimenopausal 13%,<br>postmenopausal 60%,<br>unclassifiable 11%  | Postmenopausal  | Premenopausal 6.1%,<br>perimenopausal 9.1%,<br>postmenopausal<br>65.5%, hysterectomy<br>19.3%  |
| Treatment Characteristics                        | of survey 35% ; ERT at<br>some<br>time before diagnosis 29% | Lumpectomy 67% (n=48);<br>mastectomy 33% (n=24);<br>tamoxifen 56% (n=40);<br>prior<br>radiation 69% (n=50); prior<br>chemotherapy 47% (n=34) | Lumpectomy 52.6%;<br>mastectomy 28.5%;<br>mastectomy with<br>reconstruction<br>18.9%; received<br>chemotherapy<br>42.2%; on tamoxifen 48.4% | Lumpectomy 55.8%;<br>mastectomy 44.2%;<br>reconstruction 23.3%;<br>received<br>adjuvant therapy 62.0%;<br>ever<br>use tamoxifen 37.4%;<br>current<br>tamoxifen only 10.4%,<br>chemotherapy only 35.0%,<br>tamoxifen and<br>tochemotherapy only 35.0%, | Mastectomy 38%;<br>lumpectomy<br>62%; current tamoxifen<br>61%;<br>past chemotherapy 46%  | Chemotherapy 42%;<br>radiotherapy to lower<br>abdomen<br>or pelvis 2.5%; bilateral<br>or pelvis 2.5%; GnRH<br>analog 3.0%; tamoxifen<br>56.0%;<br>anastrozole 7.5% |
| Disease<br>Characteristics                       |   | Stage I or II  | Stage I or II   | Stage 0, I, or II   | Stage I - II  | Not reported   |
| Race/Ethnicity                                   |   | Asian (n=1) 1.4%,<br>Black (n=5) 7%,<br>Hispanic (n=1) 1.4%,<br>White (n=65) 90%   | White 83.5%. Black<br>8.9%, Other 7.6%  | White 70.2%. African<br>American 11.6%,<br>Hispanic 7.3%, Asian<br>8.5%, Other 2.4%   | White 92%, Non-White<br>8%  | Caucasian 95.2%,<br>Afro-Caribbean 1.1%,<br>Asian 3.7%   |
| Age in<br>Years<br>(Mean<br>and<br>SD,<br>Range) |   | 54.5 (5.9)   | 55.6<br>initial<br>survey;<br>58.5<br>at follow-<br>up  | 49.5,<br>range<br>= 30 -<br>61.6  | 54.5,<br>range<br>= 43.1 -<br>70.3  | 53.9<br>(8.21),<br>range =<br>29<br>to 65  |
| Sample<br>Size                                   |   | 72   | 763   | 577   | 61  | 200  |
| Study Design                                     |   | Randomized<br>controlled trial   | Longitudinal  | Cross-sectional   | Cross-sectional   | Cross-sectional  |
| Authors  |   | Ganz et al.,<br>2000 <sup>32</sup>   | Ganz et al.,<br>2002 <sup>34</sup>  | 2003 <sup>35</sup> et al.,<br>2003 <sup>35</sup> 2003 <sup>35</sup> et al.,   | Greendale et<br>al., 2001 <sup>33</sup>   | Gupta et al.,<br>2006 <sup>43</sup>  |

| Time Since<br>Diagnosis /<br>Treatment           | Not reported   | 1 - 2 years<br>53%, 3<br>- 5 years 33%,<br>equal to or<br>greater<br>Han 6 years<br>14%  | Not reported   | 3.6 (2.6) years                     | 4.52 (3.8) years  | Sample 1: 36<br>mos,<br>range = 10 -<br>78;   |
|--|--|--|--|-------------------------------------|---|---|
| Position in Disease /<br>Treatment Trajectory    | Not reported   | At least one year post<br>diagnosis  | Scheduled to start<br>endocrine treatment  | At least one year from therapy      | At least one year from<br>diagnosis; had completed<br>treatment except hormonal<br>therapy, not undergoing<br>breast reconstruction   | Sample 1: diagnosed 1 - 5<br>years earlier; Sample 2:<br>disease free for 2 - 10<br>years; Sample 3: recently |
| Menopausal Status                                | Not reported   | Not reported   | Mean of 10 years<br>postmenopausal   | Not reported                        | Currently having<br>menstrual cycles 19%<br>(n=9)   | Not reported  |
| Treatment Characteristics                        | Surgery: lumpectomy + AD<br>= 58.1%; modified radical =<br>41.9%; receiving AC or<br>CMF | Radiation 65%;<br>mastectomy<br>58%; no systemic treatment<br>6%; chemotherapy 89%;<br>tamoxifen 49%; ovarian<br>suppression 15%;<br>aromatase<br>inhibitors 4%. At time of<br>survey:<br>Tamoxifen only 36%,<br>ovarian<br>suppression 9%, &<br>aromatase<br>aromatase<br>surves ovarian<br>suppression 9%, & | Adjuvant hormonal<br>treatment<br>80% (n = 132); palliative<br>treatments 20% (n = 32) | Not reported                        | Mastectomy without<br>reconstruction 33% (n=16);<br>mastectomy with<br>reconstruction<br>19% (n=9); breast<br>conservation<br>48% (n=23); past<br>conservation<br>48% (n=23); past<br>chemotherapy 74% (n=34);<br>tamoxifen only in past 17%<br>(n=8); tamoxifen currently<br>(n=2); currently taking<br>other<br>hormonal therapy 4% (n=2) | Chemotherapy: Sample 1:<br>38%: Sample 2: 62%;<br>Sample  |
| Disease<br>Characteristics                       | Axillary node-<br>negative estrogen<br>receptor-negative                                 | Stage 0 - III  | Not reported   | Not reported                        | Stage 0 to IIIA   | Sample 1: 0 - II;<br>Sample 2: 0 - II;<br>Sample 3: 1 - II;<br>Sample 4: High                                 |
| Race/Ethnicity                                   | White 74.4%, Black<br>18.8%, Other 3.7%,<br>Unknown 3.1%                                 | Caucasian 89%,<br>African American 2%,<br>Other 9%, Missing 1%   | Not reported   | White 93%                           | African American<br>100%  | Sample 1: White 77%,<br>Black 14%, Other 9%;<br>Sample 2: White 70%,  |
| Age in<br>Years<br>(Mean<br>and<br>SD,<br>Range) | $\leq 49 =$<br>50.6%;<br>50 -<br>59 =<br>32.5%;<br>$\geq 60 =$<br>16.9%                  | 36.2   | 62   | 58.3 (4.0)                          | 49.29<br>(8.3),<br>range =<br>30<br>to 77   | Sample<br>1:<br>56 (11.5),  |
| Sample<br>Size                                   | 160  | 371  | 164  | 123                                 | 48  | Sample<br>1: 863;<br>Sample<br>2: 577;  |
| Study Design                                     | Longitudinal   | Cross-sectional  | Longitudinal   | <b>Cross-sectional</b>              | Randomized<br>controlled trial  | Cross-sectional   |
| Authors  | Land et al.,<br>2004 <sup>37</sup>   | D Leining et al.,<br>2006 <sup>44</sup> et al.,<br>2006 <sup>44</sup> et al.,  | T Morales et al.,<br>2004 <sup>38</sup>  | Deske et al.,<br>2004 <sup>39</sup> | 2006 <sup>45</sup>  | Stanton et al.,<br>2005 <sup>41</sup>   |

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| Time Since<br>Diagnosis /<br>Treatment           | Sample 2: 71<br>mos,<br>range = 18 -<br>140;<br>Sample 3: 7<br>mos,<br>range = 1 - 19;<br>Sample 4: NA   |
|--|--|
| Position in Disease /<br>Treatment Trajectory    | completed treatment;<br>Sample 4: NA   |
| Menopausal Status                                |  |
| Treatment Characteristics                        | 3: 50%; Sample 4: NA.<br>Surgery<br>(umpectomy) Sample 1:<br>51%;<br>Sample 2: 56%; Sample 3:<br>67%; Sample 4: NA.<br>Tamoxifen<br>Tamoxifen<br>(current) Sample 1: 47%;<br>Sample 2: 18%; Sample 3:<br>54%; Sample 4: 0  |
| Disease<br>Characteristics                       | risk   |
| Race/Ethnicity                                   | Black 12%, Other<br>16%;<br>Sample 3: White 86%,<br>Black 7%, Other 7%;<br>Sample 4: White 96%,<br>Black 3%, Other 1%  |
| Age in<br>Years<br>(Mean<br>and<br>SD,<br>Range) | range = $31-$<br>31-<br>31-<br>31-<br>31-<br>32: 50<br>(5.6),<br>(5.6),<br>(5.6),<br>(5.6),<br>(5.6),<br>33-<br>62;<br>33-<br>57<br>(11.4),<br>range = $3:57$<br>(11.4),<br>range = $3:57$<br>87;<br>87;<br>87;<br>range = $22-$<br>62,<br>range = $22-$<br>82,<br>range = $22-$<br>62,<br>range = $22-$<br>82,<br>range = $22-$<br>83,<br>range = $22-$<br>84,<br>range = $2$ |
| Sample<br>Size                                   | Sample 3: 560; Sample 4: 208   |
| Study Design                                     |  |
| Authors  |  |

 Breast Cancer Prevention Trial Symptom Checklist from the National Surgical Adjuvant Breast and Bowel Project

 Dot
 = quality of life

 BCDL
 = quality of life

 BCS
 = breast cancer survivors

C indicates breast cancer CMF chemotherapy regimen = cyclophosphamide, methotrexate, and 5-fluorouracil CMF chemotherapy regimen = doxorubicin and cyclophosphamide CME = axillary node dissection

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#### Table 2

Assessment of menopausal and urinary symptoms by studies included in the systematic review

| Authors                              | Assessment of Menopausal<br>Symptoms           | Assessment of Urinary Symptoms  | Prevalence/Severity of Urinary Symptoms   |
|--------------------------------------|--|---|---|
| Alfano et al.,<br>2006 <sup>42</sup> | 16 items from BCPT Symptom<br>Checklist        | In past year, difficulty with bladder<br>control when laughing or crying and<br>difficulty with bladder control at<br>other<br>times; bother: 0 = <i>not at all</i> to 4 =<br><i>extremely</i>  | Difficulty with bladder control when laughing<br>or crying = 46% (mean<br>severity = $1.8 (0.9)$ ); difficulty with bladder<br>control at other times =<br>58.2% (mean severity = $1.8 (1.0)$ )   |
| Avis et al.,<br>2004 <sup>36</sup>   | 15 items from BCPT Symptom<br>Checklist        | In past 4 weeks, how bothered have<br>you been by difficulty with bladder<br>control when laughing or crying / at<br>other times (1 = not at all to 5 =<br>very<br>much)                        | Bladder control - laughing: not at all 74.8%, a<br>little 9.9%, somewhat<br>8.9%, quite a bit 4.0%, very much 2.5%;<br>bladder control - other: not<br>at all 73.9%, a little 14.3%, somewhat 6.4%,<br>quite a bit 3.5%, very<br>much 2.0%; difficulty with bladder control<br>reported as bothersome by<br>less than 30%   |
| Avis et al.,<br>2005 <sup>40</sup>   | 15 items from BCPT Symptom<br>Checklist        | In past 4 weeks, how bothered have<br>you been by difficulty with bladder<br>control when laughing or crying / at<br>other times (1 = not at all to 5 =<br>very<br>much)                        | Difficulty with bladder control (age<br>categories): 25-34 (n=25), 16%;<br>35-39 (n=41), 22.0%; 40-44 (n=54), 30.2%;<br>45-50 (n=82), 51.2%;<br>Total N = 202, 35.3%; p = .0007 - problems<br>increased with age  |
| Chin et al.,<br>2009 <sup>46</sup>   | FACT-ES  | In past 7 days, 4 questions about<br>urinary tract symptoms since<br>endocrine<br>therapy; asked to indicate how true<br>a<br>statement was for them: $0 = not$ at<br>all<br>to $4 = very$ much | Dysuria, none = $87\%$ , mild $(1/2) = 10\%$ ,<br>moderate/severe $(3/4) = 2\%$ ;<br>urinary incontinence, none = $63\%$ , mild $(1/2)$<br>= $30\%$ ,<br>moderate/severe $(3/4) = 3\%$ ; urinary urgency,<br>none = $57\%$ , mild $(1/2)$<br>= $27\%$ , moderate/severe $(3/4) = 14\%$ ;<br>increased urinary tract<br>infections, none = $88\%$ , mild $(1/2) = 8\%$ ,<br>moderate/severe $(3/4) = 4\%$  |
| Couzi et al.,<br>1995 <sup>31</sup>  | Investigator-developed<br>questionnaire        | In last 4 weeks, difficulty with<br>bladder<br>control  | Reported symptom 36% ( $n = 66 / 183$ ); 55% of those reported<br>symptom severity as mild, 22% as moderate, 23% as severe  |
| Ganz et al.,<br>2000 <sup>32</sup>   | 7 items adapted from BCPT<br>Symptom Checklist | In past 4 weeks, how bothered have<br>you been by difficulty with bladder<br>control when laughing or crying / at<br>other times (0 = <i>not at all</i> to 4 =<br><i>extremely</i> )            | Reported "stress urinary incontinence" at<br>baseline = 51% ; 1 reported<br>urinary incontinence only, 8 reported urinary<br>incontinence and hot<br>flashes, 27 reported urinary incontinence, hot<br>flashes, and vaginal<br>dryness; 1 reported urinary incontinence and<br>vaginal dryness; at<br>baseline urinary scale score for all women =<br>0.59 (0.82); effect of<br>intervention on urinary incontinence not<br>reported separately from<br>menopausal symptoms |
| Ganz et al.,<br>2002 <sup>34</sup>   | Items from BCPT Symptom<br>Checklist           | In past 4 weeks, how bothered have<br>you been by difficulty with bladder<br>control when laughing or crying / at<br>other times (0 = not at all to 4 =<br>extremely)                           | Frequency of bladder problems when<br>laughing or crying ( $P = .003$ )<br>and at other times ( $P = .007$ ) increased<br>significantly over time   |
| Ganz et al.,<br>2003 <sup>35</sup>   | 42 items from BCPT Symptom<br>Checklist        | In past 4 weeks, how bothered have<br>you been by difficulty with bladder<br>control when laughing or crying / at<br>other times (0 = <i>not at all</i> to 4 =<br><i>extremely</i> )            | Approximations from graph: 25 - 34 years = 21%, 35 - 39 years = 20%, 40 - 44 years = 35%, 45 - 51 years = 38%   |
| Greendale et al., $2001^{33}$        | Items from BCPT Symptom<br>Checklist           | In past 4 weeks, difficulty with<br>bladder<br>control when laughing or crying,   | Urinary incontinence score mean = 14.8 (20.2), range = 0 to 100   |

| Authors                               | Assessment of Menopausal<br>Symptoms  | Assessment of Urinary Symptoms   | Prevalence/Severity of Urinary Symptoms  |
|---------------------------------------|---|--|--|
|                                       |   | difficulty with bladder control at<br>other<br>times; bother: 0 = <i>not at all</i> to 4 =<br><i>extremely</i>   |  |
| Gupta et al.,<br>2006 <sup>43</sup>   | Menopausal Rating Scale with<br>2xyxweek recall   | Urinary problems (difficulty<br>urinating,<br>increased need to urinate, bladder<br>incontinence); severity: 0 = mild to<br>4 =<br>severe  | Reported urinary problems = 55%; reported<br>moderate to severe<br>symptoms = 39%  |
| Land et al.,<br>2004 <sup>37</sup>    | 17 items from existing<br>instruments including the BCPT<br>Symptom Checklist                                     | In past 7 days, bladder problems   | CMF versus AC: ratio of the odds of<br>reporting being at least'a little<br>bit bothered by bladder problems = 4.2, 99.8<br>CI = 1.262, 13.767, p =<br>.0002   |
| Leining et<br>al., 2006 <sup>44</sup> | 16 items from BCPT Symptom<br>Checklist   | In past 4 weeks, how bothered have<br>you been by difficulty with bladder<br>control when laughing or crying / at<br>other times (0 = <i>not at all</i> to 4 =<br><i>extremely</i> )   | Reported loss of bladder control "slightly<br>bothersome or more severe<br>symptoms:" laughter 26%, other 25%  |
| Morales et<br>al., 2004 <sup>38</sup> | Leuven Menopause Form   | In past 7 days, did you have<br>frequent<br>urination (even at night) and<br>urgency,<br>urine loss when coughing, sneezing<br>and laughing: not at all; yes, with<br>minor<br>inconvenience; yes, with moderate<br>inconvenience; yes, with severe<br>inconvenience; yes, intolerable | Endocrine therapy naive patients (n = 144)<br>prevalence of urinary<br>problems at baseline = 28% (n = 41);urinary<br>problems at baseline (n<br>= 164): tamoxifen first line patients: mild to<br>moderate = 23%;<br>randomized trial of tamoxifen or letrozole<br>patients: mild to moderate<br>= 23%; NSAI first-line patients: mild to<br>moderate = 39%; (N)SAI<br>previous tamoxifen patients: mild to moderate<br>= 25%; urinary<br>problems at 1 month (n = 163): tamoxifen<br>first line patients: mild to<br>moderate = 35%; randomized trial of<br>tamoxifen or letrozole patients:<br>mild to moderate = 28%; NSAI first-line<br>patients: mild to moderate =<br>43%; (N)SAI previous tamoxifen patients:<br>mild to moderate = 37%;<br>urinary problems at 3 months (n = 162):<br>tamoxifen or letrozole<br>patients: mild to moderate = 32%; NSAI first-<br>line patients:<br>mild to moderate = 36%; randomized trial of<br>tamoxifen or letrozole<br>patients: mild to moderate = 32%; NSAI first-<br>line patients: mild to<br>moderate = 35%; (N)SAI previous tamoxifen<br>patients: mild to moderate = 32%; NSAI first-<br>line patients: mild to<br>moderate = 35%; (N)SAI previous tamoxifen<br>patients: mild to<br>moderate = 35%; (N)SAI previous tamoxifen<br>patients: mild to |
| Oleske et<br>al., 2004 <sup>39</sup>  | Symptom Rating Scale (later<br>modified for use in the National<br>Surgical Adjuvant Breast and<br>Bowel Project) | In past 7 days, difficulty in bladder control  | Reported symptoms = 39%: mild 25%,<br>moderate 16%, severe 4%  |
| Schover et al., 2006 <sup>45</sup>    | 7 items adapted from BCPT<br>Symptom Checklist  | In past 4 weeks, how bothered have<br>you been by difficulty with bladder<br>control when laughing or crying / at<br>other times (0 = <i>not at all</i> to 4 =<br><i>extremely</i> )   | Mean = .67 (1.2) at baseline   |
| Stanton et<br>al., 2005 <sup>41</sup> | 42 item from BCPT Symptom<br>Checklist  | In past 4 weeks, difficulty with<br>bladder<br>control (when laughing or crying);<br>difficulty with bladder control (at<br>other<br>times); presence / absence = $1/0$ ;<br>bother: $0 = not$ at all to $4 =$<br><i>extremely</i>   | Sample 1: 0.52 (.47 to .58); Sample 2: 0.38 (.<br>33 to .43); Sample 3:<br>0.32 (.28 to .38); Sample 4: 0.40 (.31 to .50)  |

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BCPT = Breast Cancer Prevention Trial Symptom Checklist from the National Surgical Adjuvant Breast and Bowel Project

QOL = quality of life

BCS = breast cancer survivors

BC indicates breast cancer

CMF chemotherapy regimen = cyclophosphamide, methotrexate, and 5-fluorouracil

- AC chemotherapy regimen = doxorubicin and cyclophosphamide
- CI = confidence interval
- PCS = Physical Component Summary Score; MCS indicates Mental Component Summary Score
- NSAI = non-steroidal aromatase inhibitors
- (N)SAI = non-steroidal and steroidal aromatase inhibitors
- Data also presented for no symptoms and severe to intolerable symptoms