OXFORD

JNCI J Natl Cancer Inst (2022) 114(10): djac113

https://doi.org/10.1093/jnci/djac113
First published online July 20, 2022
Editorial

EDITORIAL

Vaginal Estrogen Therapy for the Genitourinary Symptoms of Menopause: Caution or Reassurance?

Elizabeth J. Cathcart-Rake, MD,* Kathryn J. Ruddy, MD, MPH

Department of Oncology, Mayo Clinic, Rochester, MD, USA

*Correspondence to: Elizabeth J. Cathcart-Rake, MD, Department of Oncology, Mayo Clinic, 200 First St SW, Rochester, MN 55901, USA (e-mail: cathcart-rake.elizabeth@mayo.edu).

Vasomotor symptoms (hot flashes and night sweats) and genitourinary symptoms (vaginal dryness, dysuria, urinary tract infections, and dyspareunia) frequently plague breast cancer survivors during adjuvant endocrine therapy (1). These symptoms worsen quality of life and can contribute to early treatment discontinuation, such that supplemental estrogens are sometimes considered to mitigate these endocrine therapy toxicities. However, the safety of systemic and vaginal estrogen use among breast cancer survivors, particularly those with estrogen receptor–positive disease, has been uncertain (2,3). In this issue of the Journal, Cold and colleagues (4) present the results of their study Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study to better elucidate the safety of exogenous hormone therapy in survivors of breast cancer.

The authors used the nationwide Danish registry of 8461 women diagnosed with early stage, estrogen receptor–positive breast cancer to identify and follow patients who received or did not receive oral menopausal hormone therapy (MHT; n = 133 patients) or vaginal estrogen therapy (VET; n = 1957 patients) postdiagnosis. Overall, survivors who received VET or MHT did not have an increased relative risk for breast cancer recurrence, nor did they have worsened overall survival, compared with patients who did not receive VET or MHT. However, the subgroup of patients who received VET and were prescribed aromatase inhibitors (n = 822 patients) did have a higher risk of recurrence than nonusers of VET on aromatase inhibitor (n = 2520 patients), with a hazard ratio of 1.39 (95% confidence interval = 1.04 to 1.85) but with no difference in mortality between the groups (hazard ratio = 0.94, 95% confidence interval = 0.70 to 1.26).

The authors should be commended for their inclusion of a large, population-based dataset of Danish breast cancer survivors. This dataset includes records of all prescription medications given over time, such that these authors were able to identify the patients of interest, evaluate for adherence, and follow outcomes over a decade. The results of the current study help inform nuanced risk and benefit discussions between patient and oncology providers about the use of VET in the management of genitourinary symptoms secondary to endocrine therapy. Prior to this study, VET had been shown to temporarily increase estradiol levels, but it was not clear whether this acute systemic absorption was enough to increase risk for recurrence or worsen survival among breast cancer survivors (5-7). Women on tamoxifen with clinically significant genitourinary symptoms should be reassured by these data as there was no impact of VET on breast cancer recurrence or overall survival in women on tamoxifen in this cohort.

However, given that women on aromatase inhibitors were at a higher risk for breast cancer recurrence if they received VET, oncology providers should pause before prescribing VET to women on aromatase inhibitors. Nonhormonal strategies to control genitourinary symptoms, including vaginal moisturizers, which can reduce vaginal dryness by approximately 60% (comparing favorably with the effect of vaginal estrogen), should first be employed (8-10). Hyaluronic acid-based vaginal gels, if applied 3-5 times per week, also appear to improve genitourinary symptoms (11). Microablative CO2 vaginal laser therapy is also being studied as a possible treatment for aromatase inhibitor–induced vaginal toxicity (12-14). The compound vaginal dehydroepiandrosterone may be a reasonable hormonal option for treatment of vaginal symptoms in patients taking aromatase inhibitors, given that 1 study showed no associated increase in circulating estrogen levels with concurrent therapy over 12 weeks, but more research is needed to determine if it is safe and effective in the long-term (15). Another potential option is to transition certain highly symptomatic women from aromatase inhibitors to tamoxifen because tamoxifen is less likely to worsen such symptoms as vaginal dryness and can counteract the acute systemic absorption of vaginal estrogen. That said, tamoxifen does not reduce the risk of breast cancer recurrence as substantially as aromatase inhibitors, and tamoxifen does increase risk of thrombosis and uterine cancer in postmenopausal women (16).

As there was no association between survival and use of VET, there may be a select group of breast cancer survivors on aromatase inhibitors who might consider VET: patients with

Received: March 28, 2022; **Accepted:** May 25, 2022

severe genitourinary symptoms who have exhausted all other options for symptom management and are not candidates for tamoxifen. However, with the substantial increase in breast cancer recurrence risk seen in this study, caution would be advised even in these patients with severe symptoms.

Patients who receive oral MHT along with aromatase inhibitors presumably will have higher hormone exposures than aromatase inhibitor users receiving VET; therefore, MHT use among breast cancer survivors being treated with aromatase inhibitors is not recommended. Somewhat surprisingly, this study did not report poorer outcomes in breast cancer survivors using oral MHT. However, there were few MHT users in the study by Cold and colleagues (4) (only 133 total, 33 of whom were on tamoxifen and 37 of whom were on aromatase inhibitor or tamoxifen followed by an aromatase inhibitor), and so the absence of an obvious detrimental impact of MHT on breast cancer recurrence or mortality is not particularly reassuring. In fact, these results may be confounded by the fact that clinicians might have felt more comfortable (in light of safety concerns) prescribing MHT to patients with very low risk for recurrence at baseline. The results of prior studies of MHT in breast cancer survivors have been mixed, (17-20), but it is important to note that there were poorer outcomes seen in such breast cancer survivors receiving MHT in the Hormonal Replacement Therapy After Breast Cancer - Is it Safe (HABITS) and Livial Intervention Following Breast Cancer; Efficacy, Recurrence, and Tolerability Endpoints (LIBERATE) randomized controlled trials (17,18).

In sum, the results of this highly clinically relevant study by Cold and colleagues (4) suggest that patients who are taking tamoxifen and experience severe genitourinary symptoms of menopause may safely initiate vaginal estrogen, as VET does not appear to statistically significant increase risk for breast cancer recurrence or survival. Patients who are taking aromatase inhibitors should try alternative strategies for management of genitourinary symptoms because VET will likely increase their risk for breast cancer recurrence.

Funding

No funding was used for this editorial.

Notes

Role of the funder: Not applicable.

Disclosures: Neither ECR nor KJR has COIs relevant to the current publication. KJR, a *JNCI* Associate Editor and coauthor on this editorial, was not involved in the editorial review or decision to publish it.

Author contributions: Both ECR and KJR: conceptualization, writing-original draft, writing-review & editing.

Data Availability

No new data were generated or analyzed in support of this research.

References

1. Arimidex T, Buzdar A, Howell A, et al. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. *Lancet Oncol*. 2006;7(8):633-643.
2. Fallowfield L, Cella D, Cuzick J, Francis S, Locker G, Howell A. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. *J Clin Oncol*. 2004;22(21):4261-4271.
3. Sussman TA, Kruse ML, Thacker HL, Abraham J. Managing genitourinary syndrome of menopause in breast cancer survivors receiving endocrine therapy. *J Oncol Pract*. 2019;15(7):363-370.
4. Cold S, Cold F, Jensen M-B, Cronin-Fenton D, Christiansen P, Ejlertsen B. Systemic or vaginal hormone therapy after early breast cancer: a Danish observational cohort study. *J Natl Cancer Inst*. 2022;114(10):1347-1354.
5. Santen RJ. Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels. *Climacteric*. 2015;18(2):121-134.
6. Kendall A, Dowsett M, Folkerd E, Smith I. Caution: vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. *Ann Oncol*. 2006;17(4):584-587.
7. Crandall CJ, Diamant A, Santoro N. Safety of vaginal estrogens: a systematic review. *Menopause*. 2020;27(3):339-360.
8. Bygdeman M, Swahn ML. Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. *Maturitas*. 1996;23(3):259-263.
9. Mitchell CM, Reed SD, Diem S, et al. Efficacy of vaginal estradiol or vaginal moisturizer vs placebo for treating postmenopausal vulvovaginal symptoms: a randomized clinical trial. *JAMA Intern Med*. 2018;178(5):681-690.
10. Loprinzi CL, Abu-Ghazaleh S, Sloan JA, et al. Phase III randomized double-blind study to evaluate the efficacy of a polycarbophil-based vaginal moisturizer in women with breast cancer. *J Clin Oncol*. 1997;15(3):969-973.
11. Carter J, Baser RE, Goldfrank DJ, et al. A single-arm, prospective trial investigating the effectiveness of a non-hormonal vaginal moisturizer containing hyaluronic acid in postmenopausal cancer survivors. *Support Care Cancer*. 2021;29(1):311-322.
12. Quick AM, Zvinovski F, Hudson C, et al. Fractional CO2 laser therapy for genitourinary syndrome of menopause for breast cancer survivors. *Support Care Cancer*. 2020;28(8):3669-3677.
13. Pagano T, De Rosa P, Vallone R, et al. Fractional microablative CO2 laser in breast cancer survivors affected by iatrogenic vulvovaginal atrophy after failure of nonestrogenic local treatments: a retrospective study. *Menopause*. 2018;25(6):657-662.
14. Gordon C, Gonzales S, Krychman ML. Rethinking the techno vagina: a case series of patient complications following vaginal laser treatment for atrophy. *Menopause*. 2019;26(4):423-427.
15. Barton DL, Shuster LT, Dockter T, et al. Systemic and local effects of vaginal dehydroepiandrosterone (DHEA): NCCTG N10C1 (Alliance). *Support Care Cancer*. 2018;26(4):1335-1343.
16. Early Breast Cancer Trialists' Collaborative Group. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386(10001):1341-1352.
17. Holmberg L, Iversen OE, Rudenstam CM, et al.; for the HABITS Study Group. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J Natl Cancer Inst*. 2008;100(7):475-482.
18. Bundred NJ, Kenemans P, Yip CH, et al. Tibolone increases bone mineral density but also relapse in breast cancer survivors: LIBERATE trial bone substudy. *Breast Cancer Res*. 2012;14(1):R13.
19. Beral V, Peto R, Pirie K, Reeves G. Menopausal hormone therapy and 20-year breast cancer mortality. *Lancet*. 2019;394(10204):1139.
20. Fahlen M, Fornander T, Johansson H, et al. Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial. *Eur J Cancer*. 2013;49(1):52-59.