Serial Assessment of Urinary Incontinence in Breast Cancer Survivors Undergoing (Neo)Adjuvant Therapy

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ABSTRACT

Background: Among breast cancer survivors, urinary incontinence (UI) is often attributed to cancer therapy. We prospectively assessed urinary symptoms before and after (neo)adjuvant treatment of early-stage breast cancer. **Methods:** With consent, women with stage I–III breast cancer completed the Urogenital Distress Inventory and the Incontinence Impact Questionnaire before and 3 months after initiating (neo)adjuvant therapy. Patients with UI were at least slightly bothered by urinary symptoms. If UI was present pretreatment, it was considered prevalent; if UI was new or worse at 3 months posttreatment, it was considered incident; if prevalent UI was no worse at 3 months posttreatment, it was considered stable. Ordinal logistic regression models identified characteristics associated with the level of prevalent UI and with the degree of UI impact on quality of life (QoL). **Results:** On pretreatment surveys, participants (N=203; age 54.5 ± 11.4 years) reported 79.8% prevalence of UI, including overactive bladder (29.1%), stress incontinence (10.8%), or both (39.9%). The level of prevalent UI increased with body mass index (BMI; $P < .05$). Of 163 participants assessed at both time points, incident UI developed in 12 of 32 patients without prevalent UI and 27 of 131 patients with prevalent UI. Regardless of whether UI was prevalent (n=162), incident (n=39), or stable (n=94) at QoL assessment, the impact of UI increased ($P < .01$) with the number and severity of UI symptoms, subjective urinary retention, and BMI. Adjusted for those characteristics, incident UI had less impact on QoL ($P < .05$) than did prevalent or stable UI. **Conclusions:** We found that UI is highly prevalent at breast cancer diagnosis and that new or worsened UI is common after (neo)adjuvant therapy. Because UI often impairs QoL, appropriate treatment strategies are needed.

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Background

Most women diagnosed with early-stage breast cancer are successfully treated with a combination of surgery with or without radiation and systemic therapy and never experience recurrent disease. As a result of successful therapy, breast cancer survivors represent the largest group of cancer survivors, with numbers exceeding 3 million.¹ With successful treatment of the disease, the focus is now on maximizing the quality of life (QoL) of breast cancer survivors. It has been difficult to distinguish the short- and long-term complications of therapy regimens, because treatments vary not only in which individual drugs are used but also in the duration of treatment. Furthermore, adverse effects of (neo)adjuvant chemotherapy may differ by menopausal status, especially for younger women who may experience menopause as a result of chemotherapy.² Many women are placed on adjuvant endocrine therapy after completion of chemotherapy, making it difficult to distinguish which symptoms are attributed to chemotherapy, chemotherapy-induced menopause, or endocrine therapy. The most common symptoms reported by breast cancer survivors include hot flashes, vaginal dryness, and urogenital complaints.³ Most of the data addressing long-term symptoms in this population come from population-based studies in women who have already completed their treatment and who may still be on endocrine therapy.^{4–7} Prospective trials are needed to ensure that the symptoms attributed to treatment are truly a result of treatment and not a preexisting problem or from another cause.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) developed the Symptom Measurement tool to assess the toxicity of chemopreventive tamoxifen in women enrolled in chemoprevention trials.⁸ When validated in women who have completed therapy for breast cancer, the 7 most common posttreatment symptoms identified were hot flashes, nausea, bladder control, vaginal problems, musculoskeletal pain, cognitive problems, and weight problems.⁶ The NSABP Symptom Measurement tool includes 2 questions about bladder control: “difficulty with bladder control (when laughing

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or crying)” and “difficulty with bladder control (at other times)”); these questions are answered using a Likert scale of 0 to 5, with 0 being “not bothersome” and 5 being “extremely bothersome.”⁸ Adjuvant endocrine trials of aromatase inhibitors compared with tamoxifen have not reported an increase in bladder symptoms.^{9,10} The Mind-Body Study reported more bladder problems in women treated with adjuvant tamoxifen.⁶ Two chemoprevention trials, the Study of Tamoxifen and Raloxifene and the Italian Randomized Tamoxifen Prevention Trial, identified a significantly higher incidence of bladder problems in women receiving tamoxifen.^{7,11}

It is estimated that 50% of women without breast cancer experience symptoms of urinary incontinence (UI), and the prevalence and incidence of UI increase with age.^{12–14} We undertook an observational study to determine UI incidence in women with newly diagnosed breast cancer and the impact of systemic therapy on bladder symptoms in women with newly diagnosed early-stage breast cancer.

Methods

Subjects

Women newly diagnosed with stage I–III breast cancer in 2015 through 2017 were eligible for study inclusion if they were literate in English or Spanish, were scheduled to receive (neo)adjuvant chemotherapy or endocrine therapy, and consented to complete the Urogenital Distress Inventory and the Incontinence Impact Questionnaire (IIQ-7)¹⁵ before and 3 months after initiation of (neo)adjuvant therapy. Patients with metastatic cancer or currently or previously undergoing treatment by a urologist were excluded from participation. Participants were approached by the treating medical oncologist or their advance practice partner. This study was approved by City of Hope National Medical Center Institutional Review Board, and all participants provided consent for study participation.

Definitions

UI was considered present if the patient was at least slightly bothered by ≥ 1 urinary symptoms. Level of UI was classified as high if at least 1 urinary symptom “greatly bothered” the patient, moderate if a symptom “moderately bothered” the patient, and low if a symptom “slightly bothered” the patient. If UI was reported pretreatment, it was considered prevalent; if UI was new or worse at 3 months posttreatment, it was considered incident; if prevalent UI was still present but not worse at 3 months posttreatment, it was considered stable.

The subtypes of UI included overactive bladder (OAB), defined as “at least slightly bothered by frequent urination” and/or “leakage related to feeling of urgency”;

stress UI, defined as “at least slightly bothered by leakage related to physical activity, coughing, or sneezing”; and mixed UI, defined as the presence of both types. Respondents whose only leakage symptom was “at least slightly bothered by small amount of leakage” were included in the OAB category.

The impact of UI on QoL was classified according to the IIQ-7 score as major (33–99), moderate (5–29), or no impact (0).

Statistical Analyses

For this exploratory study, statistical significance ($P < .05$) was unadjusted for multiple hypothesis testing.

Demographic characteristics (age, menopausal status, body mass index [BMI], race/ethnicity), history of smoking, and parity (0, 1, 2, ≥ 3 births) were evaluated for association with the level of prevalent UI in all participants who completed a baseline (pretreatment) assessment. The evaluation used ordinal logistic regression.

Factors associated with the level of QoL impact of UI were explored among participants who reported UI at the pre- or posttreatment assessment. Variables considered for association with QoL impact were category of UI (prevalent, incident, or stable), number and severity of UI symptoms, subjective urinary retention, age, menopausal status, BMI, race/ethnicity, and cancer treatment. Variables were tested for multivariable association with QoL impact using ordinal logistic regression with a generalized estimating equation to account for potential correlation between repeated surveys per patient. Any variable that improved the model’s fit to the observed data was retained.

Results

Of 210 women invited to participate, 203 (96.7%) consented to participate and completed pretreatment surveys: their mean age was 54.5 years (± 11.4 years) and their mean BMI was 29.0 kg/m² (± 6.8). Participants represented the diverse racial and ethnic catchment area; most were non-Hispanic white women ($n = 112$; 55.2%), 38 (18.7%) were Hispanic, 31 (15.3%) were Asian, 11 (5.4%) were black, and 11 (5.4%) were unspecified. Ten (4.9%) were current smokers, 48 (23.7%) were former smokers, and 145 (71.4%) had never smoked. Thirty-five (17.2%) were nulliparous, 37 (18.2%) had given birth once, 77 (37.9%) had given birth twice, and 49 (24.1%) had given birth ≥ 3 times. Five patients had no data on childbearing recorded (Table 1). Of the 163 participants who contributed information on both pretreatment and posttreatment visits, 72 (44.2%) received endocrine therapy (half received a selective estrogen receptor modulator and the other half received an aromatase inhibitor), 60 (36.8%) received a taxane-based regimen, 29 (17.8%) received an anthracycline-based regimen,

Table 1. Characteristics of Respondents to Pretreatment Surveys (N=203)

Characteristic	n (%)
Age by menopausal status	
25–49 y	
Pre-/Perimenopausal	63 (31.0)
Postmenopausal	12 (5.9)
50–64 y	
Pre-/Perimenopausal	11 (5.4)
Postmenopausal	79 (38.9)
65–83 y	
Postmenopausal	38 (18.7)
Self-reported race/ethnicity	
Non-Hispanic white	112 (55.2)
Hispanic	38 (18.7)
Asian	31 (15.3)
Black	11 (5.4)
Not stated	11 (5.4)
BMI, kg/m ²	
Lean (<20)	13 (6.4)
Normal (20 to <25)	54 (26.6)
Overweight (25 to <30)	55 (27.1)
Obese (≥30)	81 (39.9)
Parity	
≥3 children	49 (24.1)
2 children	77 (37.9)
1 child	37 (18.2)
No children	35 (17.2)
Unavailable	5 (2.5)
History of cigarette smoking	
Never-smoker	145 (71.4)
Former smoker	48 (23.7)
Current smoker	10 (4.9)

Abbreviation: BMI, body mass index.

and 2 (1.2%) received no treatment (1 had stage IV disease and the other declined treatment).

Before initiation of (neo)adjuvant therapy, 162 (79.8%) of 203 participants reported prevalent UI, including 59 (29.1%) with OAB, 22 (10.8%) with stress incontinence, and 81 (39.9%) with mixed UI. A single characteristic, BMI, was associated with the level of prevalent UI, with a cumulative odds ratio of 1.04 (95% CI, 1.01–1.08; $P=.025$) for every additional unit of BMI. Perimenopausal/postmenopausal status was associated with prevalent UI (cumulative odds ratio, 1.80; 95% CI, 1.05–3.07; $P=.031$) only if BMI was not accounted for. No association was observed with other demographic characteristics, parity, or smoking history.

Figure 1. Summary of pretreatment and posttreatment findings. Abbreviation: UI, urinary incontinence.

Among the 162 patients who reported prevalent UI on the pretreatment questionnaire, the impact of prevalent UI on QoL was major in 13.6% and moderate in 29.6% of patients with prevalent UI, leaving 56.8% of patients with prevalent UI reporting no impact on QoL.

Of the 203 participants, 200 initiated treatment of breast cancer, and 163 completed both pretreatment and posttreatment questionnaires (Figure 1).

Of 163 participants completing serial assessments, incident UI developed in 12 of 32 patients without prevalent UI and 27 of 131 patients with prevalent UI. At 3 months posttreatment, UI that was present before cancer treatment remained stable in 94 of 131 patients.

Regardless of whether UI was prevalent, incident, or stable, QoL was adversely impacted by the number and severity of UI symptoms, by subjective urinary retention, and by BMI. Moreover, adjusted for the latter characteristics, incident UI had less impact on QoL than did prevalent or stable UI (Table 2). Neither demographic characteristics nor type of cancer treatment was associated with the impact of UI on QoL (data not shown).

Discussion

To our knowledge, this is the first prospective study to address the incidence and impact of UI in patients with early-stage breast cancer receiving (neo)adjuvant therapy. It is noteworthy that 79.8% of women had UI before

Table 2. Factors Independently Associated With the Impact of UI on Quality of Life

Independent Risk Factor	Cumulative Odds Ratio	95% CI	P Value
Subjective urinary retention			
Moderate/Great vs mild/none	13.53	4.28–42.79	<.001
Severity of distress from UI			
Great vs moderate-to-none	6.31	3.24–12.27	<.001
Number of UI symptoms			
2 vs 1	3.50	2.02–6.08	<.001
BMI			
Per additional unit	1.06	1.02–1.11	.003
Type of UI			
Incident vs prevalent/stable	0.40	0.17–0.94	.036

Abbreviations: BMI, body mass index; UI, urinary incontinence.

initiation of systemic therapy. In the United States, the estimated prevalence of UI in women (aged ≥ 20 years) ranges from 15.7% (moderate-to-severe leakage) to 51.1% (small leakage within the past 12 months).^{16,17} After 3 months of systemic therapy, 87.7% of our participants had UI, and the risk for developing UI did not vary by type of breast cancer therapy. Despite the high incidence of symptoms, the impact of UI on QoL was considered major or moderate in 41% of patients, and surprisingly, 59% reported no impact on their QoL. It is noteworthy that the impact of UI on QoL was greater in those receiving endocrine therapy than in those receiving chemotherapy.

Despite the high incidence of UI in the general population, data have indicated that only 25% to 60% of women ever seek treatment.^{18,19} UI is a problem that causes embarrassment and is often considered to be a natural consequence of aging.¹⁹ Our data suggest that the incidence of UI in patients with early-stage breast cancer may be higher than in the general population and may also be impacted by adjuvant therapy. A number of therapeutic options may improve UI, including anticholinergic agents, physical therapy, behavioral modifications, and percutaneous tibial nerve stimulation. It is incumbent on caregivers to recognize the high incidence of UI in the breast cancer survivor population in order to educate patients and refer them for appropriate treatment.

This is a single-institution study in a racially and ethnically diverse population receiving different types of chemotherapy and endocrine therapy. The study period was strictly defined as 3 years. Many of the women in this study went on to receive additional endocrine therapy, and we do not know the impact of that additional therapy on urinary symptoms. Because we did not observe patients longer, we do not know if symptoms of UI improved with time. In addition, the data did not allow us to draw conclusions about which individual chemotherapy regimens or endocrine treatments were more likely to cause or worsen symptoms of UI. Furthermore, we did not examine the possible causes of UI (we are prospectively studying women with UI symptoms with further genitourinary workup to identify the etiology of their pelvic floor disorders).

Conclusions

Our findings identified UI as a common problem in patients with early-stage breast cancer at baseline with new or worsening symptoms developing with treatment. The incidence we observed seems higher than one would expect of women in this age group (age 54.5 ± 11.4 years) without breast cancer. This frequency raises the question of whether risk factors for developing breast cancer overlap with those for developing UI, an extremely common problem in breast cancer survivors. Yet current survivorship guidelines do not address incontinence.²⁰ We have initiated clinical trials to address the treatment of UI in this population.

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References

1. American Cancer Society. Cancer Facts & Figures 2017. Accessed January 16, 2020. Available at: <http://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf>
2. Yoo C, Yun MR, Ahn JH, et al. Chemotherapy-induced amenorrhea, menopause-specific quality of life, and endocrine profiles in premenopausal women with breast cancer who received adjuvant anthracycline-based chemotherapy: a prospective cohort study. *Cancer Chemother Pharmacol* 2013;72:565–575.
3. Ganz PA, Greendale GA, Petersen L, et al. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. *J Natl Cancer Inst* 2000;92:1054–1064.

4. Cook ED, Iglehart EI, Baum G, et al. Missing documentation in breast cancer survivors: genitourinary syndrome of menopause. *Menopause* 2017;24:1360–1364.
5. Ganz PA, Cecchini RS, Julian TB, et al. Patient-reported outcomes with anastrozole versus tamoxifen for postmenopausal patients with ductal carcinoma in situ treated with lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. *Lancet* 2016;387:857–865.
6. Ganz PA, Petersen L, Bower JE, et al. Impact of adjuvant endocrine therapy on quality of life and symptoms: observational data over 12 months from the Mind-Body Study. *J Clin Oncol* 2016;34:816–824.
7. Land SR, Wickerham DL, Costantino JP, et al. Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 2006;295:2742–2751.
8. Cella D, Land S, Chang C, et al. Symptom measurement in the Breast Cancer Prevention Trial (BCPT) (P-1): psychometric properties of a new measure of symptoms for midlife women. *Breast Cancer Res Treat* 2008;109:515–526.
9. Cella D, Fallowfield L, Barker P, et al. Quality of life of postmenopausal women in the ATAC ("Arimidex," tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for early breast cancer. *Breast Cancer Res Treat* 2006;100:273–284.
10. Fallowfield LJ, Kilburn LS, Langridge C, et al. Long-term assessment of quality of life in the Intergroup Exemestane Study: 5 years post-randomisation. *Br J Cancer* 2012;106:1062–1067.
11. Veronesi U, Maisonneuve P, Rotmensz N, et al. Tamoxifen for the prevention of breast cancer: late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. *J Natl Cancer Inst* 2007;99:727–737.
12. Herzog AR, Diokno AC, Brown MB, et al. Two-year incidence, remission, and change patterns of urinary incontinence in noninstitutionalized older adults. *J Gerontol* 1990;45:M67–74.
13. Minassian VA, Yan X, Lichtenfeld MJ, et al. Predictors of care seeking in women with urinary incontinence. *Neurourol Urodyn* 2012;31:470–474.
14. Stanton AL, Bernaards CA, Ganz PA. The BCPT symptom scales: a measure of physical symptoms for women diagnosed with or at risk for breast cancer. *J Natl Cancer Inst* 2005;97:448–456.
15. Uebersax JS, Wyman JF, Shumaker SA, et al. Short forms to assess life quality and symptom distress for urinary incontinence in women: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. *Neurourol Urodyn* 1995;14:131–139.
16. Markland AD, Richter HE, Fwu CW, et al. Prevalence and trends of urinary incontinence in adults in the United States, 2001 to 2008. *J Urol* 2011;186:589–593.
17. Nygaard I, Barber MD, Burgio KL, et al. Prevalence of symptomatic pelvic floor disorders in US women. *JAMA* 2008;300:1311–1316.
18. Harris SS, Link CL, Tennstedt SL, et al. Care seeking and treatment for urinary incontinence in a diverse population. *J Urol* 2007;177:680–684.
19. Waetjen LE, Xing G, Johnson WO, et al. Factors associated with reasons incontinent midlife women report for not seeking urinary incontinence treatment over 9 years across the menopausal transition. *Menopause* 2018;25:29–37.
20. Sanft T, Denlinger CS, Armenian S, et al. NCCN Clinical Practice Guidelines in Oncology: Survivorship. Version 2.2019. Accessed January 16, 2020. To view the most recent version, visit [NCCN.org](https://www.nccn.org).