Usefulness of patient-reported outcomes to assess the effectiveness of topical hormonal therapy for gynecologic symptoms after antihormonal treatment for breast cancer

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ABSTRACT

The aim of this retrospective study was to assess the efficacy of topical hormonal therapy (THT) to relieve vaginal symptoms resulting from antihormonal therapy in women with hormone receptor–positive breast cancer. A total of 74 breast cancer patients who received THT for vaginal complaints were retrospectively identified and statistically matched with 74 control breast cancer patients with vaginal complaints with no documented use of THT. Symptom scores were recorded from the center's proprietary patient-reported outcomes database, Patient Care Monitor (ConcertoHealthAI, Boston). A baseline score was noted at the initiation of antihormonal therapy and was followed at 6 and 12 months. The median differences between baseline, 6-month, and 12-month scores were analyzed. Repeated measures analysis of variance assessed the impact of topical hormonal replacement. There was no statistically significant difference in score change between the two groups at 6 and 12 months. In the active THT group, there were no statistically significant differences in vaginal complaints or sexual problems over time: $\{F(2, 146) = 0.99, P = 0.369; \text{ and } F(2, 146) = 1.56, P = 0.217\}$, respectively. In this study, the use of topical hormonal replacement was not effective in alleviating vaginal symptoms.

KEYWORDS Atrophic vaginitis; breast cancer; patient-reported outcomes; topical estrogen

Atrophic vaginitis is reported in one-third of postmenopausal women and is more common in breast cancer survivors on adjuvant endocrine therapy.^{1–3}

For non–breast cancer patients, the preferred therapy for mild to moderate symptoms of atrophic vaginitis is nonhormonal topical moisturizers and lubricants.⁴ Additionally, systemic hormonal therapy and topical hormonal therapy (THT) have proven to be very useful for moderate to severe atrophic vaginitis in healthy postmenopausal women.^{5,6} However, the efficacy and safety of THT in breast cancer survivors is controversial.⁷ For patients with significant complaints, practitioners have cautiously recommended a short course of THT (estrogen or testosterone).⁷ Given the lack of clear

evidence supporting or refuting the use of THT in breast cancer patients, the treatment of atrophic vaginitis in breast cancer survivors remains challenging.⁸ We conducted a retrospective analysis to study the efficacy of THT in relieving vaginal complaints in breast cancer patients receiving endocrine therapy.

METHODS

Data were collected for this retrospective analysis from electronic medical records and a proprietary patient-reported outcomes database: The Patient Care Monitor (PCM; ConcertoHealthAI, Boston) at West Cancer Center (Memphis, Tennessee). The University of Tennessee Institutional Review Board approved this study.

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Received December 13, 2019; Revised February 24, 2020; Accepted March 6, 2020.

Table 1. Baseline characteristics of breast cancer patients in the topical hormonal therapy group and control group

Characteristics	Total (<i>n</i> = 148)	Active THT group (<i>n</i> = 74)	Control group (<i>n</i> = 74)	<i>P</i> value
Age, mean (SD) (years)	53 ± 9	53.1 ± 8	52 ± 8	0.078*
Stage				0.93 [†]
0	10 (7%)	6 (8%)	4 (6%)	
1	78 (53%)	39 (53%)	39 (53%)	
2	42 (29%)	21 (28%)	21 (29%)	
3	17 (11%)	8 (11%)	9 (12%)	
Unknown	1 (0.01%)	0	1 (0.01%)	
Prior chemotherapy	83 (56%)	41 (55%)	42 (57%)	0.868 [‡]
Endocrine therapy				0.3 [‡]
Aromatase inhibitor	67 (45%)	29 (39%)	38 (51%)	
Tamoxifen	35 (30%)	24 (32%)	21 (28%)	
Both	46 (24%)	21 (28%)	12 (20%)	
Treatment years, median (IQR)	5 (3–5)	5 (2–5)	5 (4–5)	0.05 [‡]
Time to vaginal symptoms (months)	6 (2–18)	23 (2–25)	11 (1–12)	0.05 [‡]

IQR indicates interquartile range; THT, topical hormonal therapy.

*Non-paired *t* test.

[†]Chi-square test.

[‡]Rank-sum test.

Using ICD-9-CM codes, we searched the electronic records and identified early breast cancer patients on antiestrogen therapy with vaginal or sexual complaints between 2002 and 2014 who received THT. To qualify for entry, topical hormonal replacement had to have been prescribed at least 1 month after the initiation of antihormonal therapy. Available local pharmacy data, electronic medical record documentation of a prescribed THT, or clinical documentation of patient-reported use of THT were utilized as evidence of active use. Additionally, to be eligible, patients had to have at least two PCM scores, 6 months apart. The control group was formed by an equal number of breast cancer patients with similar characteristics who were not using any THT. They were statistically matched 1:1 using propensity score matching with calipers of 0.01.

The PCM is an electronic patient-reported outcome system that delivers a validated symptom survey, which patients complete before every clinic visit; it involves a complete review of symptoms. Survey items relevant to the current project included vaginal problems such as itching and dryness, as well as sexual dysfunction and loss of interest in sex. The patient graded these symptoms from 0 to 10, with 0

being an absence of symptoms and 10 being the most severe. The PCM also includes quality of life measures, specifically focusing on anxiety and depression. Patients complete the survey at every visit, enabling the clinician to follow symptom score over time and intervene as needed. We recorded the baseline PCM score for vaginal complaints and sexual problems at the initiation of THT. These patients were followed in the clinic, and their symptom score was observed over time. We assessed their score before and after topical hormonal replacement and trended it for 12 months. Similarly, in the control group, baseline PCM scores were documented at the start of antihormonal therapy.

The baseline characteristics of the patients in both case and control groups were compared using an unpaired *t* test, chi-square test, and rank-sum test. We calculated the mean, median, and 95% confidence interval of baseline patient characteristics and symptom scores in the PCM. Median differences between baseline scores and scores at 6 months and 12 months of the case and control groups were compared using the Mann-Whitney *U* test. A one-way repeated measures analysis of variance was run on the case group patients to determine if there were differences in symptom score due to the THT. All statistical analyses were performed using Stata (version 12.0; StataCorp). Statistical significance for all the tests was set at *P* < 0.05.

RESULTS

Of the 5479 patients at the West Cancer Center identified with vaginal complaints, only 5% were confirmed to be prescribed THT. In this group, 74 out of 5479 patients were confirmed to have had at least two PCM reports, at least 6 months apart, following the start of antiestrogen therapy.

Demographic data and clinical characteristics of patients from both the case and control groups are illustrated in [Table 1](#). There were no significant differences in age, breast cancer stage, prior chemotherapy treatment, or adjuvant endocrine therapy between the two groups. The median time to development of vaginal symptoms was 23 months in the active THT group and 11 months in the control group. In the case group, 63 patients used an estrogen form of topical therapy and 11 patients used a testosterone form.

The median and mean baseline values for the PCM scores of vaginal complaints, sexual problems, and anxiety and depression are presented in [Table 2](#). The median reported baseline vaginal and sexual complaint scores were significantly higher in the active THT group (*P* < 0.0001 and *P* = 0.0002, respectively). As shown in [Table 3](#), there was no statistically significant difference in change of PCM score between the two groups at 6 and 12 months.

The repeated measures analysis of variance results showed that THT elicited no statistically significant differences in vaginal complaints or sexual problems over its time course, {*F* (2, 146) = 0.99, *P* = 0.369; (*F* (2, 146) = 1.56, *P* = 0.217}, respectively.

Table 2. Baseline self-reported scores for vaginal complaints, sexual problems, and anxiety/depression for those treated with topical hormonal therapy and matched controls

Baseline scores	Treatment group		Control group		P value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Vaginal complaints*	3.1 ± 3.4	2 (0-5)	1.0 ± 2	0 (0-0)	<0.0001
Sexual problems	3 ± 3.6	2 (0-5)	1.5 ± 3	0 (0-0)	0.0002
Anxiety/depression	1.9 ± 3.4	0 (0-25)	2.3 ± 4	0 (0-3)	0.4239

IQR indicates interquartile range.

*Vaginal complaints include vaginal itching, dryness, and unspecified vaginal problems.

Table 3. Symptom score change between baseline and the 6- and 12-month evaluation periods for those treated with topical hormonal therapy and matched controls

Variable	Symptom score change			
	6 months – baseline		12 months – baseline	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Vaginal complaints				
Treatment group	0.4 ± 3.5	0 (–1 to 0)	–0.2 ± 4	0 (–2 to 1)
Control group	0.2 ± 3.4	0 (0–0)	0.2 ± 3	0 (0–0)
P value*		0.361		0.196
Sexual problems				
Treatment group	0.5 ± 2.4	0 (0–1)	0.7 ± 3.7	0 (–1 to 0)
Control group	0.1 ± 2.3	0 (0–0)	0.5 ± 3.7	0 (0–0)
P value*		0.573		0.891

IQR indicates interquartile range; SD, standard deviation.

*There were no statistically significant differences between the two groups (Mann-Whitney U test).

DISCUSSION

THT is an effective option for treating symptoms of atrophic vaginitis in postmenopausal women with no breast cancer history.^{6,8} However, its use and safety in breast cancer patients continue to be debated due to the paucity of data regarding symptom relief and recurrence rates. In this retrospective study, we found that patients with increased severity of vaginal symptoms utilized more THT. However, we failed to demonstrate that THT was effective in relieving vaginal symptoms in women with breast cancer on adjuvant endocrine therapy.

Currently, per internationally accepted standards, non-hormonal topical therapies such as vaginal moisturizers and lubricants are the preferred line of treatment for atrophic vaginitis in breast cancer patients.⁹ Lifestyle modifications such as smoking cessation, avoidance of irritants through proper vulvovaginal hygiene, regular coitus, and stress management are also advocated.^{10–12} Notably, the North American Menopause Society and the American College of Obstetricians and Gynecologists support careful consideration

of local hormonal therapy for breast cancer patients who do not respond to nonhormonal therapy.^{9,13} Nevertheless, physicians and patients are hesitant to use local hormonal therapy due to the lack of long-term safety data. Similarly, in our study, we found that only 5% of patients with vaginal symptoms used THT.

The cornerstone of estrogen receptor–positive breast cancer is deprivation of estrogen signaling either through complete estrogen suppression or blockade of estrogen receptor activation. This strategy, however, harms other systemic functions depending on estrogen signaling.¹⁴

Systemic estrogen therapy, delivered in the form of oral medications or transdermal patches, is well studied in healthy menopausal women to alleviate menopausal symptoms, including atrophic vaginitis.¹² However, the consensus is to avoid systemic estrogen therapy in breast cancer patients because of the inconsistent results on its safety.^{14,15} For instance, the HABITS (Hormonal Replacement Therapy after Breast Cancer—Is It Safe?) trial, which analyzed the association of systemic hormonal therapy with breast cancer, was prematurely stopped due to reports of significant risks of increased breast cancer.¹⁶ On the other hand, the Stockholm trial did not report increased breast cancer recurrence in the systemic hormone replacement arm.¹⁷ In addition, some observational studies and a systematic review did not find that use of systemic hormone therapy was associated with an increased risk of developing breast cancer in patients with high-risk features such as having a significant family history or a *BRCA1* or *BRCA2* mutation.^{18–20}

Local estrogen therapies mainly comprise estradiol preparations and conjugated estrogens that are available in various preparations such as vaginal creams, gels, inserts, rings, and estrogen-embedded intrauterine devices. The reports of the level of estrogen absorption with local estrogen therapy are inconsistent.^{21,22} The prospective clinical studies assessing local hormonal therapies on breast cancer patients are limited by their small sample size. For instance, Pfeiler et al's prospective study demonstrated no increase in serum estrogen levels after administration of vaginal estriol for 2 weeks in 10 postmenopausal women with a history of breast cancer on an aromatase inhibitor.²³ Also, Melisko et al's randomized clinical trial (*N* = 69) reported a modest (12%) increase in

serum estrogen levels with intravaginal testosterone cream and no increase with an estradiol-releasing vaginal ring.²⁴ In contrast, Wills et al's prospective clinical study demonstrated elevated circulating estradiol levels in postmenopausal women ($N = 24$) with a history of estrogen receptor–positive breast cancer who were using tablets or intravaginal estradiol rings.²⁵ Likewise, Kendall et al reported serum estrogen levels in six postmenopausal women with a history of breast cancer undergoing aromatase inhibitor therapy and using vaginal estradiol tablets for atrophic vaginitis. They reported a substantial increase in serum estradiol levels at 2 weeks, after which most serum estradiol levels decreased to close to baseline within 4 weeks. These elevated serum estradiol levels were concerning, but it was uncertain if the topical therapy decreased or reversed the estrogen suppression caused by aromatase inhibitors.²⁶ Finally, although some available retrospective studies have not demonstrated unfavorable breast cancer outcomes with local estrogen therapy, it is not possible to come to any conclusions.^{27,28}

Limitations include the retrospective nature of our study. Additionally, a considerable number of patients were excluded from the case group because they did not have two PCM reports at least 6 months apart. Additionally, tools like the PCM are susceptible to random measurement error. We were also unable to document adherence with THT during the period between symptom determination with the PCM.

Our study failed to demonstrate a benefit in the breast cancer population when compared to the control group. This finding differed from that of Melisko et al who showed improvement in vaginal symptoms with treatment.²⁴ Certainly, the study limitations mentioned above may play a role, but importantly Melisko et al lacked a nontreatment control for comparison. Additionally, breast cancer patients may present with more severe symptoms due to a stronger hypoestrogenic state from a physiologic reduction in estrogen at menopause plus the use of estrogen-depriving medications. Unfortunately, this study was not able to compare the severity of symptoms at presentation to that of a noncancer population. Moreover, in this real-world cohort, when prescribed, patients were advised to use these medications sparingly due to the assumed potential risk of disease recurrence. For most patients in this study, THT was recommended two to three times a week, compared to daily use of the estradiol silicone ring for 12 weeks or daily use for 2 weeks followed by three times a week for 10 weeks for topical THT in the study by Melisko et al.²⁴ Nevertheless, this study provides valuable clinical information and reiterates the need for prospective trials to confirm the findings.

In conclusion, we did not observe significant relief in vaginal symptoms with use of THT in women with a history of breast cancer on adjuvant hormonal therapy.

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1. Santoro N, Komi J. Prevalence and impact of vaginal symptoms among postmenopausal women. *J Sex Med.* 2009;6(8):2133–2142. doi:10.1111/j.1743-6109.2009.01335.x.
2. Marino JL, Saunders CM, Emery LI, Green H, Doherty DA, Hickey M. Nature and severity of menopausal symptoms and their impact on quality of life and sexual function in cancer survivors compared with women without a cancer history. *Menopause.* 2014;21(3):267–274. doi:10.1097/GME.0b013e3182976f46.
3. Baumgart J, Nilsson K, Stavreus-Evers A, et al. Urogenital disorders in women with adjuvant endocrine therapy after early breast cancer. *Am J Obstet Gynecol.* 2011;204(1):26.e1–7. doi:10.1016/j.ajog.2010.08.035.
4. North American Menopause Society. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. *Menopause.* 2013;20(9):888–902. doi:10.1097/GME.0b013e3182a122c2.
5. Suckling JA, Kennedy R, Lethaby A, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database System Rev.* 2006;(4): CD001500. doi:10.1002/14651858.CD001500.pub2.
6. Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev.* 2016;(8): CD001500. doi:10.1002/14651858.CD001500.pub3.
7. Ponzzone R, Biglia N, Jacomuzzi ME, Maggiorotto F, Mariani L, Sismondi P. Vaginal oestrogen therapy after breast cancer: is it safe? *Eur J Cancer.* 2005;41(17):2673–2681. doi:10.1016/j.ejca.2005.07.015.
8. Mazzarello S, Hutton B, Ibrahim MFK, et al. Management of urogenital atrophy in breast cancer patients: a systematic review of available evidence from randomized trials. *Breast Cancer Res Treat.* 2015; 152(1):1–8. doi:10.1007/s10549-015-3434-z.
9. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause.* 2017;24(7):728–753. doi: 10.1097/GME.0000000000000921.
10. Pruthi S, Simon JA, Early AP. Current overview of the management of urogenital atrophy in women with breast cancer. *Breast J.* 2011; 17(4):403–408. doi:10.1111/j.1524-4741.2011.01089.x.
11. Kalogeraki A, Tamiolakis D, Relakis K, et al. Cigarette smoking and vaginal atrophy in postmenopausal women. *In Vivo.* 1996;10(6):597–600.
12. Sika CS. Atrophic vaginitis. *Dermatol Ther.* 2010;23(5):514–522. doi:10.1111/j.1529-8019.2010.01354.x.
13. Farrell R; American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice; American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice. ACOG committee opinion no. 659: the use of vaginal estrogen in women with a history of estrogen-dependent breast cancer. *Obstet Gynecol.* 2016;127(3): e93–e96. doi:10.1097/AOG.0000000000001351.
14. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. *CA Cancer J Clin.* 2016;66(1):43–73. doi:10.3322/caac.21319.
15. Pritchard KI, Khan H, Levine M. Clinical practice guidelines for the care and treatment of breast cancer: 14. The role of hormone replacement therapy in women with a previous diagnosis of breast cancer. *CMAJ.* 2002;166(8):1017–1022.
16. Holmberg L, Anderson H; HABITS Steering and Data Monitoring Committees. HABITS (hormonal replacement therapy after breast cancer—is it safe?), a randomised comparison: trial stopped. *Lancet.* 2004;363(9407):453–455. doi:10.1016/S0140-6736(04)15493-7.

17. von Schoultz E, Rutqvist LE; Stockholm Breast Cancer Study Group. Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. *J Natl Cancer Inst.* 2005;97(7):533–535. doi:10.1093/jnci/dji071.
18. Birrer N, Chinchilla C, Del Carmen M, Dizon DS. Is hormone replacement therapy safe in women with a *BRCA* mutation? A systematic review of the contemporary literature. *Am J Clin Oncol.* 2018;41(3):313–315. doi:10.1097/COC.000000000000269.
19. Anderson GL, Chlebowski RT, Rossouw JE, et al. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. *Maturitas.* 2006;55(2):103–115. doi:10.1016/j.maturitas.2006.05.004.
20. Rebbeck TR, Friebe T, Wagner T, et al; PROSE Study Group. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in *BRCA1* and *BRCA2* mutation carriers: the PROSE Study Group. *J Clin Oncol.* 2005;23(31):7804–7810. doi:10.1200/JCO.2004.00.8151.
21. Kokot-Kierepa M, Bartuzi A, Kulik-Rechberger B, Rechberger T. [Local estrogen therapy—clinical implications—2012 update]. *Ginek Pol.* 2012;83(10):772–777.
22. Trinkaus M, Chin S, Wolfman W, Simmons C, Clemons M. Should urogenital atrophy in breast cancer survivors be treated with topical estrogens? *Oncology.* 2008;13(3):222–231. doi:10.1634/theoncologist.2007-0234.
23. Pfeiler G, Glatz C, Königsberg R, et al. Vaginal estriol to overcome side-effects of aromatase inhibitors in breast cancer patients. *Climacteric.* 2011;14(3):339–344. doi:10.3109/13697137.2010.529967.
24. Melisko ME, Goldman ME, Hwang J, et al. Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial. *JAMA Oncol.* 2017;3(3):313–319. doi:10.1001/jamaoncol.2016.3904.
25. Wills S, Ravipati A, Venuturumilli P, et al. Effects of vaginal estrogens on serum estradiol levels in postmenopausal breast cancer survivors and women at risk of breast cancer taking an aromatase inhibitor or a selective estrogen receptor modulator. *J Oncol Pract.* 2012;8(3):144–148. doi:10.1200/JOP.2011.000352.
26. Kendall A, Dowsett M, Folkard E, Smith I. Caution: vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. *Ann Oncol.* 2006;17(4):584–587. doi:10.1093/annonc/mdj127.
27. Le Ray I, Dell'Aniello S, Bonnetain F, Azoulay L, Suissa S. Local estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case-control study. *Breast Cancer Res Treat.* 2012;135(2):603–609. doi:10.1007/s10549-012-2198-y.
28. Dew JE, Wren BG, Eden JA. A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. *Climacteric.* 2003;6(1):45–52. doi:10.1080/cmt.6.1.45.52.