Original Research

Safety of Vaginal Estrogen Therapy for Genitourinary Syndrome of Menopause in Women With a History of Breast Cancer

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OBJECTIVE: To assess the risk of recurrence of breast cancer associated with vaginal estrogen therapy in women diagnosed with genitourinary syndrome of menopause with a history of breast cancer using a large U.S. claims database.

METHODS: A U.S. health research network (TriNetX Diamond Network) was queried from January 2009 to June 2022. Our cohort consisted of women diagnosed with breast cancer within 5 years before the initial genitourinary syndrome of menopause diagnosis. Patients with *active disease*, defined as those undergoing mastectomy, radiation treatment, or chemotherapy within 3 months before diagnosis of genitourinary syndrome of menopause, were excluded. *Recurrence* was defined as mastectomy, radiation, chemotherapy, or secondary malignancy within 3 months to 5 years after the initiation of vaginal estrogen therapy for genitourinary syndrome of menopause. The study cohort included those with three or more vaginal estrogen prescriptions. The control cohort included women with breast cancer without any vaginal estrogen prescriptions after genitourinary syndrome of menopause diagnosis. Propensity matching was performed. A subanalysis by positive estrogen receptor status, when available, was performed.

RESULTS: We identified 42,113 women with a diagnosis of genitourinary syndrome of menopause after breast cancer diagnosis with any estrogen receptor status, 5.0% of whom received vaginal estrogen. Of the initial cohort, 10,584 patients had a history of positive estrogen receptor breast cancer, and 3.9% of this group received vaginal estrogen. Risk of breast cancer recurrence was comparable between those who received vaginal estrogen and those who did not in both the any estrogen receptor (risk ratio 1.03, 95% CI 0.91–1.18) and positive estrogen receptor (risk ratio 0.94, 95% CI 0.77–1.15) status analyses.

CONCLUSION: In a large, claims-based analysis, we did not find an increased risk of breast cancer recurrence within 5 years in women with a personal history of breast cancer who were using vaginal estrogen for genitourinary syndrome of menopause.

(Obstet Gynecol 2023;00:1–9)
DOI: 10.1097/AOG.0000000000005294

With improvements in the screening and treatment of breast cancer, the number of female survivors continues to rise, with a reported 5-year survival rate of up to 90%. However, several of the systemic treatments for breast cancer, including endocrine therapy, chemotherapy, and radiotherapy, can result in a new or worsened hypoestrogenic state.[1] Lack of circulating estrogen can lead to genitourinary syndrome of menopause, which encompasses symptoms associated with decreased sex steroids related to the urinary and genital systems and can include sexual dysfunction.[2–4] More than 70% of postmenopausal women who survive breast cancer and are treated with systemic therapies subsequently experience genitourinary syndrome of menopause.[1] Although there are many treatments for genitourinary syndrome of menopause, one of the most effective options for vulvovaginal atrophy is vaginal estrogen therapy.[5]

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Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/23

Vaginal estrogen therapy provides a low dose of estrogen locally to the genitourinary tissues. Several studies have shown that use of this treatment leads to a statistically significant improvement in symptoms of genitourinary syndrome of menopause compared with placebo.[6] Systemic estrogen therapy is contraindicated in breast cancer survivors because up to 75% of tumors are hormone receptor responsive. Recent reviews have described the controversy surrounding the use of vaginal estrogen in women with a history of breast cancer because of concerns about systemic estrogen absorption and possible increased cancer recurrence risk.[4,5]

Currently, few survivors of breast cancer with genitourinary syndrome of menopause are prescribed vaginal estrogen because of concerns about cancer recurrence, leading to undertreatment of genitourinary syndrome of menopause in this population.[5] A recent expert consensus statement cited a paucity of safety data as a primary contributor to clinicians' reluctance to use vaginal estrogen in women at a high risk for breast cancer.[7] This concern is likely amplified in women with a history of breast cancer, making the decision to use vaginal estrogen even more challenging. We sought to analyze the association of vaginal estrogen therapy with recurrence rates in female survivors of breast cancer using a claims database approach.

METHODS

We conducted a cohort analysis using electronic health records (EHRs) linked with insurance claims acquired from the TriNetX Diamond research network. TriNetX provides access to electronic medical records (diagnoses, procedures, medications, laboratory values, and genomic information) in conjunction with medical insurance and pharmaceutical claims from more than 212 million patients throughout the entire United States from 92 health care organizations and payer types, including commercial, Medicare, Medicaid, and Veterans Affairs services. Information on demographics, diagnoses from International Classification of Disease, Tenth Revision (ICD-10) codes, procedures from Current Procedural Terminology (CPT) codes, and medication codes based on the Veterans Affairs National Formulary were recorded within TriNetX and used for analysis. All data are de-identified according to the standard defined in Section 164.514(a) of the Health Insurance Portability and Accountability Act Privacy Rule. TriNetX and this study are IRB exempt. Any patient counts less than 10 are obfuscated to ensure patient anonymity. In addition, only aggregate patient counts and statistical summaries are provided to maintain de-identification.

The TriNetX database was queried from January 2009 to June 2022 with a selection criteria based on ICD-10 codes. A patient was considered to have a diagnosis of breast cancer and genitourinary syndrome of menopause if the corresponding ICD code was linked to the patient's EHR in the database. All cohorts included women aged 18 years or older with an initial diagnosis of genitourinary syndrome of menopause (ICD-10 N90.5, N95.2) occurring 3 months to 5 years after a diagnosis of breast cancer (C50, Z86.000). The vaginal estrogen cohort included women who received three or more vaginal estrogen (Veterans Affairs code GU5000) prescriptions, including vaginal estradiol (R4083) or conjugated estrogens (R4099), with at least one prescription within 1 year after their initial genitourinary syndrome of menopause diagnosis. The control cohort excluded women with any vaginal estrogen prescriptions within 1 year after their initial genitourinary syndrome of menopause diagnosis (Fig. 1). A secondary analysis was conducted comparing the vaginal estrogen and control cohorts for patients with positive estrogen receptor status of breast cancer (Z71.0) when available. A subanalysis evaluating the effect of concurrent aromatase inhibitor use with vaginal estrogen compared with vaginal estrogen alone in estrogen receptor–positive women was conducted. *Concurrent aromatase inhibitor use* was defined as receiving at least three aromatase inhibitor prescriptions within the same time period.

Patients with a diagnosis of any primary malignancy other than breast cancer in the 5 years before or after their initial genitourinary syndrome of menopause diagnosis were excluded. Patients with *active breast cancer* at the time of their initial genitourinary syndrome of menopause diagnosis, defined as those receiving radiation oncology treatment (CPT 1010843, 63620, 63621), chemotherapy (TriNet Curated Code 1002, Veterans Affairs code 56946 paclitaxel, 253337 bevacizumab, 194000 capecitabine, 2555 cisplatin, 1045453 eribulin, 4179 etoposide, 282357 fulvestrant, 12574 gemcitabine, 480167 lapatinib, 1601374 palbociclib, 1298944 pertuzumab, 224905 trastuzumab, 39541 vinorelbine, 72962 docetaxel, or 3639 doxorubicin), or mastectomy (1014812, 19303–19307; International Classification of Diseases, Ninth Revision 85.33–85.36, 85.40–85.48), within 3 months before their initial diagnosis of genitourinary syndrome of menopause were also excluded.[8,9]

The primary study outcome was *breast cancer recurrence*, defined as the need for mastectomy, radiation,

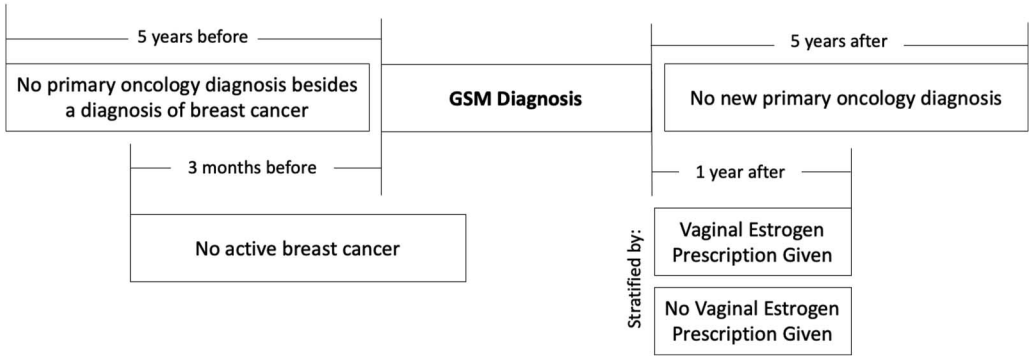

Fig. 1. Study cohorts created after index diagnosis. GSM, genitourinary syndrome of menopause.
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or chemotherapy, or occurrence of secondary malignancy (ie, breast cancer metastasis) (ICD-10 C77, C78, C79.1–C79.7, C79.82, C79.89, C79.9) within 3 months to 5 years after initiation vaginal estrogen therapy for genitourinary syndrome of menopause.[8,9] A 1:1 matching was performed depending on the propensity scores generated by TriNetX by greedy-nearest-neighbor algorithms with a caliper width of 0.1 pooled SD. To alleviate bias ensuing from nearest-neighbor algorithms, TriNetX randomizes the order of rows. Propensity-score matching was performed with age at initiation of vaginal estrogen therapy for genitourinary syndrome of menopause, current age, race, ethnicity, family history of breast neoplasm (Z80.3), history of hormone therapy (Z79.890), anastrozole prescriptions (84,857), letrozole prescriptions (72,965), exemestane prescriptions (258,494), overweight and obesity (E66), and tobacco use (Z72.0) as covariates for initial analysis. Propensity-score matching was performed with age at initiation of vaginal estrogen therapy for genitourinary syndrome of menopause, current age, race, ethnicity, family history of breast neoplasm (Z80.3), history of hormone therapy (Z79.890), overweight and obesity (E66), and tobacco use (Z72.0) as covariates for subanalysis pertaining to concurrent aromatase inhibitor use. Absolute values greater than 0.1 standardized mean difference on covariate balance were considered positive for covariate imbalance. A two-sided $\alpha<.05$ was considered statistically significant. Risk ratios (RRs) with 95% CIs were calculated for all outcomes. Differences in recurrence-free survival between groups were examined using the Kaplan-Meier method.

RESULTS

We identified 42,113 women with a diagnosis of genitourinary syndrome of menopause after breast cancer, including 1,003 with ductal carcinoma in situ, with a positive, negative, or unknown estrogen receptor status. Among this group, 2,111 women (5.0%) were in the vaginal estrogen group. This population was compared with an equal number of propensity-score–matched patients in a control group (Table 1). Risk of breast cancer recurrence was not different between groups, with a recurrence rate of 17.6% in the vaginal estrogen group and 17.1% in the control group (RR 1.03, 95% CI 0.91–1.18) (Table 2). When stratified by type of intervention after recurrence, there was no difference between groups for risk of mastectomy (RR 0.79, 95% CI 0.44–1.44), chemotherapy (RR 1.12, 95% CI 0.97–1.29), or radiation treatment (RR 0.65, 95% CI 0.36–1.20). Women in the vaginal estrogen group had a lower risk of secondary malignancy (RR 0.52, 95% CI 0.37–0.72) compared with those in the matched control group.

After an initial breast cancer diagnosis, there were 732 recurrence events overall, with 372 recurrence events in the vaginal estrogen group and 360 recurrence events in the control group. No significant differences in recurrence-free survival were observed between groups (hazard ratio [HR] 0.98, 95% CI 0.85–1.14) (Fig. 2). No significant difference in all-cause mortality at 5 years was observed (2.8% vs 3.8% for women in the vaginal estrogen group compared with those in the control group, RR 0.74, 95% CI 0.53–1.03). Vaginal estrogen use was associated with a decreased risk for all-cause mortality at 10 years compared with the control group (3.0% vs 4.3%, RR 0.70, 95% CI 0.51–0.96).

Among our study population of women with a diagnosis of genitourinary syndrome of menopause after breast cancer (n=42,113), 12,620 (30.0%) had estrogen status available: 10,584 had a history of estrogen receptor–positive breast cancer, and 2,036 had a history of estrogen receptor–negative breast

Table 1. Cohorts Before and After Propensity-Score Matching

	Before Matching			After Matching		
	Vaginal Estrogen	No Vaginal Estrogen	Mean Std Diff	Vaginal Estrogen	No Vaginal Estrogen	Mean Std Diff
History of any ER status breast cancer						
Cohort population	2,111	40,002		2,109	2,109	
Age at index (y)	65.8±10.7 (100)	65.8±10.5 (100)	0.002	65.8±10.8 (100)	66.1±10.5 (100)	0.028
Current age (y)	72.5±10.5 (100)	72.5±10.3 (100)	0.004	72.5±10.5 (100)	72.7±10.2 (100)	0.024
Unknown race	1,147 (54.3)	27,889 (69.7)	0.321	1,147 (54.4)	1,138 (54.0)	0.008
Unknown ethnicity	1,138 (53.9)	26,923 (67.3)	0.277	1,137 (53.9)	1,122 (53.2)	0.014
Black	34 (1.6)	997 (2.5)	0.062	34 (1.6)	26 (1.2)	0.032
Hispanic or Latina	47 (2.2)	1,196 (3.0)	0.048	47 (2.2)	48 (2.3)	0.003
White	923 (43.7)	10,929 (27.3)	0.348	921 (43.7)	937 (44.4)	0.015
Tobacco use	359 (17.0)	4,069 (10.2)	0.200	357 (16.9)	366 (17.4)	0.011
Family history of malignant neoplasm of breast	330 (15.6)	5,539 (13.8)	0.050	330 (15.6)	321 (15.2)	0.012
Overweight and obesity	311 (14.7)	6,655 (16.6)	0.052	311 (14.8)	305 (14.5)	0.008
Hormone therapy	116 (5.5)	677 (1.7)	0.205	114 (5.4)	107 (5.1)	0.015
Anastrozole use	212 (10.0)	3,111 (7.8)	0.079	212 (10.0)	190 (9.0)	0.036
Letrozole use	118 (5.6)	1,640 (4.1)	0.069	117 (5.6)	100 (4.7)	0.036
Exemestane use	73 (3.5)	867 (2.2)	0.078	71 (3.4)	63 (3.0)	0.022
History of ER+ breast cancer						
Cohort population	410	10,174		409	409	
Age at index (y)	64.8±10.1 (100)	63.9±10.6 (100)	0.088	64.7±10.1 (100)	64.9±10.5 (100)	0.016
Current age (y)	71.2±9.83 (100)	70.2±10.6 (100)	0.102	71.2±9.79 (100)	71.3±10.4 (100)	0.012
Unknown race	249 (60.7)	7,438 (73.1)	0.265	249 (60.9)	245 (59.9)	0.020
Unknown ethnicity	243 (59.3)	7,210 (70.9)	0.245	243 (59.4)	239 (58.4)	0.020
Black	*	195 (1.9)		*	*	
Hispanic or Latina	*	285 (2.8)		*	*	
White	157 (38.3)	2,498 (24.6)	0.299	156 (38.1)	163 (39.8)	0.035
Tobacco use	56 (13.7)	972 (9.6)	0.128	55 (13.4)	51 (12.5)	0.029
Family history of malignant neoplasm of breast	94 (22.9)	2,162 (21.2)	0.040	94 (23.0)	90 (22.0)	0.023
Overweight and obesity	60 (14.6)	1,962 (19.3)	0.124	60 (14.7)	60 (14.7)	<0.001
Hormone therapy	20 (4.9)	274 (2.7)	0.115	19 (4.6)	14 (3.4)	0.062
Anastrozole use	91 (22.2)	1,187 (11.7)	0.284	90 (22.0)	88 (21.5)	0.012
Letrozole use	39 (9.5)	639 (6.3)	0.120	39 (9.5)	31 (7.6)	0.070
Exemestane use	27 (6.6)	329 (3.2)	0.156	27 (6.6)	30 (7.3)	0.029

Std Diff, standard difference; ER, estrogen receptor.
Data are n, mean±SD (%), or n (%) unless otherwise specified.
* Any values less than 10 are obfuscated by TriNet to ensure patient anonymity.

cancer. Of these, 410 (3.9%) with a history of estrogen receptor–positive and 101 (5.0%) with a history of estrogen receptor–negative breast cancer were in the vaginal estrogen group. Significantly fewer individuals with a history of estrogen receptor–positive breast cancer (P=.02) received vaginal estrogen compared with those with a history estrogen receptor–negative breast cancer. Patients with a history of estrogen receptor–positive breast cancer with vaginal estrogen prescriptions were then compared with patients in a propensity-score–matched control group with a history of estrogen receptor–positive breast cancer who never received vaginal estrogen therapy (Table 1). Risk of breast cancer recurrence within 3 months to 5 years after vaginal estrogen therapy initiation was not different between groups (RR 0.94, 95% CI 0.77–1.15) (Table 2).

Among those with estrogen receptor–positive breast cancer, there were 258 total recurrence events, with 125 recurrence events in the vaginal estrogen group and 133 recurrence events in the control group. There was no difference in recurrence-

Table 2. Risk of Breast Cancer Recurrence After Vaginal Estrogen Therapy for Genitourinary Syndrome of Menopause

	History of Any ER Status Breast Cancer		History of ER+ Breast Cancer	
	Vaginal Estrogen	No Vaginal Estrogen	Vaginal Estrogen	No Vaginal Estrogen
Included women (n)	2,109	2,109	409	409
Mastectomy procedure (%)	0.9	1.1	*	*
RR (95% CI)	0.79 (0.44–1.44)			
Chemotherapy (%)	16.1	14.4	28.8	28.4
RR (95% CI)	1.12 (0.97–1.29)		1.02 (0.82–1.26)	
Radiation treatment (%)	0.8	1.2	2.9	3.7
RR (95% CI)	0.65 (0.36–1.20)		0.80 (0.38–1.69)	
Secondary malignancy (%)	2.4	4.6	6.4	6.8
RR (95% CI)	0.52 (0.37–0.72)		0.93 (0.55–1.56)	
Overall recurrence (%)	17.6	17.1	30.6	32.5
RR (95% CI)	1.03 (0.91–1.18)		0.94 (0.77–1.15)	

ER, estrogen receptor; RR, risk ratio.
* Any values less than 10 are obfuscated by TriNet to ensure patient anonymity.

free survival between the two groups (HR 0.88, 95% CI 0.69–1.12) (Fig. 3).

A subanalysis was performed comparing women with concurrent vaginal estrogen and aromatase inhibitor (anastrozole, letrozole, or exemestane) prescriptions with those with vaginal estrogen only. Among the 2,111 women in the vaginal estrogen group, 91 received aromatase inhibitor prescriptions. Risk of breast cancer recurrence was significantly higher in women receiving concurrent vaginal estrogen and aromatase inhibitor compared with vaginal estrogen only, with a recurrence rate of 77.8% compared with 15.6% (RR 5, 95% CI 3.05–8.19) (Tables 3 and 4). Similarly, among the 410 women with a history of estrogen receptor–positive breast cancer who received vaginal estrogen, 41 received concurrent aromatase inhibitor prescriptions. Risk of breast cancer recurrence was significantly higher in the concurrent aromatase inhibitor group compared with the vaginal estrogen only group (76.32% vs 28.95%, RR 2.64, 95% CI 1.55–4.47) (Tables 3 and 4).

After an initial breast cancer diagnosis of any estrogen receptor status, there were 70 recurrence events in the concurrent aromatase inhibitor prescription group and 14 recurrence events in the vaginal estrogen only group. Average time to recurrence in the concurrent aromatase inhibitor prescription group was 140 days. Significant differences in recurrence-free survival were observed between the two groups (HR 9.88, 95% CI 5.50–17.73) (Fig. 4). No mortality event was observed at the 5- or 10-year follow-up.

Among those with estrogen receptor–positive breast cancer, there were 29 recurrence events among women with history of concurrent aromatase inhibitor use and 11 recurrence events in the vaginal estrogen only cohort. Average time to recurrence in the concurrent aromatase inhibitor prescription group with a history of estrogen receptor–positive breast

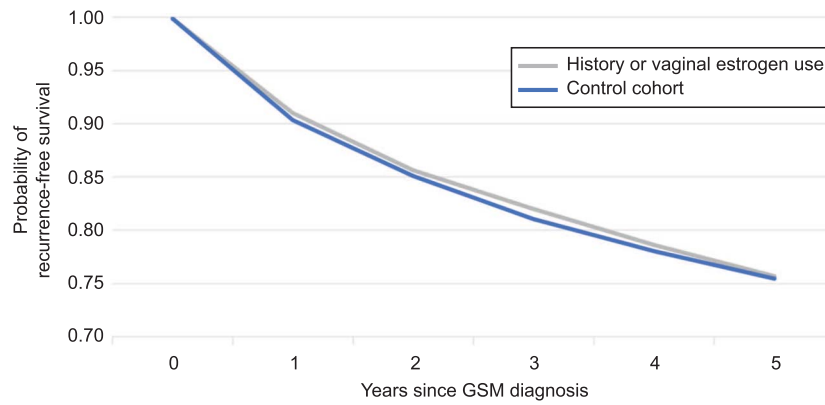

Fig. 2. Recurrence-free survival after vaginal estrogen therapy for genitourinary syndrome of menopause (GSM). Log-rank $P=.822$; hazard ratio 0.98; 95% CI 0.85–1.14.

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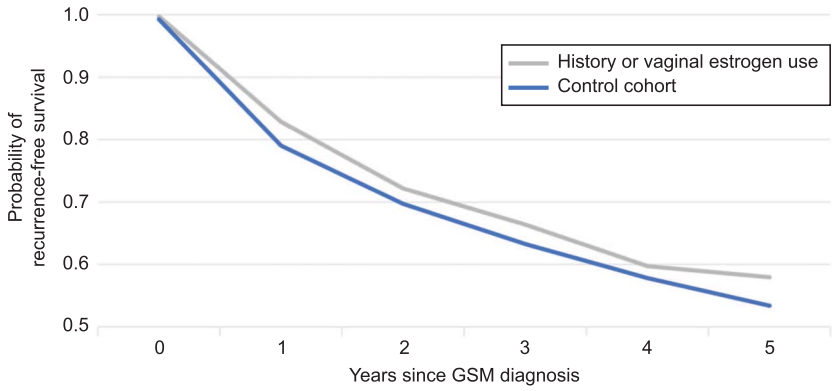

Fig. 3. Recurrence-free survival after vaginal estrogen therapy for genitourinary syndrome of menopause (GSM) among those with a history of estrogen receptor–positive breast cancer. Log-rank $P=.286$; hazard ratio 0.88; 95% CI 0.69–1.12.

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Table 3. Cohorts Before and After Propensity-Score Matching

	Before Matching			After Matching		
	Vaginal Estrogen With AI	Vaginal Estrogen Without AI	*P*	Vaginal Estrogen With AI	Vaginal Estrogen Without AI	*P*
History of any ER status breast cancer						
Cohort population	91	1,690		90	90	
Age at index (y)	63.5±10.2 (100%)	65.7±10.9 (100%)	.205	63.6±10.2 (100%)	62.8±10.4 (100%)	.097
Current age (y)	70±9.68 (100%)	72.4±10.6 (100%)	.239	70±9.72 (100%)	69±10.3 (100%)	.098
Unknown race	51 (56.0)	926 (54.8)	.025	50 (55.6)	52 (57.8)	.045
Unknown ethnicity	44 (48.4)	931 (55.1)	.135	44 (48.9)	46 (51.1)	.044
Black	*	30 (1.8)		*	*	
Hispanic or Latina	*	37 (2.2)		*	*	
White	39 (42.9)	729 (43.1)	.006	39 (43.3)	38 (42.2)	.022
Family history of malignant neoplasm of breast	23 (25.3)	258 (15.3)	.249	22 (24.4)	24 (26.7)	.051
Overweight and obesity	14 (15.4)	239 (14.1)	.025	13 (14.4)	13 (14.4)	<.001
Tobacco use	11 (12.1)	263 (15.6)	.153	11 (12.2)	12 (13.3)	.035
Hormone therapy	*	88 (5.21)				
History of ER+ breast cancer						
Cohort population	41	234		38	38	
Age at index (y)	61.9±9.31 (100%)	65.2±10.5 (100%)	.339	61.8±9.56 (100%)	61.3±11 (100%)	.058
Current age (y)	67.9±9.05 (100%)	71.6±10.2 (100%)	.389	67.8±9.15 (100%)	67.5±10.2 (100%)	.049
Unknown race	24 (58.5)	151 (64.5)	.123	22 (57.9)	20 (52.6)	.106
Unknown ethnicity	21 (51.2)	150 (64.1)	.263	20 (52.6)	17 (44.7)	.158
Black	*	*		*	*	
Hispanic or Latina	*	*		*	*	
White	16 (39.0)	81 (34.6)	.092	16 (42.1)	18 (47.4)	.106
Family history of malignant neoplasm of breast	11 (26.8)	55 (23.5)	.077	*	*	
Overweight and obesity	*	28 (11.0)		*	*	
Tobacco use	*	33 (14.1)		*	*	
Hormone therapy	*	*		*	*	

AI, aromatase inhibitor; ER, estrogen receptor.
Data are n, mean±SD (%), or n (%) unless otherwise specified.
* Any values less than 10 are obfuscated by TriNet to ensure patient anonymity.

Table 4. Risk of Breast Cancer Recurrence After Vaginal Estrogen and Aromatase Inhibitor Therapy for Genitourinary Syndrome of Menopause

	History of Any ER Status Breast Cancer		History of ER+ Breast Cancer	
	Vaginal Estrogen With AI	Vaginal Estrogen Without AI	Vaginal Estrogen With AI	Vaginal Estrogen Without AI
Included women (n)	90	90	38	38
Overall recurrence (%)	77.8	15.6	76.3	29.0
RR (95% CI)	5.00 (3.05–8.19)		2.64 (1.55–4.47)	

ER, estrogen receptor; AI, aromatase inhibitor; RR, risk ratio.

cancer was 154 days. Significant differences in recurrence-free survival were observed between the two groups (HR 4.82, 95% CI 2.36–9.84) (Fig. 4). No mortality event was observed at the 5- or 10-year follow-up.

DISCUSSION

Genitourinary syndrome of menopause remains the leading cause of sexual dysfunction among breast cancer survivors, with more than 50% of patients reporting at least mild sexual concerns.[5,10] Changes in sexual function are associated with decreased quality of life, increased disease-related distress, and increased symptom severity.[10,11] Although several studies have demonstrated the efficacy of vaginal estrogen in reducing genitourinary syndrome of menopause symptoms, nonhormonal therapy remains the first-line therapy for genitourinary syndrome of menopause in individuals with a history of breast cancer because of concerns of possible cancer recurrence caused by hormonal therapy.[5,6,12] In this cohort study, we found no significant difference in cancer recurrence risk within 5 years between breast cancer survivors with and those without prescriptions for vaginal estrogen therapy for a diagnosis of genitourinary syndrome of menopause. The same result was found when we assessed only women with a history of estrogen receptor–positive breast cancer. Consistent with previous studies, an increased risk of breast cancer recurrence was seen with concurrent aromatase inhibitor and vaginal estrogen use, with the greatest risk in the first year after therapy initiation for genitourinary syndrome of menopause diagnosis.[13] As seen in other studies, our results suggest that vaginal estrogen may be underprescribed in this population, with only about 5% of patients receiving three or more vaginal estrogen prescriptions.[7] Furthermore, only 4% of patients with a history of estrogen receptor–positive breast cancer received vaginal estrogen after a genitourinary syndrome of menopause diagnosis.

There are no current guidelines for the use of vaginal estrogen in patients with genitourinary syndrome of menopause. However, the use of vaginal estrogen has been shown to provide a significant benefit to patients with genitourinary syndrome of

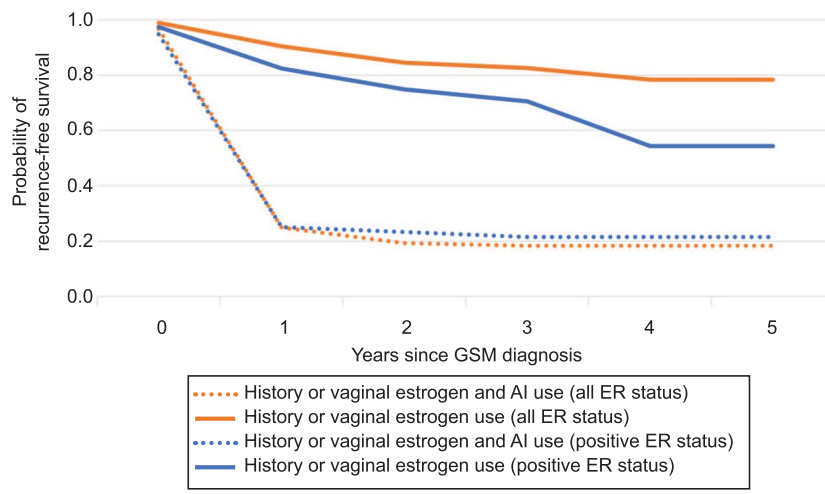

Fig. 4. Recurrence-free survival after vaginal estrogen and concurrent aromatase inhibitor (AI) therapy for genitourinary syndrome of menopause (GSM). All estrogen receptor (ER) log-rank $P<.001$; hazard ratio 9.88; 95% CI 5.50–17.74. ER-positive log-rank $P<.001$; hazard ratio 4.82; 95% CI 2.36–9.84.

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menopause, in part because of revascularization of the vaginal tissue.[7,14,15] The low use of vaginal estrogen therapy in patients with a history of breast cancer with genitourinary syndrome of menopause is likely attributable to concerns about increased cancer recurrence risk in this population as a result of the Food and Drug Administration's black box warning when prescribing vaginal estrogen.[7,16,17] Increased cancer recurrence has been associated with systemic hormonal treatments, which leads to an increase in circulating estrogen levels.[17] However, vaginal estrogen has not been shown to elevate systemic levels of estrogen above the normal postmenopausal range.[4] A recent meta-analysis of 11 studies of local hormonal treatment, including nine studies on vaginal estrogen therapy, demonstrated a lack of systemic absorption of sex hormones, supporting the low risk of breast cancer recurrence associated with this therapy.[18]

Despite the evidence of minimal systemic absorption, few studies have examined the association between cancer recurrence risk and vaginal estrogen therapy, including a lack of data from randomized clinical trials. In one small, single-institution study of 20 postmenopausal patients, of whom three had a history of breast cancer, the authors found no new cancer or cancer recurrence after at least 1 year of vaginal estrogen use.[19] A large nested case–control study found no increased relative risk of cancer recurrence with the use of local estrogen during concurrent use of tamoxifen or aromatase inhibitors or after treatment with these medications.[20] A recent Danish cohort study of 8,461 women described no increased risk of recurrence or mortality in postmenopausal women with a history of early-stage breast cancer after treatment with vaginal estrogen therapy or menopausal hormone therapy.[13] Similar to the Danish study, we observed a significantly increased risk of breast cancer recurrence among those with concurrent vaginal estrogen and aromatase inhibitor prescriptions.[13] It is possible that this increased risk may be multifactorial, including the characteristic of breast cancer, the dosage of vaginal estrogen and aromatase inhibitors, and the temporal relationship of breast cancer diagnosis to vaginal estrogen therapy initiation for genitourinary syndrome of menopause, but data are limited. It is important to note that we did not observe an increased risk of breast cancer recurrence when controlling for total number of individual anastrozole, letrozole, and exemestane prescriptions between the cohorts; the risk was seen only with concurrent prescriptions, although our study was likely underpowered to detect those risk differences.

In addition to our large sample size, a major strength of this study was the ability to collect long-term data on cancer recurrence up to 5 years after a patient's initial diagnosis of genitourinary syndrome of menopause. This finding is important because symptoms of genitourinary syndrome of menopause can return without long-term use of vaginal estrogen therapy.[21] The TriNetX Diamond Network has strengths with significant generalizability on a national level by encompassing more than 1.8 million health care professionals who cover 99% of U.S. health care plans. Furthermore, the database can capture complete health information by linking patient identifiers from participating health care organizations to pharmaceutical data, insurance claims, and EHRs. We limited selection bias by categorizing our cohorts with the use of CPT and ICD-10 codes.

The TriNetX database presents inherent limitations, including de-identification for patient anonymity and lack of availability of cancer staging data before estrogen therapy. In addition, our secondary analyses and subanalyses included smaller cohorts with limited power. Furthermore, to establish a clear association between vaginal estrogen initiation and the diagnosis of genitourinary syndrome of menopause, our study used specific criteria for medication prescription, limiting it to within 1 year of the genitourinary syndrome of menopause diagnosis. As a result, it is worth noting that a subset of patients in the control group might have received vaginal estrogen beyond the 1-year mark after their diagnosis. Another major limitation is the lack of granular data, including dosage and time frame of prescriptions, as well as actual patient use and compliance. Finally, we are unable to differentiate new or prior breast cancer staging and grading, providing potential biases of our conclusions. We hope our results will help health care professionals when considering the use of vaginal estrogen therapy for genitourinary syndrome of menopause for their patients with a history of breast cancer, although individual patient characteristics such as genetic predisposition, personal and family oncologic history, and overall health status should be considered. It is essential to emphasize that further evidence from randomized clinical trials is necessary to supplement our current understanding of this treatment approach.

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PEER REVIEW HISTORY

Received February 28, 2023. Received in revised form May 11, 2023. Accepted May 25, 2023. Peer reviews and author correspondence are available at http://links.lww.com/AOG/D262.