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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

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Abstract

Therapies utilised in breast cancer management have been found to induce or worsen the genitourinary symptoms of menopause (GSM), a group of physical symptoms associated with the systemic loss of estrogen. These symptoms are often undertreated due to concerns surrounding cancer recurrence, especially when considering treatments with possible pro-estrogenic effects. As breast cancer prognosis continues to improve, clinicians are increasingly focussing on managing these symptoms amongst survivors. This systematic review primarily aimed to determine the risk of breast cancer recurrence amongst survivors using vaginal hormones and selective estrogen receptor modulator therapies recommended for use in GSM in the United Kingdom amongst currently published randomised clinical trials (RCTs). The secondary aim was to determine whether these RCTs demonstrated a significant rise in serum estrogen levels following the use of these therapies. A literature search revealed three RCTs suitable for assessment, two evaluating vaginal estrogen and one evaluating vaginal DHEA treatment. Our review determined that amongst published RCTs, no studies have aimed to assess for breast cancer recurrence; however among the studies observing for serious adverse effects of vaginal estrogen preparations, none have reported an increased incidence. Furthermore, these studies did not report a persistent or significant increase in serum estrogen levels following the use of vaginal estrogen products and low concentration (3.25 mg/day) DHEA gel. Larger RCTs studying commonly used vaginal preparations and selective estrogen receptor modulator treatments for GSM over longer follow-up periods will be vital to better assess the risk of breast cancer recurrence in survivors receiving these treatments.

Keywords

Menopause, breast cancer, estrogen, vasomotor symptoms, urogenitalatrophy, hormone replacement therapy

Introduction

Breast cancer continues to be one of the most diagnosed cancers in the UK with over 55,000 women diagnosed each year between 2016 and 2018.[1] In recent years, a decline in mortality rates has been seen amongst women diagnosed with breast cancer given improvements in diagnosis and management. However, the use of certain treatment modalities including chemotherapy agents and adjuvant endocrine therapies such as aromatase inhibitors (AIs) to manage breast cancer has been found to induce or worsen genitourinary symptoms of menopause (GSM) in both pre- and postmenopausal women.[2–4]

The GSM are a group of physical changes and symptoms, including vulvovaginal dryness, burning, irritation, dyspareunia, and urinary symptoms of urgency, dysuria or recurrent urinary tract infection (UTI) which are associated with the systemic loss of estrogen.[5] Studies have shown that these symptoms have a negative impact on quality of life in breast cancer survivors due to a variety of issues including low self-esteem, body image and reduced sexual

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function.[6–8] As the prognosis of breast cancer improves for women, it is vital that a greater focus is maintained on optimising patient's quality of life and managing the long-term side effects of cancer treatment as part of the aftercare for survivors.[9]

Hormonal estrogen treatment is the current gold standard in managing GSM in healthy postmenopausal women; however, the use of systemic estrogens in breast cancer survivors has been determined to be unsafe due to an increased risk of disease recurrence.[10,11]

Vaginal hormonal estrogen remains the first-line hormonal therapy in the United Kingdom for breast cancer survivors experiencing genitourinary symptoms of menopause.[12,13] Studies have shown that vaginal estrogen effectively relieves the GSM and significantly improves vaginal mucosal health and vaginal pH in postmenopausal women.[5] Furthermore in healthy postmenopausal women, the Women's Health Initiative observational study determined that the risk of breast cancer was not increased following the use of vaginal estrogens.[14] Studies determining this risk of cancer recurrence following vaginal estrogen therapy amongst breast cancer survivors however remain conflicting.[15,16]

Other more recently approved vaginal hormonal therapies include dehydroepiandrosterone (DHEA), an androgen precursor which partially transforms into estrogen through aromatisation in the vaginal wall.[17] This therapy has been found to effectively manage symptoms of GSM within clinical trials in healthy postmenopausal women and that the strictly local effect of Prasterone correlated with the lack of significant drug-related adverse events.[18] Ospemifene is yet another treatment approved for the management of moderate-to-severe GSM in healthy postmenopausal women and is a selective estrogen receptor modulator (SERM) that acts by binding to estrogen receptors in hormone-responsive tissues.[19] It has a pro-estrogenic effect on the vaginal tissues but an anti-estrogenic effect at the level of the breast tissue.[19] Meta-analyses in healthy postmenopausal women have indicated that Ospemifene significantly improves symptoms associated with postmenopausal vulvovaginal symptoms compared to placebo and additionally has a good safety profile.[20,21] However, due to lack of sufficient safety data, both DHEA and Ospemifene are currently not recommended for treatment of GSM in breast cancer survivors.

Whilst there is a clarity on the efficacy and safety of vaginal hormones and selective estrogen receptor modulating therapies in the management of GSM in women without a history of breast pathology, there remain reservations amongst doctors and women about the safety of these treatments in women with a history of breast cancer and the potential risk of breast cancer recurrence particularly with treatments containing estrogen or having a pro-estrogenic effect. The WISDOM study conducted in the United States, surveying 644 clinicians, determined that only 34% of obstetricians and gynaecologists and only 17% of primary care clinicians felt comfortable prescribing vaginal estrogen therapies for vulval and vaginal symptoms to postmenopausal women with a personal history of breast cancer due to concerns about estrogen exposure.[22]

In order to bring more clarity to this clinical question, this systematic review aims to primarily assess the safety of vaginal hormones and selective estrogen receptor modulators for the management of GSM with regards to the risk of cancer recurrence amongst breast cancer survivors amongst current published randomised clinical trials (RCTs), particularly those therapies or preparations currently licensed and recommended for use in postmenopausal women in the United Kingdom. The secondary aim of this review was to determine whether these identified RCTs demonstrated any significant rise in serum estrogen levels noted following the use of vaginal treatments in women having these therapies.

Materials and methods

Study selection

This review aimed to assess current medical literature to determine the risk of breast cancer recurrence in breast cancer survivors using vaginal hormonal therapies or oral selective estrogen receptor modulator treatment to treat symptoms associated with GSM.

Inclusion criteria for selecting the studies were as follows: i) studies recruiting women (age >18) who have been diagnosed with and treated for breast cancer; ii) randomised clinical trials (RCTs) including vaginal hormones or selective estrogen receptor modulators currently recommended for the management of GSM in healthy postmenopausal women under guidelines in the United Kingdom including vaginal estrogens, vaginal DHEA and oral Ospemifene within at least one intervention arm of the trial; iii) completed studies with fully published results; and iv) publications in English. RCTs were selected for evaluation within this study as this is the gold-standard methodology for assessing true cause and effect relationships between a therapeutic intervention and any potential outcomes unlike observational or non-randomised studies.[23] RCTs only evaluating vaginal testosterone cream were not assessed in this study as this is not currently recommended for use in the UK for the management of GSM symptoms in postmenopausal women.[24]

Literature search

A systematic literature review was conducted by the authors searching the following databases: Cochrane Library (1996–December 2022), Ovid MEDLINE (1946–

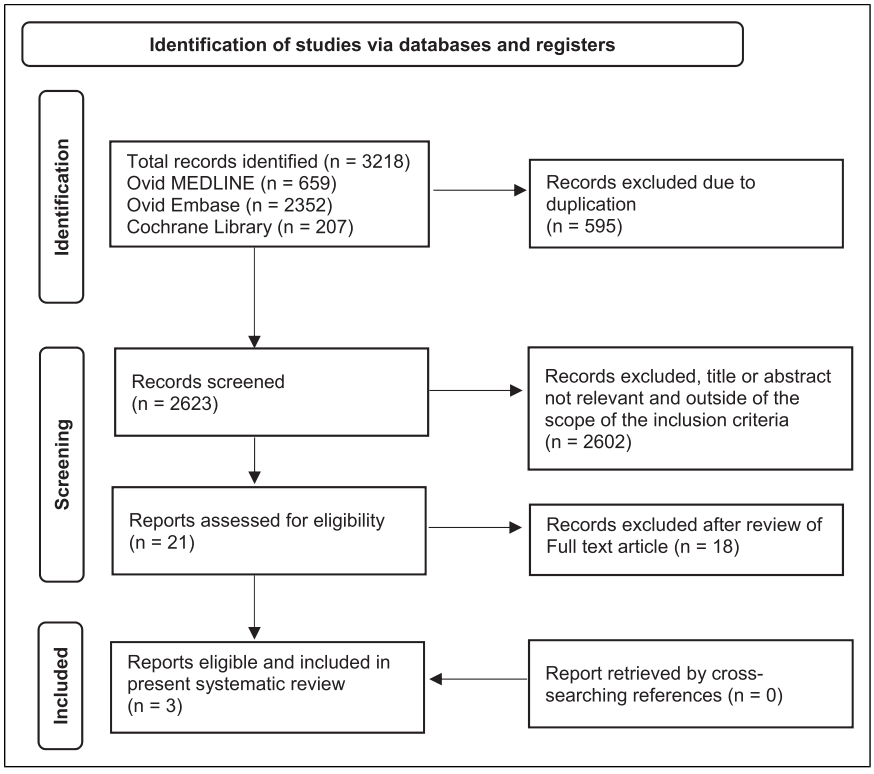

Figure 1. PRISMA flow chart summarising the process of identifying eligible randomised clinical studies.[25]

December 2022) and Ovid Embase (1974–December 2022). This was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as outlined in Figure 1.[25] Searches were conducted using relevant MeSH terms and keywords related to 'breast cancer', 'menopause', 'climacteric', 'genitourinary system', 'genitourinary syndrome of menopause', 'vaginal atrophy', 'vaginal hormonal therapy', 'estrogen', 'Ospemifene' and 'DHEA'. In addition to electronic database searching, bibliographies from relevant publications were cross searched for any further relevant studies. Identified citations were imported into EndNote and duplicates removed. Only the most updated results of a same study were selected. References of included studies were cross searched in order to identify any additional studies. The search was re-run prior to submission on 16th December 2022, and no new studies were identified.

Data extraction

Data collected from each publication were as follows: name of the first author, year of the most updated publication, interventional treatment(s), comparator treatment, treatment regimens, total number of randomised breast cancer survivors, time points at which the study participants were assessed, recorded serum estrogen levels and any recorded episodes of breast cancer recurrence. A thorough analyses and assessment of all included reports were performed independently by both authors, and any disagreement was solved among the authors.

Quality assessment

The studies included within this review were qualitatively assessed using the latest version of the CONSORT 2010 25-item checklist.[26] Evidence of each article entirely fulfilling a single checklist item scored one point and those without complete evidence scored zero for that item.[27] As such, each article scores a minimum of 0 and a maximum of 37. Each article has been divided into three categories based on the score: high-quality (article score >24.67), moderate-quality (12.34< study score <24.67) and poor-quality (study score <12.34). The quality of the articles was assessed by one author (IH), and any disagreements were settled by consulting the additional author (VST). Table 1 presents the results of this assessment.

Results

Electronic searches of the included databases using the medical terms cited above produced 3218 records. After removing duplicates, 2623 publications remained. Of these, 2602 records were excluded following assessment of the title or abstract and 18 on assessment of the full-text due to

Table 1. Quality assessment scores of each article according to the CONSORT checklist (2010).[26]

Paper	Title and abstract	Introduction	Methods	Results	Discussion	Other information	Total score	Quality
Melisko et al, 2016[30]	2	2	10	6	2	3	25	High
Barton et al, 2018[28]	1	2	7	5	2	2	19	Moderate
Hirschberg et al, 2020[29]	2	2	9	5	2	0	20	Moderate

not fulfilling the inclusion criteria in whole (Figure 1). A total of 3 RCTs were found and analysed, with none retrieved by cross searching references. The final 3 articles deemed eligible for inclusion within this systematic review included 1 trial comparing vaginal ET versus placebo, 1 trial comparing vaginal ET with topical testosterone and 1 trial comparing different dosages of DHEA gel with a vaginal moisturiser.[28–30] Interventions included in this review were vaginal estrogen in the form of creams and rings and DHEA in the form of a gel. No studies that fit our inclusion criteria included Ospemifene as a treatment intervention. Overall, 577 breast cancer survivors in total were included within these studies, with 90 randomised to receive vaginal estrogen products and 295 randomised to receive vaginal DHEA gel (Table 2).

None of the studies included within this systematic review aimed to determine the rate of breast cancer recurrence within their study groups. Hirschberg et al and Melisko et al did aim to assess the risk of death or serious adverse events within their treatment groups as an endpoint and did not note any incidences of breast cancer recurrence following the use of vaginal estrogen products (Table 2).[29,30]

With regards to assessment of serum estrogen levels following treatment, Hirschberg et al noted a transient rise in median estriol (E3) levels at week-1 assessment point in their interventional group receiving E3 gel which normalised over the treatment period. At the 12-week assessment point and at 30 +/− 5 days following the last dose of E3 gel, median serum estrogen levels progressively returned to baseline levels.[29] The significance of these oscillations however was not measured. Melisko et al determined that within their intervention group receiving the Estring estradiol (E2) ring, no persistent increase in serum E2 levels was detected at 12 weeks when compared to baseline levels. This was defined as an E2 greater than 10 pg/mL and at least 10 pg/mL above baseline after treatment initiation on 2 consecutive tests at least 2 weeks apart. A persistent elevation in serum E2 levels was however noted in 12% of patients in the comparator group receiving intravaginal testosterone (IVT). Transient E2 elevation was seen in 11% of patients treated with a vaginal ring and in 12% of those treated with IVT (a transient elevation in E2 was defined as elevation without confirmation on consecutive blood draw with ongoing use of the assigned treatment).[30] Barton et al determined that serum E2 levels were significantly increased from baseline at 12 weeks in the intervention group receiving 6.5 mg/day DHEA ($p < .5$). However, no significant increase in concentrations of serum E2 was noted in the intervention group receiving 3.25 mg/day ($p = .5$). Additionally, no significant increase in E2 concentrations was noted from baseline in a sub-group analysis of all patients receiving AIs included within either intervention group (Table 2).[28]

Discussion

To our knowledge, this is one of very few systematic reviews that has been conducted in order to determine the risks of breast cancer recurrence following the use of vaginal hormone or selective estrogen receptor modulating therapies amongst current published RCTs. Our study has determined that within current RCTs, no studies have aimed to specifically assess for episodes of breast cancer recurrence. However, no episodes of breast cancer recurrence have been noted by Hirschberg et al or Melisko et al who aimed to assess for serious adverse events or mortality following the use of vaginal estrogen products.[29,30] Furthermore, no persistent increase in serum estrogen levels was detected following the use of the vaginal Estring or E3 gel, and no significant increases were seen following the use of 3.25 mg/d DHEA moisturiser gel in breast cancer survivors for the duration of the studies.[28–30]

Overall, data from non-randomised interventional studies suggest that vaginal estrogen for treatment of GSM may not be associated with an increased risk of recurrence or mortality from breast cancer in survivors. A recent cohort study conducted by Cold et al concluded that overall vaginal estrogen therapy was not associated with an increased risk of breast cancer recurrence or mortality.[15] However interestingly, Cold et al noted through a sub-group analysis that an increased risk of recurrence, but not mortality, was seen in patients receiving vaginal estrogen therapy with adjuvant AIs.[15] This study is the first to report this potential increased risk. Researchers of ongoing RCTs are continuing to evaluate serum estrogen levels and the risk of breast cancer recurrence in BC patients receiving adjuvant AIs and treated with vaginal estrogen therapies. These studies will be critical in helping to further elucidate the safety of these treatments.[31]

Systemic absorption of vaginal estrogens would be of particular concern for women with contraindication to hormonal treatments, such as breast cancer survivors. This

Table 2. RCTs assessing the safety of vaginal and oral selective estrogen receptor modulator therapies for treatment of genitourinary syndrome of menopause in breast cancer survivors.

Author and year	Total number of breast cancer survivors as study participants	Intervention regimen (n)	Comparator regimen (n)	Patient Characteristics	Assessment points	Serum estrogen levels	Recurrence of breast cancer
Melisko et al, 2016[30]	76	Estring 2 mg silicone ring, inserted once a day for 90 days (*n* = 40)	0.5 g 1% intravaginal testosterone (IVT), 0.5 g a day for 2 weeks, 3 times a week from weeks 3 to 10 (*n* = 36)	Treated with an aromatase inhibitor for at least 30 days	Assessed at baseline, 4 and 12 weeks	Mean values Estring ring at baseline 26.8 pg/mL IVT at baseline 9.0 pg/mL A transient elevation in estradiol was observed in 12% of patients' using IVT (range, 11–113 pg/mL. Persistent elevation in estradiol observed in and additional 12% of patients' using IVT (range, 16–45 pg/mL) A transient elevation in estradiol was observed in 11% of patients' using the Estring ring (range, 11–29 pg/mL). No persistent elevation in estradiol was seen in any patients' using the Estring vaginal ring	No recurrence noted

(continued)

Table 2. (continued)

Author and year	Total number of breast cancer survivors as study participants	Intervention regimen (n)	Comparator regimen (n)	Patient Characteristics	Assessment points	Serum estrogen levels	Recurrence of breast cancer
Barton et al, 2018[28]	440	i) DHEA 3.25 mg/d moisturiser gel of 12 weeks (n = 147). ii)DHEA 6.5 mg/d moisturiser gel for 12 weeks (n = 149)	Control plain moisturiser, 1 syringe of gel daily every night for 12 weeks (n = 147)	If patients on endocrine therapy (tamoxifen or aromatase inhibitors), they must have been receiving the treatment for 2 months prior to the start of the trial without planned changes	Assessed at baseline and at 12 weeks following daily application	Change in mean concentration of estradiol from baseline levels Plain moisturiser – 0.2 ± 2.5 pg/mL, 3.25 mcg/dL DHEA 0.9 ± 5.0, 6.5 mcg/dL DHEA - 0.6 ± 1.9 Serum estradiol was significantly increased from baseline at 12 weeks in those on 6.5 mg/day DHEA but not those on 3.25 mg/day and not in those on aromatase inhibitors	No recurrence noted
Hirschberg et al, 2020[29]	61	0.005% (50 ug/g) Estriol vaginal gel, 1 g a day for 3 weeks, 2 g a week during weeks 4–12 (n = 50)	Non-hormonal moisturising gel, 1 g a day for 3 weeks, 2 g a week during weeks 4–12 (n = 11)	Hormone receptor positive and any HER2 status, treated with an aromatase inhibitor for at least 6 months	Assessed 2 weeks prior to the start of treatment, at baseline and at weeks 1, 3, 8 and 12 of treatment and 30 +/− 5 days after the last dose	Median estriol levels Estriol gel at baseline 0.5 pg/mL, week 1 3.9 pg/mL, week 3 1.9 pg/mL, week 8 0.5 pg/mL and week 12 0.5 pg/mL Moisturising gel at baseline 0.5 pg/mL, week 1 0.5 pg/mL, week 3 0.5 pg/mL, week 8 0.5 pg/mL and week 12 0.5 pg/mL Estriol levels increased initially and normalised by week 12, and estradiol and estrone remained mostly undetectable throughout the study	No recurrence noted

concern is particularly highlighted by Kendall et al who demonstrated a temporary elevation in serum estrogen level in breast cancer patients treated with AIs who received vaginal estrogen treatment.[32] However, it is important to note that vaginal estrogen was administered at 25 mcg dose (higher than the 10 mcg pessaries twice weekly commonly used now) in this study. Similar findings where serum estrogen levels were initially raised were additionally demonstrated within the study conducted by Hirschberg et al. However, it is notable that the rise seen in serum estrogen levels within these studies is transient with maximal concentrations being reached soon after application.[29,32]

In a recent meta-analysis conducted by Pavlovic et al, it was further determined that amongst the current literature treatment with vaginal estrogens is not associated with significant systemic absorption in postmenopausal women with a history of breast cancer.[33] This is thought to be due to the initial rapid absorption of estrogen through a thinner postmenopausal atrophic vaginal mucosa. This rate of absorption then begins to fall as the vaginal mucosa thickens and restores following continuous treatment. Furthermore, the initial concentration of serum estrogen following the application of vaginal estrogen has been found to be dose dependent as reported by a recently updated systematic review.[34]

Serum estrogen levels may also be dependent on the formulation of vaginal hormone treatments. Research has determined that E3 is much less potent than E2 or estrone (E1), and in vivo does not exhibit conversion back to these more powerful natural estrogens.[35,36] In addition, E3 is considered to be a much more short-acting estrogen.[37] Promestriene, a synthetic analogue of E2, has also demonstrated lower serum absorption rates and has been found to not alter to plasma gonadotrophin or E2 levels when applied topically.[38] Peripherally, DHEA appears to act through the local biosynthesis and action of its estrogenic and androgenic metabolites, E1, E2 and dihydrotestosterone. Studies have determined that these active androgens and estrogens exert their action within the same cells in which they were formed with little leakage of these hormones into the systemic circulation.[39] However, the clinical significance of any increase in serum estrogen following onset of vaginal hormone treatment no matter how transient is currently unknown, and further studies are required to determine what concentration rise in serum estrogen and for what duration would be significantly impactful on the long-term risk of breast cancer recurrence.

Although data are limited, no increase in incidence or risk of breast cancer recurrence has been noted in women with GSM treated with Ospemifene. In a meta-analysis of 6 RCTs comparing Ospemifene 60 mg/day versus placebo for side effects and safety, the data found that there was no significant increase in treatment-associated serious adverse effects including death.[20] Rather, data from animal studies have determined that Ospemifene may instead impart a chemoprotective effect as the drug was found to inhibit tumour growth and was not found to have pro-estrogenic effects on breast tissue.[40] A Post Authorisation Safety Study (PASS), a retrospective observational cohort analysis assessing healthy postmenopausal women, further determined that in practise Ospemifene treatment has demonstrated a low incidence of venous thromboembolism, and no increased risk of cerebrovascular events, vaginal bleeding, endometrial cancer and other gynaecological pathologies.[41] However, currently there are no RCTs available evaluating safety parameters such as serum estrogen levels or the risk of breast cancer recurrence within breast cancer survivors which would provide confirmation of previous observational findings.

The VIBRA pilot study determined that there were no severe adverse events recorded following the administration of 6.5 mg/d vaginal DHEA amongst breast cancer survivors.[42] Furthermore, no significant rise in serum estradiol levels was found at the 6 month assessment point.[42] However, these findings are to some extent different to the findings of Barton et al who found the higher 6.5 mg/d concentration of DHEA led to a significant increase in serum estradiol levels from baseline, and this was however not seen in those receiving the lower concentration 3.25 mg/d DHEA gel and not in those on AIs.[28] This was not determined to be due to a dose-dependent conversion of DHEA to systemic estradiol.[28] One possible explanation was stated to be due to normal variations in E2 levels between individuals; however, the reason why remains otherwise unknown.[21] This sub-group analysis is not possible within the VIBRA study as all the recruited patients' for the study had been taking AIs as per the inclusion criteria.[42] Furthermore, it is important to note that the dose of AI prescribed to women treated for breast cancer may not completely inhibit the aromatase in the body and breast tissue and some conversion of androgens or precursors to estrogen cannot be ruled out and cannot be entirely assessed through the measurement of serum E2 levels alone.[43]

Overall, we see a vital need for further study to determine changes in serum E2 and serum testosterone levels amongst patients' prescribed both the 3.25 mg/d and 6.5 mg/d concentration of DHEA gel over a much longer follow-up period and to determine if any associated rise in these hormone levels has any significant impact on breast cancer recurrence rates.

Limitations

A major limitation is the lack of literature published within this area. We found only three small RCTs which could be included in this review, and none of the interventions studied are currently the first-line most recommended medications for management of GSM in the UK (such as

10 mcg estrogen pessaries or 0.1% or 0.01% E3 creams). Another significant limitation of this review is that the follow-up duration of the studies included was short and therefore may not accurately assess the long-term safety of vaginal hormone modulator preparations. This is echoed by a recent review conducted by Merlino et al who assessed the therapeutic choices for GSM in breast cancer survivors. They also suggested that the current data available demonstrate that vaginal treatments are effective for the therapy of GSM in breast cancer survivors and however also emphasised the need for larger clinical trials with longer follow-ups in this group of women to address safety concerns.[44]

Cold et al demonstrate observational data that suggests a potential rise in breast cancer recurrence within a subgroup of patients receiving vaginal estrogen therapy with adjuvant AIs. Future RCTs will be vital in determining the safety of vaginal hormone treatments and in order to further qualify the risk within this sub-group of patients'.[15] In addition, Ospemifene, an approved selective estrogen receptor modulator for the management of GSM, was not assessed due to the lack of appropriate trials for this review.

Furthermore, the heterogenicity of interventions and formulations amongst the trials included within this assessment along with small sample sizes means that the trials may not be sufficiently powered to detect differences amongst these different treatments.

Clinical implications

Based on results from observational studies and other prospective and retrospective non-randomised studies, current clinical guidance is that vaginal estrogen preparations may be used for treatment of severe GSM in breast cancer survivors as second-line treatment option when lubricants or moisturisers have failed. It is recommended that such treatment be initiated in liaison with the oncology team and consideration should be given to switching from an AI to tamoxifen for endocrine therapy. Our review supports this approach based on the limited evidence obtained through the RCTs on this subject. Discussion of lack of evidence and long-term data and individualisation of benefits versus risks in relation to quality of life of women should be important components of clinical decision making.

Conclusions

Our review has determined that within the existing RCTs, no studies have aimed to specifically assess for breast cancer recurrence following the use of vaginal estrogens or hormone receptor modulators for treatment of GSM in breast cancer survivors. However, among current RCT studies observing for adverse effects of these preparations, none have reported an increased incidence of breast cancer recurrence. Additionally, none of the RCTs assessed within this review have reported a persistent increase in serum estrogen levels following the use of the vaginal estrogen products and no significant increase in serum estrogen levels following the use of low-concentration (3.25 mg/d) DHEA gel. Data reported amongst observational studies has identified a potential risk of recurrence amongst a subgroup of patients receiving vaginal estrogen therapy with adjuvant AIs, and therefore further RCTs using commonly used vaginal preparations with longer duration of follow-up and larger participant numbers are required to assess the risk of breast cancer recurrence in survivors receiving adjuvant treatments. Further trials assessing the risk of breast cancer recurrence in women taking approved selective estrogen receptor modulators for the management of GSM will also be vital in determining the safety of this therapy modality.

Practice points

The safety and the potential risk of breast cancer recurrence amongst breast cancer survivors using vaginal hormones and selective estrogen receptor modulators for the management of the genitourinary symptoms of menopause is currently debated.

Published data from randomised clinical trials shows that no studies have aimed to assess for breast cancer recurrence; however, among studies observing for serious adverse effects of vaginal estrogen, none have reported an increased incidence of recurrence. Furthermore, none of the studies have reported a significant increase in serum estrogen levels following the use of the vaginal estrogen and low-concentration DHEA gel.

Larger randomised trials studying approved vaginal hormone preparations and over a longer follow-up period will be vital to better assess the risk of breast cancer recurrence in survivors receiving these treatments.

Ethical approval

This study was deemed exempt by the University College London Research Ethics Committee under provision 'Research involving information freely available in the public domain' and therefore did not require ethical approval from the board prior to the conduction of the research.

Contributorship

IH and VST contributed to the conception and design of the article. IH performed the literature search and wrote the first draft of the review. IH and VST reviewed the drafts and approved the final version of the article.

Declaration of conflicting interests

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