Vaginal estrogen use in breast cancer survivors: a systematic review and meta-analysis of recurrence and mortality risks

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OBJECTIVE: To assess the risk of breast cancer recurrence, breast cancer-specific mortality, and overall mortality for breast cancer survivors receiving vaginal estrogen therapy for genitourinary syndrome of menopause.

DATA SOURCES: From the inception of each database to April 6th, 2024, a systematic literature search was conducted in Google Scholar, PubMed, EMBASE, CINAHL, NCBI, and Science Direct. A secondary search was conducted on September 26th, 2024 utilizing Google Scholar, PubMed, EMBASE, CINAHL, and Science Direct.

STUDY ELIGIBILITY CRITERIA: We identified studies that reported on breast cancer recurrence defined per individual review criteria and considered both local and distant recurrence.

STUDY APPRAISAL AND SYNTHESIS METHODS: Three reviewers evaluated studies with eligibility criteria in mind. Breast cancer recurrence was the primary outcome. The secondary outcomes included: breast cancer mortality and overall mortality. Pooled unadjusted odds ratios with 95% confidence intervals were calculated using a random-effects model. We assessed the 95% prediction intervals to calculate the likely range within which we can expect to observe future individual values, based on a current model or dataset. We calculated the fragility index to evaluate the robustness of the pooled estimates.

RESULTS: Of 5522 articles identified, 8 observational studies were included in this meta-analysis. The use of vaginal estrogen in patients with a history of breast cancer was not associated with an increased risk of breast cancer recurrence (6 articles, 24,060 patients, odds ratio, 0.48; 95% confidence interval, 0.23—0.98). There was no increase in the risk of breast cancer mortality (4 articles, 61,695 patients, odds ratio 0.60; 95% confidence interval 0.18—1.95). Lastly, there was no increase in overall mortality with use of vaginal estrogen in breast cancer survivors (5 articles 59,724, odds ratio 0.46; 95% confidence interval 0.42—0.49).

CONCLUSION: The use of vaginal estrogen in patients with a history of breast cancer does not appear to be associated with an increased risk of breast cancer recurrence, breast cancer-specific mortality, or overall mortality.

Key words: breast cancer mortality, breast cancer recurrence, genitourinary syndrome of menopause, vaginal atrophy, vaginal estrogen

Introduction

Breast cancer is prevalent and treatment outcomes continue to improve.[1] Accordingly, more than 4 million breast cancer survivors currently reside in the US.[2] Many treatment methods for breast cancer can contribute to a patient developing genitourinary syndrome of menopause (GSM) which has become increasingly prevalent in breast cancer patients.[1] GSM refers to atrophic genital and lower urinary tract changes which result from loss of estrogen. For instance, bilateral oophorectomy may be performed in premenopausal women with breast cancer. Chemotherapy can also be used to treat breast cancer in premenopausal women, which often induces menopause. Aromatase inhibitors, widely used to prevent recurrent breast cancer in menopausal women with hormone receptor positive tumors, exacerbate GSM.[3] This condition often causes sexual dysfunction and impairs quality of life.[3] Accordingly, obstetrician-gynecologists and others who provide care to adult patients routinely see patients with a personal history of breast cancer who are experiencing symptomatic GSM, often with accompanying sexual dysfunction.[4]

Vaginal estrogen is highly effective in treating symptomatic GSM.[5] However, since the Food and Drug Administration (FDA) lists a personal history of breast

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AJOG at a Glance

Why was this study conducted?

For breast cancer survivors, genitourinary syndrome of menopause (GSM) can greatly impair a woman's quality of life. However, many clinicians are hesitant to prescribe vaginal estrogen to treat GSM in patients with a history of breast cancer due to fear of the patient developing recurrent disease.

Key findings

This systematic review and meta-analysis included a small number of observational studies assessing the association between vaginal estrogen use and breast cancer recurrence. The pooled data from these studies suggest that vaginal estrogen use is not significantly associated with an increased risk of breast cancer recurrence among survivors experiencing GSM.

What does this add to what is known?

This meta-analysis offers cautious reassurance regarding the safety of vaginal estrogen use in breast cancer survivors, based on the available observational data. While the findings may help providers feel more confident in considering off-label vaginal estrogen for this population, further research is needed to confirm these results. This could potentially improve the quality of life for breast cancer survivors, though clinical decisions should continue to be made on a case-by-case basis.

cancer as a contraindication to use of all types of estrogens, including vaginal estrogen, safety concerns prevent many obstetrician-gynecologists and other clinicians from prescribing vaginal estrogen to breast cancer survivors.[4] To assess the safety of vaginal estrogen in women with a history of breast cancer, we conducted a systematic review and meta-analysis of studies which have addressed the association between vaginal estrogen use and breast cancer recurrence, breast cancer-specific mortality and overall mortality.

Methods

Prior to conducting the literature searches, we registered the protocol with PROSPERO (ID: CRD42023479950) on September 12, 2023. This systematic review was conducted following the Cochrane Handbook for Systematic Reviews of Interventions and the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, utilizing the Population, Intervention, Comparison, Outcomes and Study design (PICOS) framework to guide the search strategy.[6,7]

The population (P) for this study included women with GSM who have a history of breast cancer. The intervention (I) was the use of vaginal estrogen therapy, with comparators (C) such as placebo, no treatment, or alternative therapies (including nonhormonal treatments). The primary outcome (O) was the breast cancer recurrence rate, including local recurrence, contralateral breast cancer, or metastasis. The study designs (S) included observational studies, such as cohort and case-control studies, whether prospective or retrospective.

The search strategy was developed with the assistance of a medical librarian and ChatGPT (OpenAI, San Francisco, CA). The medical librarian facilitated access to databases such as Google Scholar, PubMed, ScienceDirect, CINAHL, and NCBI, while ChatGPT was used to craft the search terms based on the PICOS framework. Studies were not excluded based on language, publication year, or country of origin. The search keywords included terms such as "vaginal estrogen," "urogenital atrophy," "genitourinary syndrome," and "breast neoplasm." Given the specific focus on breast cancer recurrence, additional terms like "breast carcinoma" and "estrogen cream" were included, especially in relevant indexing fields.

Eligibility criteria, information sources, search strategy

We initially conducted a comprehensive literature search from inception to November 10, 2023, with the assistance of a medical librarian. The search was extended to April 6, 2024, to capture newly published studies. The databases searched included Google Scholar, PubMed, NCBI, ScienceDirect, EMBASE, and CINAHL. Three reviewers (M.B., A.M.K., J.M.) independently screened abstracts to exclude studies that clearly did not meet the inclusion criteria. For studies with potential relevance or those not definitively excluded in the initial screening, full-text articles were reviewed to determine final eligibility. Studies were included irrespective of language, country, or year of publication. A revised search, excluding 'outcomes' and focusing on relevant terms for vaginal estrogen treatment, was conducted on September 26th, 2024. This search did not yield any additional studies for inclusion. The full search syntaxes are available in the Appendix.

Inclusion criteria

Studies were eligible for inclusion if they examined the use of vaginal estrogen in any formulation among patients with a history of breast cancer, and if they compared outcomes to breast cancer patients who did not use vaginal estrogen. The studies had to report on at least one of the following outcomes: breast cancer recurrence, breast cancer-specific mortality, or overall mortality. Studies that assessed additional outcomes but still met these criteria were considered relevant for inclusion. We included observational studies, such as cohort and case-control studies (both prospective and retrospective).

Exclusion criteria

Studies were excluded if they focused on systemic hormone therapy with or without vaginal estrogen in breast cancer survivors. Additionally, studies that did not assess vaginal estrogen use in breast cancer survivors or did not report on the specific outcomes of interest were excluded from the study. After a full-text review, 13 articles were excluded. 6 studies were excluded based on the use of systemic hormone therapy with or without the use of vaginal estrogen.[8–13] Four studies were excluded for no

outcome of interest identified, primarily these studies evaluated estradiol levels and did not look at breast cancer recurrence, breast cancer mortality or overall mortality.[14–17] Additionally, we excluded 3 studies due to repeating information.[18–20]

Study selection

Three reviewers (M.B., A.M.K., J.M.) independently screened abstracts to identify studies that potentially met the inclusion criteria. After the abstract screening, the full-text articles of selected studies were reviewed to confirm eligibility. Any discrepancies between the reviewers were resolved through discussion with the senior author (L.S.R.). In cases where additional data clarification was necessary, the team contacted 3 authors (McVicker, O'Meara, and Le Ray).[21–23] McVicker and O'Meara were contacted to verify the data in a number of women instead of person-years. Le Ray was contacted for chart interpretation for final data analysis.

Data extraction

The primary outcome of interest in this study was the risk of breast cancer recurrence among breast cancer survivors in relation to the use or nonuse of vaginal estrogen. Secondary outcomes included breast cancer-specific mortality and overall mortality. Three reviewers (M.B., A.M.K., J.M.) independently extracted data, and any discrepancies were discussed and resolved with the senior author (L.S.R.). Microsoft Excel was used for data collection and sharing among the review team.

Assessment of quality of the included studies

To assess the quality of the included studies, 2 independent reviewers (M.B., J.M.) assigned Newcastle-Ottawa scores. Studies scoring between 7 and 9 were categorized as having a low risk of bias, those scoring 5 to 6 were considered to have a moderate risk of bias, and those scoring below 5 were considered to have a high risk of bias. Any discrepancies between the reviewers were resolved through discussion with the senior author (L.S.R.).

Data synthesis

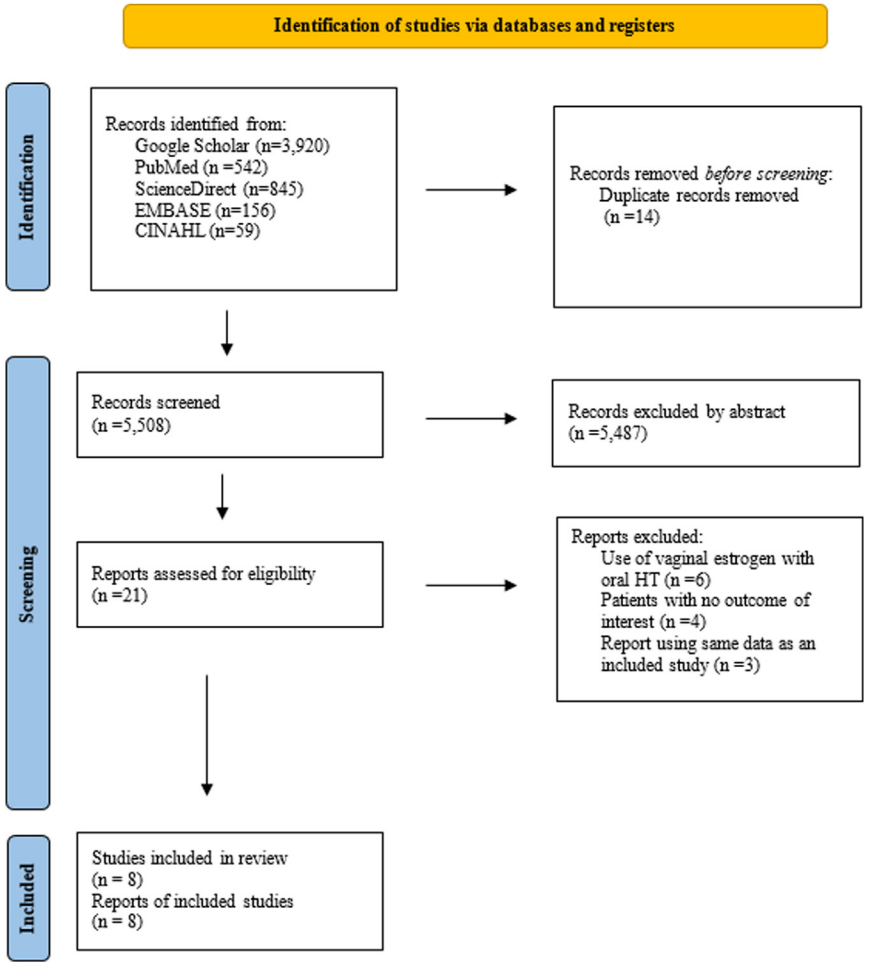
For quantitative analyses, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for categorical outcomes using a random-effects model (DerSimonian and Laird).[24]

Statistical significance was set at a 2-sided P value of $<.05$. To evaluate the robustness of the summary effects, we calculated the fragility index (FI), which indicates the number of events that would need to change from a nonevent to an event (or vice versa) to shift the statistical significance of the results.[25] A low FI indicates a more fragile study, while a high FI suggests greater robustness.[25] For nonsignificant outcomes, the reverse fragility index (RFI) was calculated.

Heterogeneity among the studies was assessed using Tau-squared and Higgins' I^2 statistic, with substantial heterogeneity defined as an I^2 value greater than 50%.[26] Additional analyses were conducted to explore the sources of heterogeneity and to enhance the robustness of the findings. These included calculating 95% prediction intervals (PIs) to estimate the range within which the effect size of a future individual study is likely to fall. Sequential leave-one-out analyses were performed to evaluate the impact of each individual study on the overall summary estimates.

Since fewer than 10 studies assessed any given outcome, funnel plots were not constructed to evaluate publication

FIGURE 1
PRISMA flow diagram



HT, hormone therapy; *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

TABLE 1
Characteristics of included studies

First author (year)	Study type	Country	Total patients	Total patients exposed to vaginal estrogen	Duration of estrogen (mean)	Type of vaginal estrogen	Breast cancer recurrence mean follow-up	NOS
Agrawal 2023[29]	Retrospective	USA	4218	2109	1 y	Cream	5 y	8
McVicker 2023[21]	Retrospective	Scotland, Wales	48,681	2551	Unknown	Tablets, Creams	Unknown	8
Sund 2022[27]	Retrospective	Sweden	11,771	921	Unknown	Cream	Unknown	8
Cold 2022[28]	Retrospective	Denmark	8328	1957	Unknown	Unknown	9.8 y	8
Le Ray 2012[22]	Retrospective	UK	8863	252	Unknown	Unknown	4.2 y	7
Dew 2003[30]	Retrospective	Australia	1472	69	1 y	Tablets, Creams	5.5 y	8
Durna 2002[31]	Retrospective	Australia	804	32	Unknown	Tablets, Creams	Unknown	8
O'Meara 2001[23]	Retrospective	USA	375	75	10 y	Creams	Unknown	7

Scoring: from 0 to 9; 0 to 2 (poor quality), 3 to 5 (fair quality), 6 to 9 (good/high quality).

NOS, Newcastle-Ottawa Score; *UK*, United Kingdom; *USA*, United States of America.

bias or small-study effects. All meta-analyses were conducted using Stata version 17.0 (StataCorp LLC, College Station, TX).

Results

Study selection

The initial database searches yielded 5522 studies. Once we eliminated the duplicated studies or those with abstracts/titles not meeting inclusion criteria, 21 studies remained. After a full-text review, we excluded 13 additional studies. Finally, 8 studies met the inclusion criteria.[21–23,27–31] Figure 1 illustrates the PRISMA flow diagram. Similar to the findings of a recent systematic review, we identified no randomized controlled trials that met the inclusion criteria.[32]

Study characteristics

The included studies varied by year, country, duration of vaginal estrogen use, and mean follow-up time.[21–23,27–31] See Table 1 for full study characteristics.

Quality of evidence of included studies

After reviewing the quality of each study, all 8 studies[21–23,27–31] were found to have a low risk of bias (Table 1).

Synthesis of results

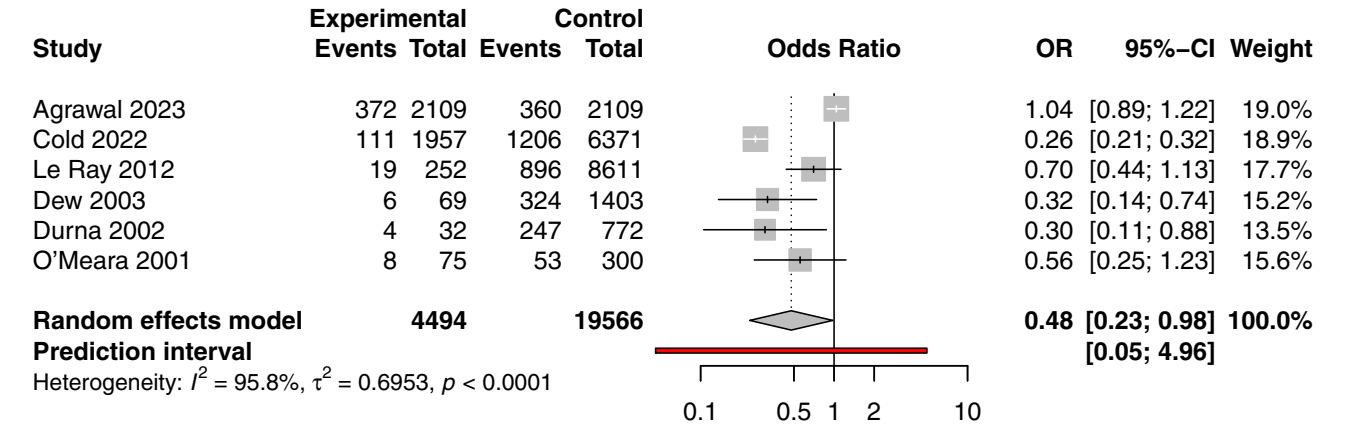
From the 6 observational studies that investigated the primary outcome—breast cancer recurrence in the context of treating GSM with vaginal estrogen—there was no association between its use and increased odds of recurrence. There was a total of 24,060 patients assessed for breast cancer recurrence. Among this group of patients using vaginal estrogen 11.6% (520/4494) of patients had a breast cancer recurrence vs 15.8% (3086/19,566) of patients not using vaginal estrogen experienced a breast cancer recurrence; OR 0.48; 95% CI, 0.23 to 0.98 (Table 2).[22,23,28–31] The *P* value was .04. The FI was calculated to be 1, indicating that the results lack robustness (Table 2).[22,23,28–31] The outcome of breast cancer recurrence displayed an I^2 of 95.8%, indicating marked heterogeneity. The 95% PI for breast cancer recurrence was (0.05, 4.96), which indicates that we can be 95% confident that the true effect size from a future individual study would fall within this range (Figure 2). In the leave-one-out analysis, the odds of breast cancer recurrence were substantially influenced by data from the Agrawal and Cold studies.[28,29] If the Agrawal[15] and Cold[17] studies are each removed from the dataset sequentially, the odds of breast cancer recurrence showed a significant reduction for those receiving vaginal estrogen (Table 3). The OR for breast cancer recurrence was 0.48 (95% CI: 0.23–0.98) when all studies were included. Both the Agrawal and Cold studies had a meaningful impact on this

TABLE 2
Pooled OR and fragility indices of outcomes

Outcome	References	Vaginal estrogen therapy, n/N (%)	Control group, n/N (%)	OR (95% CI)	*P* value	FI/RFI	Heterogeneity, I^2
Breast cancer recurrence	22,23,28–31	520/4494 (11.6)	3086/19,566 (15.8)	0.48 (0.23-0.98)	0.04	1	95.80%
Breast cancer mortality	21,23,27,31	285/3579 (8.0)	6885/58,116 (11.8)	0.60 (0.18-1.95)	0.41	69	98.1%
Overall mortality	21,23,28,30,31	806/4684 (17.2)	12,869/55,040 (23.4)	0.46 (0.42-0.49)	<0.01	16	0.00%

95% CI, 95% confidence intervals; *FI*, fragility index; *OR*, odds ratio; *RFI*, reverse fragility index.

FIGURE 2
Forest plot for breast cancer recurrence



CI, confidence interval; *OR*, odds ratio.

reduction. Specifically, excluding the Agrawal study shifted the OR to 0.39 (95% CI: 0.23−0.67), indicating that its inclusion significantly contributed to the overall reduction. Similarly, excluding the Cold study changed the OR to 0.60 (95% CI: 0.36−0.98), further highlighting its influence on the observed reduction. Funnel plots were not performed due to the limited amount of studies.

From the 4 studies which investigated the secondary outcome of breast cancer-specific mortality with the use of vaginal estrogen therapy, there was no increased odds of breast cancer-specific mortality with the use of vaginal estrogen. There were 61,695 total participants included. Of those patients, 8.0% (285/3579) of patients using vaginal estrogen experienced breast cancer-specific mortality compared to 11.8% (6885/58,116) of patients not using vaginal estrogen. OR 0.60; 95% CI 0.18 to 1.95 (Table 2).[21,23,27,31] *P* value was .41. The reverse FI was calculated to be 69, indicating robust results, implying that one would need to remove 69 events from the group with fewer events for the meta-analysis results to become statistically significant (Table 2).[21,23,27,31] The I^2 for breast cancer mortality was 98.1%, indicating excessive heterogeneity. The PI for breast cancer mortality was (0.01, 34.69) (Figure 3). For breast cancer mortality, excluding the Sund study led to results showing that the use of vaginal estrogen was associated with significantly greater protection (Table 4).[27]

TABLE 3
Leave-one-out analysis for breast cancer recurrence

Study omitted	OR (95% CI)
Agrawal (2023)[29]	0.39 (0.23−0.67)
Cold (2022)[28]	0.60 (0.36−0.98)
Le Ray (2012)[22]	0.43 (0.18−1.03)
Dew (2003)[30]	0.51 (0.23−1.14)
Durna (2002)[31]	0.51 (0.23−1.13)
O'Meara (2001)[23]	0.46 (0.20−1.05)

CI, confidence interval; *OR*, odds ratio.

Regarding the secondary outcome of overall mortality, the use of vaginal estrogen was not associated with increased odds of overall mortality. The total number of participants studied were 59,724, with deaths observed among 17.2% (806/4684) of those using vaginal estrogen vs 23.4% (12,869/55,040) among those not using vaginal estrogen; OR of 0.46; 95% CI 0.42 to 0.49 (Table 2).[21,23,28,30,31] The *P* value was <.01. The FI was 16, indicating that altering the outcomes of 16 events in the group of patients receiving vaginal estrogen would lead to this association no longer achieving statistical significance (Table 2).[21,23,28,30,31] The I^2 of overall mortality was 0%. The PI for overall mortality was (0.40, 0.51) (Figure 4). The odds of overall mortality were not unduly influenced by data from a single study (Table 5). In all, the results for overall mortality have the strongest evidence given its low heterogeneity and tight CI (0.42−0.49).

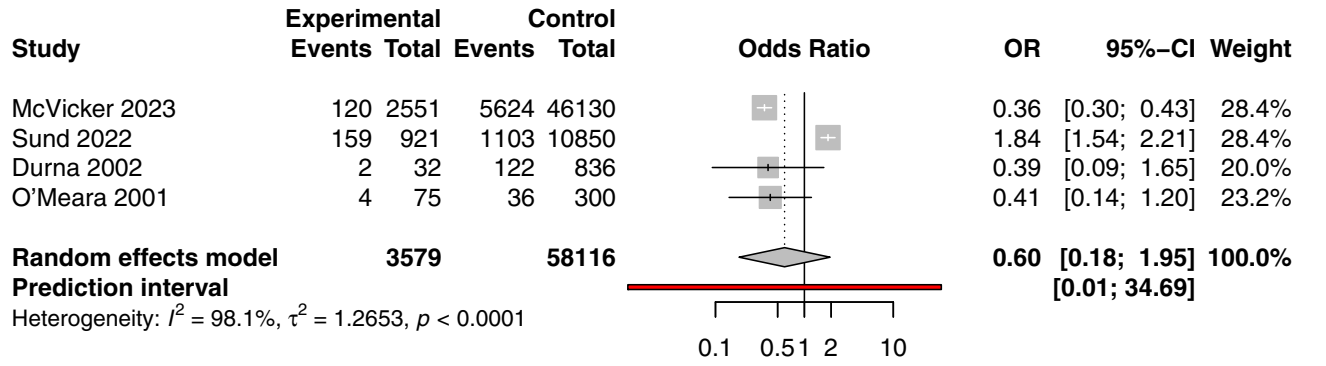
Comment

Principal findings

This meta-analysis provides insights regarding use of vaginal estrogen in breast cancer survivors suffering from GSM, challenging existing FDA labeling that contraindicates estrogen use in this large patient population. The meta-analysis indicates that vaginal estrogen does not appear to increase the risk of breast cancer recurrence, and similarly, does not elevate breast cancer-specific or overall mortality. These findings suggest that vaginal estrogen is likely safe for breast cancer survivors, potentially altering the risk assessment for prescribing this treatment in this clinical setting. Furthermore, the robustness of the nonsignificant results, as highlighted by the high RFI, adds confidence to these conclusions.

Additionally, the analysis revealed a statistically significant association between the use of vaginal estrogen and a reduction in overall mortality among

FIGURE 3
Forest plot for breast cancer mortality



CI, confidence interval; *OR*, odds ratio.

breast cancer survivors. Although all studies reported a reduction in overall mortality among vaginal estrogen users, with ORs ranging from 0.43 to 0.60, statistical heterogeneity was observed in the study outcomes. This heterogeneity may be attributed to variations in study populations, methodologies, and follow-up durations across the included studies. Despite the consistent direction of the effect, these differences could influence the degree of the reported effect sizes, as indicated by the I^2 statistic. These findings pave the way for updating clinical guidelines to allow broader use of vaginal estrogen in managing GSM among breast cancer survivors.

Exploring the lack of increase in adverse outcomes

In women using vaginal estrogen, serum levels of estradiol in general remain within the postmenopausal range.[5] In addition, use of vaginal estrogen, even when long-term, is not associated with an elevated risk of breast cancer.[33] Accordingly, it is not surprising that we did not identify an elevated risk of adverse breast cancer outcomes with use of vaginal estrogen.

A likely explanation for the favorable outcomes we observed when vaginal estrogen is used by breast cancer survivors is selection bias, which occurs when baseline characteristics of groups being studied are not comparable.[34] This type of bias is sometimes referred to as 'healthy user' bias.[35] For example, among breast cancer survivors, those who are healthier may be more sexually active, and therefore more likely to consult a physician regarding vaginal dryness during intercourse. Accordingly, healthier survivors with a better prognosis may be more likely to be prescribed vaginal estrogen. In the Cold study, nonusers of vaginal estrogen were older, had larger tumors, and were more likely to have lymphatic spread than users.[28] In the Durna study, users of vaginal estrogen were younger, had smaller tumors, and had fewer positive axillary lymph nodes than nonusers.[31] In the O'Meara study, users of vaginal estrogen were less likely to have axillary node involvement and had smaller tumors than nonusers.[23] In the McVicker study, when the authors controlled for cancer stage and grade, the reduction in risk of breast cancer-specific mortality associated with vaginal estrogen use was attenuated.[21] Each of these observations suggests that selection/healthy user bias likely is responsible for the reduced risk of recurrence and mortality in vaginal estrogen users. Notably, in the reports which controlled for selection/healthy user bias, adjusted analysis did not find that vaginal estrogen was associated with an elevated risk of breast cancer recurrence or mortality.[21,23,28,31]

Two of the studies suggested that concomitant use of vaginal estrogen and aromatase inhibitors was associated with an elevated risk of breast cancer recurrence.[28,29] In the Agrawal study, only 10% of those with estrogen receptor-positive tumors received aromatase inhibitor therapy.[29] In the Cold study, the proportion of menopausal women who used aromatase inhibitors was also low.[28] Given the low prevalence of aromatase inhibitor use, it is likely that patients who were felt to be at higher risk for recurrent disease were preferentially prescribed aromatase inhibitors, leading to bias.[36] Of note, the Sund and the McVicker studies found that concomitant use of aromatase inhibitors and vaginal estrogen was not associated with a higher risk of breast cancer-specific mortality.[21,27]

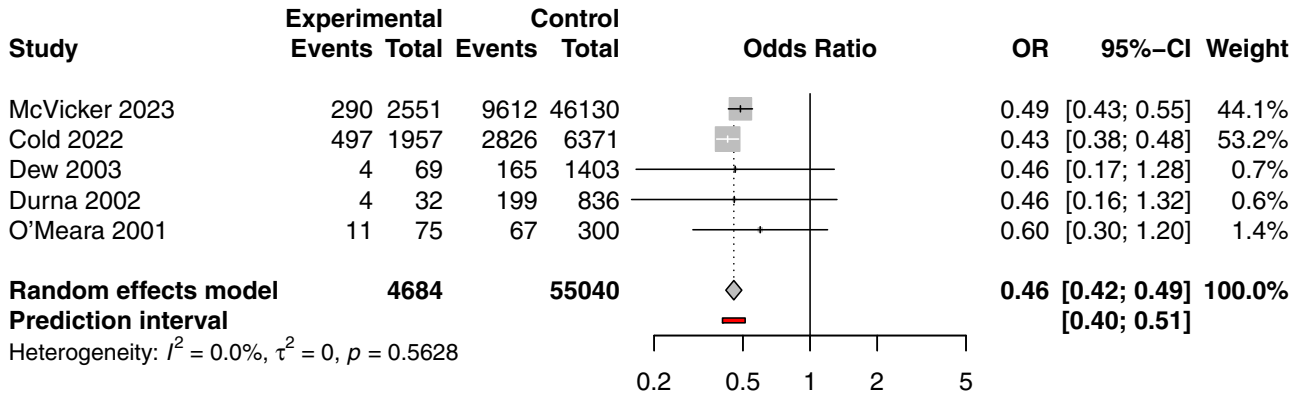
With respect to tumor characteristics, use of vaginal estrogen was not associated with an elevated risk of recurrence[28,29] or breast cancer-specific mortality[21] among breast cancer survivors with estrogen receptor-positive tumors. None of the included reports referred to tumor gene expression profiles (eg, Oncotype DX 21-gene

TABLE 4
Leave-one-out analysis for breast cancer mortality

Study omitted	OR (95% CI)
McVicker (2023)[21]	0.75 (0.21–2.61)
Sund (2022)[27]	0.35 (0.29–0.42)
Durna (2002)[31]	0.66 (0.16–2.63)
O'Meara (2001)[23]	0.66 (0.16–2.74)

CI, confidence interval; *OR*, odds ratio.

FIGURE 4
Forest plot for overall mortality



CI, confidence interval; *OR*, odds ratio.

Recurrence Score [Exact Sciences Corporation, Redwood, CA]), likely reflecting that widespread use of these profiles has only occurred in recent years.[37]

If vaginal estrogen use increases the risk of breast cancer recurrence or mortality, risks should increase with increasing duration of vaginal estrogen use. Unfortunately, many of the included studies did not detail the specific time period of use. The Sund study, however, looked at short term (<90 days) and long-term use (>90 days of exposure).[27] Compared with no use of vaginal estrogen, this study did not find statistically significant differences in risk of breast cancer mortality risk with short- or long-term vaginal estrogen exposure among survivors who concomitantly used aromatase inhibitors or tamoxifen. In contrast, long-term exposure to vaginal estrogen therapy without simultaneous endocrine treatment was associated with a 'decreased risk for breast cancer mortality' which the authors did not quantify. The authors speculated that the breast cancer survivors who did not receive tamoxifen or aromatase inhibitors constituted a group at intrinsically lower risk for recurrence (consistent with the 'healthy user' bias described above).[27]

TABLE 5
Leave-one-out analysis for overall mortality

Study omitted	OR (95% CI)
McVicker (2023)[21]	0.43 (0.38–0.48)
Cold (2022)[28]	0.48 (0.43–0.55)
Dew (2003)[30]	0.45 (0.41–0.49)
Durna (2002)[31]	0.45 (0.41–0.49)
O'Meara (2001)[23]	0.45 (0.41–0.49)

CI, confidence interval; *OR*, odds ratio.

Comparison with existing literature

In the existing literature, to the best of our knowledge, there are no systematic reviews and meta-analyses for vaginal estrogen use in patients with a history of breast cancer looking at their risk of breast cancer recurrence, breast cancer-specific mortality or overall mortality.[32] The American College of Obstetricians and Gynecologists 2021 Committee Opinion addressing the treatment of GSM in women with a history of breast cancer states: "If nonhormonal treatments have failed to adequately address symptoms, after discussion of risks and benefits, low-dose vaginal estrogen may be used in individuals with a history of breast cancer, including those taking tamoxifen. For individuals taking aromatase inhibitors, low-dose vaginal estrogen can be used after shared decision-making between the patient, gynecologist, and oncologist." The Opinion goes on to state: "Formulations that have been shown to be associated with serum estradiol levels of less than 20 pg/ml are 4-μg estradiol insert, 7.5-μg estradiol ring, and 10-μg estradiol inserts and tablets."[38]

Strengths and limitations

This systematic review and meta-analysis has several strengths that contribute to the consistency and validity of this review's findings. First, having multiple reviewers involved in the literature search reduced the element of bias and allowed for increased accuracy on data review. We conducted a thorough and detailed search using Google Scholar and a medical librarian facilitated a thorough search, reducing the likelihood of missing relevant studies. This meta-analysis employed a random-effects model to accommodate clinical heterogeneity among the review populations evaluated in the selected studies. Two reviewers scoring each study with the Newcastle-Ottawa system increased the reliability of quality assessment. The use of sequential leave-one-out analysis showed the robustness of the review's outcomes and allowed for the identification of individual studies that could have impacted the overall result if left out of the meta-analysis.

A meta-analysis is fundamentally dependent on the quality of the studies it encompasses, as its findings are derived from the collective strength and reliability of the included research. Even

though the systematic review and meta-analysis have several strengths, there are limitations to take into consideration. Due to the limited number of reports available, this systematic review yielded a small number of studies. Furthermore, all of the selected studies are observational as we identified no randomized controlled trials of vaginal estrogen in breast cancer survivors.[32] The use of the Newcastle-Ottawa Scale can also be looked at as a limitation, if assessing for grade, each study would have had a lower quality. Additionally, studies varied in terms of duration of vaginal estrogen use, formulation/dose of vaginal estrogen use, and limited follow-up times, limiting the clinical applicability of the findings. An additional limitation of this review was the high heterogeneity found in the analysis of breast cancer recurrence and breast cancer-specific mortality, likely a result of the variability of population sizes, demographics, and outcome variables.

Conclusions and implications

Although this systematic review and meta-analysis provide a level of reassurance regarding the safety of vaginal estrogen use in breast cancer survivors, we acknowledge that the findings are based exclusively on observational studies, and therefore subject to bias. We believe a randomized trial assessing the safety of vaginal estrogen for women with a personal history of breast cancer would be ethical, albeit expensive and challenging due to the need for large numbers of participants followed over many years. Such a trial would provide more definitive data to guide clinical recommendations in this setting.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the author(s) used ChatGPT, (Open AI, San Francisco, CA) in order to correct grammar and syntax in addition to creation of search syntax using keywords. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication. ■

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REFERENCES

1. Bodai BI, Tuso P. Breast cancer survivorship: a comprehensive review of long-term medical issues and lifestyle recommendations. Perm J 2015;19:48–79.
2. Caru M, Abdullah S, Qiu L, et al. Women with metastatic breast cancer don't just follow step-count trends, they exceed them: an exploratory study. Breast Cancer Res Treat 2023;200:265–70.
3. Lubián López DM. Management of genitourinary syndrome of menopause in breast cancer survivors: an update. World J Clin Oncol 2022;13:71–100.
4. Faubion SS, Larkin LC, Stuenkel CA, et al. Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from the North American Menopause Society and the International Society for the Study of Women's Sexual Health. Menopause 2018;25:596–608.
5. The NAMS 2020 GSM Position Statement Editorial Panel. The 2020 genitourinary syndrome of menopause position statement of the North American Menopause Society. Menopause 2020;27:976–92.
6. Higgins JPT, Thomas J, Chandler J, et al, eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Cochrane; 2024. Available at: www.training.cochrane.org/handbook. Accessed September 29, 2024.
7. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
8. DiSaia PJ, Brewster WR, Ziogas A, Anton-Culver H. Breast cancer survival and hormone replacement therapy: a cohort analysis. Am J Clin Oncol 2000;23:541–5.
9. Fahlén 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;49:52–9.
10. Crandall CJ, Hovey KM, Andrews CA, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. Menopause 2018;25:11–20.
11. Pritchard KI. Hormone replacement in women with a history of breast cancer. Oncologist 2001;6:353–62.
12. Decker DA, Pettinga JE, VanderVelde N, Huang RR, Kestin L, Burdakin JH. Estrogen replacement therapy in breast cancer survivors: a matched-controlled series. Menopause 2003;10:277–85.
13. Ugras SK, Layeequr Rahman R. Hormone replacement therapy after breast cancer: yes, no or maybe? Mol Cell Endocrinol 2021;525:111180.
14. 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;8:144–8.
15. Pavlović RT, Janković SM, Milovanović JR, et al. The safety of local hormonal treatment for vulvovaginal atrophy in women with estrogen receptor-positive breast cancer who are on adjuvant aromatase inhibitor therapy: meta-analysis. Clin Breast Cancer 2019;19:e731–40.
16. Krause M, Wheeler TL, Richter HE, Snyder TE. Systemic effects of vaginally administered estrogen therapy: a review. Female Pelvic Med Reconstr Surg 2010;16:188–95.
17. Comini ACM, Carvalho BM, Moreira MJB, et al. Safety and serum estradiol levels in hormonal treatments for vulvovaginal atrophy in breast cancer survivors: a systematic review and meta-analysis. Clin Breast Cancer 2023;23:835–46.
18. Lupo M, Dains JE, Madsen LT. Hormone replacement therapy: an increased risk of recurrence and mortality for breast cancer patients? J Adv Pract Oncol 2015;6:322–30.
19. Merlino L, D'Ovidio G, Matys V, et al. Therapeutic choices for genitourinary syndrome of menopause (GSM) in breast cancer survivors: a systematic review and update. Pharmaceuticals (Basel) 2023;16:550.
20. Col NF, Kim JA, Chlebowski RT. Menopausal hormone therapy after breast cancer: a meta-analysis and critical appraisal of the evidence. Breast Cancer Res 2005;7:R535–40.
21. McVicker L, Labeit AM, Coupland CAC, et al. Vaginal estrogen therapy use and survival in females with breast cancer. JAMA Oncol 2024;10:103–8.
22. 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;135:603–9.
23. O'Meara ES, Rossing MA, Daling JR, Elmore JG, Barlow WE, Weiss NS. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. J Natl Cancer Inst 2001;93:754–62.
24. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

25. Lin L, Xing A, Chu H, et al. Assessing the robustness of results from clinical trials and meta-analyses with the fragility index. Am J Obstet Gynecol 2023;228:276–82.
26. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
27. Sund M, Garmo H, Andersson A, Margolin S, Ahlgren J, Valachis A. Estrogen therapy after breast cancer diagnosis and breast cancer mortality risk. Breast Cancer Res Treat 2023;198:361–8.
28. Cold S, Cold F, Jensen MB, 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;114:1347–54.
29. Agrawal P, Singh SM, Able C, et al. Safety of vaginal estrogen therapy for genitourinary syndrome of menopause in women with a history of breast cancer. Obstet Gynecol 2023;142:660–8.
30. Dew JE, Wren BG, Eden JA. A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. Climacteric 2003;6:45–52.
31. Durna EM, Wren BG, Heller GZ, Leader LR, Sjoblom P, Eden JA. Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality. Med J Aust 2002;177:347–51.
32. Hussain I, Talaulikar VS. A systematic review of randomised clinical trials - the safety of vaginal hormones and selective estrogen receptor modulators for the treatment of genitourinary menopausal symptoms in breast cancer survivors. Post Reprod Health 2023;29:222–31.
33. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases. BMJ 2020;371:m3873.
34. Schulz KF, Grimes DA. The Lancet Handbook of essential concepts in clinical research 2006.
35. Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. J Gen Intern Med 2011;26:546–50.
36. Pederson HJ, Faubion SS, Pruthi S, Goldfarb S. RE: systemic or vaginal hormone therapy after early breast cancer: a Danish observational cohort study. J Natl Cancer Inst 2023;115:220–1.
37. Dinan MA, Mi X, Reed SD, Hirsch BR, Lyman GH, Curtis LH. Initial trends in the use of the 21-gene recurrence Score assay for patients with breast cancer in the medicare population, 2005-2009. JAMA Oncol 2015;1:158–66.
38. Treatment of urogenital symptoms in individuals with a history of estrogen-dependent breast cancer: clinical consensus. Obstet Gynecol 2021;138:950–60.

Appendix

Search syntax:

Initial search

PubMed

((((("breast"[tiab] OR "mamma"[tiab] OR "mammary"[tiab]) AND ("malignan*"[tiab] OR "cancer*"[tiab] OR "neoplasm*"[tiab] OR "carcinoma*"[tiab] OR "tumour*"[tiab] OR "tumor*"[tiab]) OR ("Breast Neoplasms"[Mesh])) AND ("Genitourinary Syndrome of Menopause" [tiab] OR "genitourinary syndrome" OR "Vulvovaginal Atrophy"[tiab] OR "Atrophic Vaginitis"[tiab] OR "vagina* atrophy"[tiab] OR "vaginal acidification"[tiab] OR "Vaginal Dryness"[tiab] OR "vaginosis"[tiab] OR "vaginosis"[tiab] OR "vulvodynia"[tiab] OR "genitourinary symptoms"[tiab] OR "dyspareunia"[tiab] or "vestibulodynia"[tiab] or "dysuria"[tiab])) AND (("vagina*" OR "vaginal capsule*" OR "vaginal gel" OR "vaginal pessary" OR "vaginal tablet" OR "vaginal ring" OR "intravaginal") AND ("estrogen*"[tiab] OR "estradiol*"[tiab] OR "oestrogen*"[tiab] OR "oestradiol*"[tiab] OR ("Estrogens" [Pharmacological Action]) OR ("Estrogens" [mh]))))) AND ("Mortality"[Mesh] OR "Survival"[Mesh] OR "Disease-Free Survival"[Mesh] OR "Progression-Free Survival"[Mesh] OR "Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh] OR "risk assessment"[mesh] OR ("oncolog*"[tiab] AND ("safety"[tiab] OR "outcome*"[tiab] OR "recurrence"[tiab]))))

Google Scholar

("breast cancer" OR "Breast Neoplasms") AND ("vaginal estrogen" OR "vaginal ring" OR "intravaginal estrogen") AND ("Mortality" OR "recurrence")

ChatGPT was used for the following search syntaxes:

ScienceDirect

("breast cancer" OR "Breast Neoplasms") AND ("vaginal estrogen" OR "vaginal ring" OR "intravaginal estrogen") AND ("Mortality" OR "recurrence")

EMBASE

("breast cancer" OR "Breast Neoplasms") AND ("vaginal estrogen" OR "vaginal ring" OR "intravaginal estrogen") AND ("Mortality" OR "recurrence")

CINAHL

"breast cancer or breast neoplasm or breast carcinoma" AND "vaginal estrogen therapy" AND "recurrence or relapse or reoccurrence"

NCBI

"breast cancer or breast neoplasm or breast carcinoma" AND "vaginal estrogen therapy" AND "recurrence or relapse or reoccurrence"

Secondary search

PubMed/MEDLINE

("Breast Neoplasms"[MeSH] OR "breast cancer"[tiab] OR "breast carcinoma"[tiab] OR "breast neoplasm*"[tiab])

AND

("Vaginal Atrophy"[MeSH] OR "Genital Diseases, Female"[MeSH] OR "genitourinary syndrome"[tiab] OR "urogenital atrophy"[tiab] OR "vulvovaginal atrophy"[tiab] OR "vaginal atrophy"[tiab])

AND

("Estrogens/administration and dosage"[MeSH] OR "Administration, Intravaginal"[MeSH] OR "Estradiol"[MeSH] OR "Estriol"[MeSH] OR "vaginal estrogen"[tiab] OR "estrogen cream"[tiab] OR "estrogen suppositor*"[tiab] OR "local estrogen"[tiab] OR "intravaginal estrogen"[tiab] OR "vaginal estradiol"[tiab] OR "estriol cream"[tiab] OR "estradiol ring"[tiab] OR "estradiol tablet*"[tiab] OR "estradiol pessar*"[tiab])

AND

(Humans[MeSH])

Embase

('breast tumor'/exp OR 'breast cancer':ti,ab OR 'breast carcinoma':ti,ab OR 'breast neoplasm*':ti,ab)

AND

('urogenital atrophy'/exp OR 'vaginal atrophy'/exp OR 'genitourinary syndrome':ti,ab OR 'urogenital atrophy':ti,ab OR 'vulvovaginal atrophy':ti,ab OR 'vaginal atrophy':ti,ab)

AND

((('estrogen'/exp OR 'estradiol'/exp OR 'estriol'/exp) AND 'vaginal drug administration'/exp) OR 'vaginal estrogen':ti,ab OR 'estrogen cream':ti,ab OR 'estrogen suppositor*':ti,ab OR 'local estrogen':ti,ab OR 'intravaginal estrogen':ti,ab OR 'vaginal estradiol':ti,ab OR 'estriol cream':ti,ab OR 'estradiol ring':ti,ab OR 'estradiol tablet*':ti,ab OR 'estradiol pessar*':ti,ab)

AND

[humans]/lim

CINAHL

((MH "Breast Neoplasms") OR TX ("breast cancer" OR "breast carcinoma" OR "breast neoplasm*"))

AND

((MH "Vaginal Atrophy" OR MH "Urogenital Atrophy" OR MH "Atrophic Vaginitis") OR TX("genitourinary syndrome" OR "urogenital atrophy" OR "vulvovaginal atrophy" OR "vaginal atrophy"))

AND

(((MH "Estrogens, Conjugated (USP)" OR MH "Estradiol" OR MH "Estrogen Replacement Therapy") AND MH "Administration, Intravaginal") OR TX("vaginal estrogen" OR "estrogen cream" OR "estrogen suppositor*" OR "local estrogen" OR "intravaginal estrogen" OR "vaginal estradiol" OR "estriol cream" OR "estradiol ring" OR "estradiol tablet*" OR "estradiol pessar*"))

AND

(MH "Human")

Science Direct

("breast cancer" OR "breast carcinoma" OR "breast neoplasm*" OR "breast tumour" OR "breast tumor")

AND

("genitourinary syndrome" OR "urogenital atrophy" OR "vulvovaginal atrophy" OR "vaginal atrophy")

AND

("vaginal estrogen" OR "estrogen cream" OR "estrogen suppositor*" OR "local estrogen" OR "intravaginal estrogen" OR "vaginal estradiol" OR "estriol cream" OR "estradiol ring" OR "estradiol tablet*" OR "estradiol pessar*")

AND

"humans"

AND

("clinical trial" OR "case study" OR "human study" OR "patient")