National Institute for Health and Care Excellence

FINAL

Menopause (update)

[B2] Managing genitourinary symptoms – breast cancer recurrence

NICE guideline NG23

Evidence reviews underpinning recommendations 1.5.13 to 1.5.18 and research recommendations 5 in the NICE guideline

November 2024

FINAL

These evidence reviews were developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-6125-439

Contents

Managing genitourinary symptoms – breast cancer recurrence

Review question

Are treatments for managing genitourinary symptoms associated with the menopause safe for women with a personal history or high inherited risk of breast cancer?

Introduction

Genitourinary symptoms associated with menopause can be severe and debilitating, normally treated by localised vaginal oestrogens. For women with a personal history of breast cancer (including those on no adjuvant therapy, tamoxifen or aromatase inhibitors) a difficult decision has to be made due to uncertainty over whether localised vaginal oestrogens can increase the risk of breast cancer recurrence, leaving women with potentially less effective options for treatment.

Summary of the protocol

Table 1: Summary of the protocol (PICO table)

Population	Women with genitourinary symptoms associated with the menopause transition and a personal history of breast cancer or otherwise at high risk of developing breast cancer (for example *BRCA1/2* carriers)
Intervention	• Local oestrogen (different preparations will be considered) • Ospemifene • Prasterone • Transvaginal laser therapy
Comparison	• Placebo (this may include non-hormonal treatment, including moisturisers and lubricants) • Sham treatment • No treatment
Outcome	**Critical** • Incidence (or recurrence) of breast cancer **Important** • Incidence of ovarian cancer • Incidence of endometrial cancer

For further details see the review protocol in Appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document (Supplement 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Overall, 4 studies were included in this review, 1 prospective cohort study (Cold 2022) and 3 retrospective cohort studies (Dew 2003, Le Ray 2012 and O'Meara 2001).

All studies included women with a history of breast cancer and compared the use of vaginal oestrogens to no treatment.

The included studies are summarised in Table 2.

See the literature search strategy in Appendix B and study selection flow chart in Appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in Appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes
Cold 2022 Prospective cohort study Denmark	N=8328 women with breast cancer Age <65 years - number (%): Vaginal oestrogen therapy (VET): 1327 (68%) Never-users: 4047 (64%) Age ≥65 years - number (%): VET: 630 (32%) Never-users: 2297 (36%)	Vaginal oestrogen	No vaginal oestrogen	• Breast cancer recurrence
Dew 2003 Retrospective cohort study Australia	N=1472 women with breast cancer Age, mean (range): only reported by group rather than overall: • Vaginal oestrogen users: 53.8 (22-83) • All other participants: 55.6 (21-96)	Vaginal oestrogen	No vaginal oestrogen	• Breast cancer recurrence
Le Ray 2012	N=10933 women with breast cancer	Vaginal oestrogen	No vaginal oestrogen	• Breast cancer recurrence

Study	Population	Intervention	Comparison	Outcomes
Retrospective cohort study UK	Used tamoxifen or aromatase inhibitors Age, mean (SD) years: 63.1 (13.7)			
O' Meara 2001 Retrospective cohort study United States	N=869 women with breast cancer Age, mean (SD) years: NR (overall or by group)	Vaginal oestrogen	No vaginal oestrogen	• Breast cancer recurrence

NR: not reported; SD: standard deviation

See the full evidence tables in Appendix D and the forest plots in Appendix E.

Summary of the evidence

For this review outcomes have been judged for clinical importance based on statistical significance. Please see Supplement 1 for further details.

Vaginal oestrogen versus no treatment

Very low-quality evidence showed no important difference for breast cancer recurrence between vaginal oestrogen and no treatment in a population of women with a history of breast cancer, that used adjuvant treatment and those that did not. There was no evidence in people at high risk of developing breast cancer, for example due to genetic risk, but no previous history of breast cancer.

Very low-quality evidence, in a population of women not using adjuvant treatment for breast cancer, showed no important difference in the risk of breast cancer recurrence for those who used local vaginal oestrogens, and those that did not.

Low quality evidence showed no important difference in the risk of recurrence in women using local vaginal oestrogens if they were using tamoxifen therapy for breast cancer, compared to those that did not use local vaginal oestrogens. Low quality evidence from one study showed that for women taking aromatase inhibitors or aromatase inhibitors in sequence with tamoxifen, the use of local vaginal oestrogens increased the risk of breast cancer recurrence. However, there was very low-quality evidence showing no difference from a separate study between use of local vaginal oestrogens or not, in those women that used either tamoxifen or aromatase inhibitors for breast cancer.

All of the evidence was downgraded for risk of bias, mainly due to not enough information available on adherence to treatment, and some issues around controlling for confounders. There were also concerns around imprecision.

There was no evidence for the outcomes incidence of ovarian cancer, or incidence of endometrial cancer.

See Appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. See Supplement 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in Appendix J.

Summary of included economic evidence

No economic studies were identified which were applicable to this review question.

One UK economic evaluation was identified for evidence review B1 (Dymond 2021). This study compared ospemifene plus lubricant or moisturiser to lubricant or moisturiser alone to treat genitourinary symptoms associated with the menopause transition in women contraindicated for local oestrogen treatment. This contraindication included those for which local oestrogen treatment was not medically appropriate (including those with a history of breast cancer), was inconvenient or had previously been ineffective including because of adverse events. Although the population of the study did not match that required for inclusion in this evidence review this study was considered by the committee in forming recommendations.

The study took a UK NHS perspective and reported outcomes in terms of cost per QALY. It found ospemifene plus moisturiser/lubricant to be cost effective at a £20,000 per QALY threshold compared to moisturiser/lubricant alone. This conclusion was robust to alternative assumptions. The study was directly applicable with minor methodological limitations in respect to review question B1. Given the population of the study it is only partially applicable to this review question.

Dymond 2021 is summarised in full in evidence review B1.

Economic model

No economic modelling was undertaken for this review. An economic model of treatments for genitourinary symptoms associated with the menopause transition, which did not exclude the population considered by this review, was developed for evidence review B1. This model was used to influence recommendations made for this review. The model is reported in full in evidence review B1. Whilst the population for the economic model include this population group it is not exclusive to it and results from the model are therefore only partially applicable to this review question.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee chose the outcome incidence or recurrence of breast cancer as the critical outcome for this review. The committee agreed that women who experience genitourinary symptoms such as vaginal dryness with a history of breast cancer are faced with a difficult choice as to whether it is safe for them to use local vaginal oestrogens. Vaginal oestrogen is absorbed into the blood stream, but to a lesser degree than systemic oestrogen. Systemic

HRT is contraindicated because of absorption of oestrogen, and therefore the impact of vaginal oestrogen on breast cancer recurrence was considered particularly important.

The committee chose incidence of ovarian cancer and incidence of endometrial cancer as important outcomes for this review. The committee agreed that women with a history of breast cancer, or at an increased risk of developing breast cancer, may also have an increased risk of developing ovarian and endometrial cancer. They therefore wanted to consider the safety of using local vaginal oestrogens on the risk of developing these cancers, too.

The quality of the evidence

The quality of the evidence was assessed with GRADE and ranged from very low to low quality. All the evidence was downgraded for risk of bias. This was due to the studies not adjusting for all the appropriate confounders, such as BMI and age at menopause. There were also concerns around deviations from the intended intervention not being investigated or taken into consideration, as successful intervention implementation was based on the assumption that all those who received a prescription for local vaginal oestrogens did go on to use the treatment. The evidence was also downgraded for concerns around imprecision.

There was a lack of evidence on ospemifene, prasterone and transvaginal laser therapy, and no evidence was identified for the outcomes: incidence of ovarian cancer or incidence of endometrial cancer.

Benefits and harms

The committee discussed the evidence on local vaginal oestrogens and the risk of breast cancer recurrence and agreed that the limitations of the evidence would need to be carefully considered when making recommendations. The committee discussed that some of the evidence had been downgraded in quality due to a lack of adjustment for important confounders regarding the prognostic variables of breast cancer, which would have an impact on the risk of recurrence. There were some uncertainties around the effect size of outcomes with wide confidence intervals making results potentially consistent with no difference, a small increase or a small decrease in breast cancer recurrence. The committee also discussed the possibility of potential bias by indication, where clinicians may prescribe local vaginal oestrogens to people who were at a lower risk of breast cancer recurrence. Given these factors, along with the relatively short length of follow-up in some studies, the committee agreed to be cautious when making recommendations.

The committee discussed the evidence comparing vaginal oestrogen to no treatment in women with a history of breast cancer. Most of the evidence showed no difference in breast cancer recurrence between women who used and did not use local vaginal oestrogens on breast cancer recurrence. There was evidence that was stratified according to whether people had used adjuvant treatment or not, and this showed no difference in breast cancer recurrence between users and non-users of local vaginal oestrogens in a population of those not using adjuvant treatment. The committee discussed the concerns around imprecision for this evidence and the wide confidence intervals around the effect estimates. The committee also discussed some of the evidence on a combined population of women who had and had not used adjuvant treatment for breast cancer, that showed no difference in risk of recurrence when using local vaginal oestrogens. The committee discussed their concerns regarding the small sample sizes of the two studies that were driving this effect, which contributed to the uncertainty in the size of this effect. There were also concerns around insufficient information in relation to any adjuvant treatment from the study characteristics related to the groups of people receiving the intervention and comparison treatment. The committee agreed that the quality of the evidence meant they could not be confident around the safety of local vaginal oestrogens. They agreed on the importance of a discussion between the clinician and the person on all available treatments. The committee agreed that

they would make a recommendation that people should be given non-hormonal local options as a first line treatment of genitourinary symptoms, as the uncertainty around local vaginal oestrogen safety (in terms of effect size and evidence quality) may mean that this would be the option with the least risk.

The committee felt the evidence for local vaginal oestrogens was inconclusive in giving a clear direction of effect, therefore they decided that local vaginal oestrogens should be considered only when non-hormonal options have been ineffective, and the person is still troubled by the genitourinary symptoms. The committee were mindful that whilst there may be a small uncertain impact of local vaginal oestrogen on increased or decreased risk of breast cancer recurrence, it would need to be balanced against any reduction in quality of life due to the symptoms experienced. The committee noted that people may not realise that non-hormonal moisturisers and lubricants could also be used in combination with vaginal oestrogen, so they agreed to highlight this.

The committee discussed the evidence related to use of local vaginal oestrogens in those taking adjuvant treatment for breast cancer, specifically tamoxifen and aromatase inhibitors. The committee discussed the evidence for tamoxifen, which showed a possible reduction in the risk of breast cancer recurrence with local vaginal oestrogen use compared with no use, however this did not reach statistical significance. The committee acknowledged that this was unlikely to be a true effect of the local vaginal oestrogens, and more likely a result of adherence to treatment. They discussed that tamoxifen use is associated with fewer genitourinary symptoms due to the mechanism of action, compared with aromatase inhibitors and therefore may lead to a decreased adherence to vaginal oestrogen and increased adherence to tamoxifen treatment.

The committee went on to discuss the evidence around the risk of breast cancer recurrence with vaginal oestrogen in people who also use aromatase inhibitors as an adjunct treatment for their breast cancer. The committee discussed that the evidence available was for a combination of aromatase inhibitors used as an adjunct to breast cancer treatment either alone, or in sequence with tamoxifen. They acknowledged that there was no evidence for aromatase inhibitor use alone. The committee agreed that the mechanism of action of aromatase inhibitors which makes genitourinary symptoms more likely, could describe why the evidence suggested an increased risk of breast cancer recurrence seen in this combined (aromatase inhibitor and/or tamoxifen) group, and not in the tamoxifen only group which has a mechanism of action which makes genitourinary symptoms less likely. It is possible that this may have led to lower adherence related to the adjuvant aromatase inhibitor treatment which was then impacting on breast cancer recurrence rather than necessarily being a direct effect of vaginal oestrogen. However, they discussed that the number of women was much smaller in this group, and also noted the overall low quality of the evidence, and therefore agreed they could not reach a conclusion regarding the effect of local vaginal oestrogens on breast cancer recurrence risk in those using aromatase inhibitors.

The committee agreed that overall, they could not be confident in the evidence with regard to the safety of local vaginal oestrogens in those taking either tamoxifen or aromatase inhibitors as adjuvant therapy for breast cancer, due to the concerns around the quality of the evidence, and lack of data on aromatase inhibitor use only. However, using their expertise the committee agreed that when vaginal oestrogen is considered for people on aromatase inhibitors, advice from an oncology specialist should be sought about treatment options which could include switching from adjuvant treatment with aromatase inhibitors to tamoxifen may be an option for those who want to use local vaginal oestrogens. .

The committee discussed, based on experience, that treatment decisions including considerations related to safety of vaginal oestrogen would need to be tailored to each person. Some people have a lower risk of breast cancer recurrence than others (as covered by NICE's guideline on early and locally advanced breast cancer). The committee decided that this was an important factor because it is worse to potentially add to the risk of those

who already have a high risk than those who have a low risk of recurrence. They also noted that vaginal oestrogen is absorbed locally. Some of it is absorbed systemically, that is, further into the body, but, compared to systemic HRT, the amount is minimal, and so it may or may not be an amount that would affect breast cancer recurrence. This makes it difficult to assess the safety of vaginal oestrogen with respect to breast cancer recurrence.

In someone with an oestrogen-receptor negative breast cancer, oestrogen does not affect the growth of cancer cells, but in someone with an oestrogen-receptor positive breast cancer, it boosts it. The committee discussed that in someone with an oestrogen-receptor positive breast cancer taking adjuvant treatment if this treatment inhibits the production of oestrogen (in the ovaries or in fat or muscle tissues), it will have no effect on any oestrogen coming from a source outside the body, and this oestrogen would then be able to bind to cancer cells and stimulate their growth but if this treatment stops oestrogen from binding to oestrogen receptors (regardless of whether the oestrogen is produced by the body or absorbed from some treatment), it will stop oestrogen, regardless of source, from binding to receptors on cancer cells and so their growth will not be stimulated.

The committee acknowledged that the population in the evidence referred to people with a history of breast cancer rather than people at a high risk of breast cancer by being a carrier of a genetic variant associated with a higher breast cancer risk (such as *BRCA1/2*). They therefore could not comment on populations with a high inherited risk of breast cancer but noted that this population would be included in the analysis review question on the effectiveness of treatments for genitourinary symptoms and would be reported as a subgroup if relevant data were identified.

The committee agreed that the uncertainty within the evidence (and the relatively small amount of identified evidence) of the effects of vaginal oestrogen on breast cancer recurrence warranted a research recommendation which was formulated to address the gaps in the evidence (for details see Appendix K).

Cost effectiveness and resource use

The recommendations for this topic mirror current practice. There may be a small increase in the use of local oestrogens if women with a history of breast cancer decide on this treatment after non-hormonal approaches have been ineffective and possible risks discussed and considered. This would lead to an increase in resource use although economic evidence from the model for review question B1 strongly suggested that such treatments were cost effective when compared to non-hormonal moisturisers and lubricants.

Other factors the committee took into account

The committee discussed that the decision to use local vaginal oestrogens for the treatment of genitourinary symptoms, in those with a personal history of breast cancer, should be made together with the person and the healthcare professional. They agreed that the evidence needed to be considered together with each individual person's risk of recurrence, and that this discussion should be a shared decision. Therefore, they agreed to cross refer to the NICE guideline on shared decision making and the NICE guideline on early and locally advanced breast cancer.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.13 to 1.5.18 and research recommendations 5 on the impact of vaginal oestrogen on breast cancer recurrence in the NICE guideline.

The committee noted that there is 1 recommendation in the NICE guideline that is relevant to all women regardless of whether or not they have a history of breast cancer

(recommendations 1.5.17 – on vaginal laser treatment) but this was underpinned by evidence and discussions in evidence review B1 – managing genitourinary symptoms (network meta-analysis).

References – included studies

Effectiveness

Cold 2022

Cold, Soren; Cold, Frederik; Jensen, Maj-Britt; Cronin-Fenton, Deirdre; Christiansen, Peer; Ejlertsen, Bent; Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study.; Journal of the National Cancer Institute; 2022

Dew 2003

Dew, J E; Wren, B G; Eden, J A; A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer; Climacteric: the journal of the International Menopause Society; 2003; vol. 6 (no. 1); 45-

Le Ray 2012

Le Ray, Isabelle; Dell'Aniello, Sophie; Bonnetain, Franck; Azoulay, Laurent; Suissa, Samy; Local estrogen therapy and risk of breast cancer recurrence among; Breast Cancer Res. Treat.; 2012; vol. 135 (no. 2); 603-609

O’Meara 2001

O'Meara ES, Rossing MA, Daling JR et al. (2001) Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. Journal of the National Cancer Institute 93(10): 754-762

Economic

Dymond 2021

Dymond, A; Holmes, H; McMaster, J; Craig, J; Davies, H; Mealing, S. and Perard, R; 2021. Economic Evaluation of Senshio®(Ospemifene) for the Treatment of Vulvovaginal Atrophy in Scotland. Applied Health Economics and Health Policy, 19, pp.123-132.

Appendices

Appendix A Review protocols

Review protocol for review question: Are treatments for managing genitourinary symptoms associated with the menopause safe for women with a personal history or high inherited risk of breast cancer?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022356165
1.	Review title	Safety of treatments for genitourinary symptoms associated with the menopause in women with a personal history or high inherited risk of breast cancer
2.	Review question	Are treatments for managing genitourinary symptoms associated with the menopause safe for women with a personal history or high inherited risk of breast cancer?
3.	Objective	To determine if localised oestrogens, ospemifene, prasterone and transvaginal laser therapy are safe in treating genitourinary symptoms in women with a personal history or high inherited risk of breast cancer.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE, MEDLINE ePub Ahead-of-Print and MEDLINE-in-Process • Epistemonikos • INAHTA • HTA via CRD Searches will be restricted by: • No date limit • English language

ID	Field	Content
		• Human studies • RCTs and Systematic Reviews Conference abstracts will be excluded from the search results The committee will decide whether searches should be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Genitourinary symptoms associated with the menopause.
6.	Population	Inclusion: Women with genitourinary symptoms associated with the menopause transition and a personal history of breast cancer or otherwise at high risk of developing breast cancer (for example BRCA1/2 carriers) Exclusion:
7.	Intervention	• Local oestrogen (different preparations will be considered) • Ospemifene • Prasterone • Transvaginal laser therapy
8.	Comparator/Reference standard/Confounding factors	• Placebo (this may include non-hormonal treatment, including moisturisers and lubricants) • Sham treatment • No treatment
9.	Types of study to be included	Include published English language, full-text papers: • Systematic reviews of RCTs • RCTs • Systematic reviews of observational studies • Observational study designs where data on treatment use are collected at the time it was prescribed such as prospective cohort studies, nested case-control studies within prospective cohorts, and record linkage studies.

ID	Field	Content
10.	Other exclusion criteria	Conference abstracts will be excluded Observational studies will need to adjust for confounders Relevant confounders may include BMI, age at menopause, family history of breast cancer
11.	Context	
12.	Primary outcomes (critical outcomes)	• Incidence (or recurrence) of breast cancer
13.	Secondary outcomes (important outcomes)	• Incidence of ovarian cancer • Incidence of endometrial cancer
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • ROBINS-I for non-randomised, controlled/cohort studies

ID	Field	Content
		The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted, and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis, then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Minimally important differences: • All-cause mortality: statistical significance • Serious intervention-related adverse effects: statistical significance Validated scales/continuous outcomes: published MIDs where available All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes; +/- 0.5x control group SD for continuous outcomes How the evidence included in NG23 will be incorporated with the new evidence: Studies meeting the current protocol criteria and previously included in the NG23 will be included in this update. The methods for quantitative analysis (data extraction, risk of bias, strategy for data synthesis, and analysis of subgroups) will be the same as for the new evidence and as outlined in this protocol.
17.	Analysis of sub-groups	Evidence will be stratified by:

ID	Field	Content	
		• Women with a personal history of breast cancer • Women at high inherited risk of breast cancer (or other hormone driven cancer) • Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes: • Type of local oestrogen • Duration of treatment Groups identified in the equality considerations section of the scope: • Age • Disability • Ethnicity • Socioeconomic status • non-binary and trans-masculine people. Where evidence is stratified or sub-grouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	

ID	Field	Content		
21.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]		
22.	Anticipated completion date	[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Guideline Alliance		

ID	Field	Content
		5b Named contact e-mail menopause@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
25.	Review team members	Senior Systematic Reviewer Systematic Reviewer
26.	Funding sources/sponsor	This systematic review is being completed by NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022356165
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication

ID	Field	Content	
		publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords		
33.	Details of existing review of same topic by same authors		
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	
37.	Relevant studies	Lensen et al A, Wolfman W, Hickey M. A core outcome set for genitourinary symptoms associated with menopause: the COMMA (Core Outcomes in Menopause) global initiative. Menopause. 2021 May 10;28(8):859-866. Christmas MM,et al. International COMMA (Core OutcoMes in MenopAuse) Consortium. Variation in outcome reporting and measurement tools in clinical trials of treatments for genitourinary symptoms in peri- and postmenopausal women: a systematic review. Menopause. 2020 Sep;27(9):1070-1080.	

BMI: body mass index; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; INAHTA: International Network of Agencies For Health Technology Assessment; MID: minimally important difference; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation; SRDR: Systematic Review Data Repository

Appendix B Literature search strategies

Literature search strategies for review question: Are treatments for managing genitourinary symptoms associated with the menopause safe for women with a personal history or high inherited risk of breast cancer?

Clinical searches

Database: Ovid MEDLINE(R) ALL <1946 to August 25, 2022>

Date of last search: 26/08/2022

#	Searches	
1	Climacteric/	4933
2	Menopause/ or Perimenopause/ or Postmenopause/	56055
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	102613
4	("change of life" or life change?).tw.	3155
5	or/1-4	116772
6	exp "Neoplasms, Ductal, Lobular, and Medullary"/	44871
7	exp Breast Neoplasms/	330302
8	"Hereditary Breast and Ovarian Cancer Syndrome"/	391
9	((breast* or mammar*) adj4 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).tw.	407014
10	genes, brca1/ or genes, brca2/	6887
11	BRCA*.tw.	23836
12	or/6-11	495264
13	5 and 12	24046
14	Vagina/ or Vulva/	42258
15	Atrophy/	33690
16	Pruritus/ or Pruritus Vulvae/	13573
17	Dehydration/	14324
18	or/15-17	61529
19	14 and 18	985
20	exp Female Urogenital Diseases/	1264365
21	(vulvovagini* or vaginitis).tw.	4848
22	((vagina? or vulva? or vulvovaginal or vulvo-vaginal or urogenital or genitourinary or genito-urinary) adj4 (atroph* or dry* or prurit* or sore* or irrita* or itch* or inflam* or pain* or burn or dyspar?euni? or dysuri? or discharge? or discomfort* or uncomfortable* or erosion or eroded or thin*)).tw.	12093
23	VVA.tw.	458
24	(labia* adj4 (adhesi* or fus*)).tw.	408
25	((vagina? or vulvovagina* or vulvo-vagina* or urogenital or genitourinary or genito-urinary) adj4 (syndrome? or symptom? or indication? or issue? or problem? or condition?)).tw.	6230
26	GSM.tw.	1839
27	Dyspareunia/	2394
28	Sexual Dysfunction, Physiological/	10306
29	((sex* or intercourse) adj4 (pain* or discomfort* or bleed* or blood* or disorder* or function* or dysfunction* or uncomfortable* or alter* or chang* or differ* or reduc*)).tw.	163117
30	or/19-29	1427586
31	exp Estrogens/	167386
32	Estrogen Replacement Therapy/	15497
33	(estrogen* or oestrogen*).tw.	170442
34	Estradiol/ or Estriol/	88870
35	(estradiol or estriol or oestradiol or oestriol).tw.	101388
36	"Estrogens, Conjugated (USP)"/	3668
37	exp Selective Estrogen Receptor Modulators/	29233
38	(selective adj (oestrogen or estrogen) adj receptor? modulator?).tw.	3627

#	Searches	
39	SERM?.tw.	2354
40	or/31-39	302718
41	Administration, Intravaginal/ or Administration, Topical/	45447
42	"Vaginal Creams, Foams, and Jellies"/	1367
43	Gels/ or Pessaries/ or Suppositories/	36240
44	(local* or topical* or intravaginal* or intra-vaginal* or vaginal* or low-dose* or low-dosage*).tw.	1807763
45	(vagina* adj4 (cream? or gel? or pessar* or ring? or tablet? or capsule? or suppositor* or ovule?)).tw.	4476
46	vagitori*.tw.	14
47	or/41-46	1850615
48	40 and 47	29758
49	(gynest or "ortho-gynest" or ovestin or imvaggis or blissel or vagifem or vagirux or estring or vaginal ring? or femring or estrace or premarin).tw.	1733
50	Dienestrol/	187
51	Estrogens, Non-Steroidal/	3355
52	(dienestrol or synestrol or dienoestrol or oestrasid).tw.	328
53	(ospemifene or osphena or ophena or senshio).tw.	204
54	or/49-53	5649
55	exp Dehydroepiandrosterone/	12042
56	DHEA?.tw.	9191
57	(prasterone or dehydroepiandrosterone or dehydroisoandrosterone or androstenolone or dha sulfate or intrarosa).tw.	13058
58	or/55-57	18424
59	Lasers/ or Lasers, Gas/ or Lasers, Solid-State/	49082
60	Low-Level Light Therapy/ or Laser Therapy/	46622
61	((treatment* or device* or therap* or appl* or fractional or surg* or scapel* or carbon dioxide* or non-ablative or transvaginal* or endovaginal* or vagina* or procedure*) adj4 (laser* or lazer*)).tw.	53788
62	((CO2 or YAG or ER:YAG or erbium?) adj4 (laser? or lazer?)).tw.	14885
63	(SMARTXIDE* or IntimaLase* or RenovaLase* or Incontilase* or Fotana*).tw.	25
64	or/59-63	116839
65	48 or 54 or 58 or 64	168793
66	13 and 30 and 65	575
67	animals/ not humans/	5006171
68	exp Animals, Laboratory/	942883
69	exp Animal Experimentation/	10210
70	exp Rodentia/	3478292
71	exp Models, Animal/	632110
72	(rat or rats or mouse or mice).ti.	1409348
73	or/67-72	6042570
74	66 not 73	552
75	limit 74 to english language	521
76	Meta-Analysis/	166214
77	Meta-Analysis as Topic/	21633
78	(meta analy* or metanaly* or metaanaly*).ti,ab.	244037
79	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.	303294
80	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	51478
81	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	74162
82	(search* adj4 literature).ab.	88357
83	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	324392
84	cochrane.jw.	16087
85	or/76-84	608989
86	randomized controlled trial.pt.	575660
87	controlled clinical trial.pt.	95003
88	pragmatic clinical trial.pt.	2139
89	randomi#ed.ab.	685149

#	Searches	
90	placebo.ab.	231081
91	drug therapy.fs.	2523433
92	randomly.ab.	389837
93	trial.ab.	613747
94	groups.ab.	2398244
95	or/86-94	5461848
96	Clinical Trials as topic.sh.	200320
97	trial.ti.	269060
98	or/86-90,92,96-97	1512333
99	COMPARATIVE STUDIES/	1911493
100	FOLLOW-UP STUDIES/	686993
101	TIME FACTORS/	1228053
102	chang$.tw.	3526687
103	evaluat$.tw.	4126414
104	reviewed.tw.	600749
105	prospective$.tw.	820143
106	retrospective$.tw.	941542
107	baseline.tw.	675487
108	cohort.tw.	708074
109	case series.tw.	95335
110	or/99-109	10832353
111	85 or 98 or 110	11590207
112	75 and 111	358

Database: Embase <1974 to 2022 August 25>

Date of last search: 26/08/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8945
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	133877
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	148098
4	("change of life" or life change?).tw.	4249
5	or/1-4	183589
6	exp breast tumor/	605211
7	exp breast cancer/	529065
8	exp breast/ and exp neoplasm/	80849
9	((breast* or mammar*) adj4 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).tw.	571403
10	tumor suppressor gene/	77190
11	BRCA*.tw.	39497
12	or/6-11	789472
13	5 and 12	42033
14	vagina atrophy/	2833
15	vaginal dryness/	3367
16	female genital pruritus/ or vaginal pruritus/ or vulva pruritus/	1985
17	exp vaginitis/	16831
18	vagina bleeding/ or "vagina discharge (disease)"/ or vagina pain/ or vaginal burning sensation/ or vaginal discomfort/ or vaginal injury/ or vulvovaginal discomfort/	21450
19	genital system disease/ or genital bleeding/ or genital edema/ or genital injury/ or genital pain/ or genital pruritus/ or genital tract infection/ or genital tract inflammation/ or female genital tract inflammation/ or gynecologic disease/	23115
20	urogenital tract disease/ or urogenital tract inflammation/ or urogenital tract injury/ or urogenital tract infection/	12153

#	Searches	
21	(vulvovagini* or vaginitis).tw.	5512
22	((vagina? or vulva? or vulvovaginal or vulvo-vaginal or urogenital or genitourinary or genito-urinary) adj4 (atroph* or dry* or prurit* or sore* or irrita* or itch* or inflam* or pain* or burn or dyspar?euni? or dysuri? or discharge? or discomfort* or uncomfortable* or erosion or eroded or thin*)).tw.	18891
23	VVA.tw.	750
24	(labia* adj4 (adhesi* or fus*)).tw.	574
25	((vagina? or vulvovagina* or vulvo-vagina* or urogenital or genitourinary or genito-urinary) adj4 (syndrome? or symptom? or indication? or issue? or problem? or condition?)).tw.	9740
26	menopause related disorder/ or menopausal syndrome/	9688
27	GSM.tw.	2594
28	Dyspareunia/	11761
29	sexual dysfunction/ or female sexual dysfunction/	32289
30	((sex* or intercourse) adj4 (pain* or discomfort* or bleed* or blood* or disorder* or function* or dysfunction* or uncomfortable* or alter* or chang* or differ* or reduc*)).tw.	218152
31	or/14-30	333087
32	exp estrogen/	289502
33	estrogen therapy/	23208
34	(estrogen* or oestrogen*).tw.	210518
35	(estradiol or estriol or oestradiol or oestriol).tw.	119431
36	selective estrogen receptor modulator/	8437
37	(selective adj (oestrogen or estrogen) adj receptor? modulator?).tw.	4903
38	SERM?.tw.	3581
39	or/32-38	399640
40	intravaginal drug administration/ or topical drug administration/	90553
41	vagina ring/ or vagina pessary/	5479
42	agents used intravaginally/	335
43	(local* or topical* or intravaginal* or intra-vaginal* or vaginal* or low-dose* or low-dosage*).tw.	2307514
44	(vagina* adj4 (cream? or gel? or pessar* or ring? or tablet? or capsule? or suppositor* or ovule?)).tw.	6614
45	vagitori*.tw.	14
46	or/40-45	2352931
47	39 and 46	43442
48	(gynest or "ortho-gynest" or ovestin or imvaggis or blissel or vagifem or vagirux or estring or vaginal ring? or femring or estrace or premarin).tw.	5677
49	Dienestrol/	667
50	(dienestrol or synestrol or dienoestrol or oestrasid).tw.	273
51	(ospemifene or osphena or ophena or senshio).tw.	347
52	or/48-51	6660
53	prasterone/	15990
54	DHEA?.tw.	12833
55	(prasterone or dehydroepiandrosterone or dehydroisoandrosterone or androstenolone or dha sulfate or intrarosa).tw.	14793
56	or/53-55	24855
57	laser/ or carbon dioxide laser/ or gas laser/ or exp YAG laser/ or gynecologic laser/	112844
58	low level laser therapy/ or laser therapy/	28622
59	((treatment* or device* or therap* or appl* or fractional or surg* or scapel* or carbon dioxide* or non-ablative or transvaginal* or endovaginal* or vagina* or procedure*) adj4 (laser* or lazer*)).tw.	66633
60	((CO2 or YAG or ER:YAG or erbium?) adj4 (laser? or lazer?)).tw.	18557
61	(SMARTXIDE* or IntimaLase* or RenovaLase* or Incontilase* or Fotana*).tw.	63
62	or/57-61	168346
63	47 or 52 or 56 or 62	239860
64	13 and 31 and 63	1319
65	animal/ not human/	1160638
66	nonhuman/	7003428
67	exp Animal Experiment/	2884046
68	exp Experimental Animal/	773019
69	animal model/	1577656

#	Searches	
70	exp Rodent/	3857443
71	(rat or rats or mouse or mice).ti.	1558971
72	or/65-71	9156677
73	64 not 72	1149
74	limit 73 to english language	1086
75	(conference abstract or conference paper or conference proceeding or "conference review").pt.	5283868
76	74 not 75	814
77	systematic review/	365722
78	meta-analysis/	254627
79	(meta analy* or metanaly* or metaanaly*).ti,ab.	312253
80	((systematic or evidence) adj2 (review* or overview*)).ti,ab.	357582
81	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	62761
82	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	88776
83	(search* adj4 literature).ab.	111042
84	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	395085
85	((pool* or combined) adj2 (data or trials or studies or results)).ab.	85386
86	cochrane.jw.	23676
87	or/77-86	859468
88	random*.ti,ab.	1825197
89	factorial*.ti,ab.	44514
90	(crossover* or cross over*).ti,ab.	119482
91	((doubl* or singl*) adj blind*).ti,ab.	260254
92	(assign* or allocat* or volunteer* or placebo*).ti,ab.	1188143
93	crossover procedure/	71247
94	single blind procedure/	47264
95	randomized controlled trial/	724060
96	double blind procedure/	197891
97	or/88-96	2716833
98	CONTROLLED STUDY/	9033630
99	TREATMENT OUTCOME/	930829
100	MAJOR CLINICAL STUDY/	4575249
101	CLINICAL TRIAL/	1041898
102	evaluat$.tw.	5749614
103	reviewed.tw.	867195
104	baseline.tw.	1146412
105	(compare$ or compara$).tw.	6968932
106	or/98-105	18007715
107	87 or 97 or 106	18799550
108	76 and 107	596

Database: Cochrane Database of Systematic Reviews (CDSR) Issue 8 of 12, August 2022

Date of last search: 26/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	443
7	{or #1-#6}	28528
8	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees	679

#	Searches	
9	MeSH descriptor: [Breast Neoplasms] explode all trees	14709
10	MeSH descriptor: [Hereditary Breast and Ovarian Cancer Syndrome] this term only	29
11	((breast* or mammar*) near/4 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)):ti,ab	38673
12	MeSH descriptor: [Genes, BRCA1] this term only	98
13	MeSH descriptor: [Genes, BRCA2] this term only	82
14	BRCA*:ti,ab	1658
15	{or #8-#14}	40787
16	#7 and #15	6154
17	MeSH descriptor: [Vagina] this term only	1411
18	MeSH descriptor: [Vulva] this term only	111
19	#17 or #18	1462
20	MeSH descriptor: [Pruritus] this term only	1427
21	MeSH descriptor: [Pruritus Vulvae] this term only	9
22	MeSH descriptor: [Dehydration] this term only	593
23	{or #20-#22}	2028
24	#19 and #23	8
25	MeSH descriptor: [Female Urogenital Diseases] explode all trees	43972
26	(vulvovagini* or vaginitis):ti,ab	782
27	((vagina? or vulva? or vulvovaginal or vulvo-vaginal or urogenital or genitourinary or genito-urinary) near/4 (atroph* or dry* or prurit* or sore* or irrita* or itch* or inflam* or pain* or burn or dyspareuni? or dysuri? or discharge? or discomfort* or uncomfortable* or erosion or eroded or thin*)):ti,ab	2663
28	(VVA):ti,ab	175
29	(labia* near/4 (adhesi* or fus*)):ti,ab	8
30	((vagina? or vulvovagina* or vulvo-vagina* or urogenital or genitourinary or genito-urinary) near/4 (syndrome? or symptom? or indication? or issue? or problem? or condition?)):ti,ab	1855
31	(GSM):ti,ab	213
32	MeSH descriptor: [Dyspareunia] this term only	227
33	MeSH descriptor: [Sexual Dysfunction, Physiological] this term only	525
34	((sex* or intercourse) near/4 (pain* or discomfort* or bleed* or blood* or disorder* or function* or dysfunction* or uncomfortable* or alter* or chang* or differ* or reduc*)):ti,ab	13862
35	{or #24-#34}	60093
36	MeSH descriptor: [Estrogens] explode all trees	1954
37	MeSH descriptor: [Estrogen Replacement Therapy] this term only	2124
38	(estrogen* or oestrogen*):ti,ab	12608
39	MeSH descriptor: [Estradiol] this term only	4455
40	MeSH descriptor: [Estriol] this term only	222
41	(estradiol or estriol or oestradiol or oestriol):ti,ab	9690
42	MeSH descriptor: [Estrogens, Conjugated (USP)] this term only	1017
43	MeSH descriptor: [Selective Estrogen Receptor Modulators] explode all trees	415
44	(selective near (oestrogen or estrogen) near receptor? modulator?):ti,ab	530
45	SERM?:ti,ab	311
46	{or #36-#45}	20708
47	MeSH descriptor: [Administration, Intravaginal] this term only	1523
48	MeSH descriptor: [Administration, Topical] this term only	6570
49	MeSH descriptor: [Vaginal Creams, Foams, and Jellies] this term only	419
50	MeSH descriptor: [Gels] this term only	2419
51	MeSH descriptor: [Pessaries] this term only	207
52	MeSH descriptor: [Suppositories] this term only	620
53	(local* or topical* or intravaginal* or intra-vaginal* or vaginal* or low-dose* or low-dosage*):ti,ab	161127
54	(vagina* near/4 (cream? or gel? or pessar* or ring? or tablet? or capsule? or suppositor* or ovule?)):ti,ab	3253
55	vagitori*:ti,ab	8
56	{or #47-#55}	164415
57	#46 and #56	4526

#	Searches	
58	(gynest or "ortho-gynest" or ovestin or imvaggis or blissel or vagifem or vagirux or estring or vaginal ring? or femring or estrace or premarin):ti,ab	970
59	MeSH descriptor: [Dienestrol] this term only	4
60	MeSH descriptor: [Estrogens, Non-Steroidal] this term only	71
61	(dienestrol or synestrol or dienoestrol or oestrasid):ti,ab	4
62	(ospemifene or osphena or ophena or senshio):ti,ab	85
63	{or #58-#62}	1131
64	MeSH descriptor: [Dehydroepiandrosterone] explode all trees	701
65	(DHEA?):ti,ab	1300
66	(prasterone or dehydroepiandrosterone or dehydroisoandrosterone or androstenolone or dha sulfate or intrarosa):ti,ab	1209
67	{or #64-#66}	1790
68	MeSH descriptor: [Lasers] this term only	687
69	MeSH descriptor: [Lasers, Gas] this term only	294
70	MeSH descriptor: [Lasers, Solid-State] this term only	763
71	MeSH descriptor: [Low-Level Light Therapy] this term only	1162
72	MeSH descriptor: [Laser Therapy] this term only	2153
73	((treatment* or device* or therap* or appl* or fractional or surg* or scapel* or carbon dioxide* or non-ablative or transvaginal* or endovaginal* or vagina* or procedure*) near/4 (laser* or lazer*)):ti,ab	9740
74	((CO2 or YAG or ER?YAG or erbium?) near/4 (laser? or lazer?)):ti,ab	2821
75	(SMARTXIDE* or IntimaLase* or RenovaLase* or Incontilase* or Fotana*):ti,ab	20
76	{or #68-#75}	12140
77	#57 or #63 or #67 or #76	19031
78	#16 and #35 and #77	119
79	"conference":pt or (clinicaltrials or trialsearch):so	608941
80	#78 not #79 in Cochrane Reviews	8

Database: Cochrane Central Register of Controlled Trials (CENTRAL) Issue 7 of 12, July 2022

Date of last search: 26/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	443
7	{or #1-#6}	28528
8	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees	679
9	MeSH descriptor: [Breast Neoplasms] explode all trees	14709
10	MeSH descriptor: [Hereditary Breast and Ovarian Cancer Syndrome] this term only	29
11	((breast* or mammar*) near/4 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)):ti,ab	38673
12	MeSH descriptor: [Genes, BRCA1] this term only	98
13	MeSH descriptor: [Genes, BRCA2] this term only	82
14	BRCA*:ti,ab	1658
15	{or #8-#14}	40787
16	#7 and #15	6154
17	MeSH descriptor: [Vagina] this term only	1411
18	MeSH descriptor: [Vulva] this term only	111
19	#17 or #18	1462
20	MeSH descriptor: [Pruritus] this term only	1427

#	Searches	
21	MeSH descriptor: [Pruritus Vulvae] this term only	9
22	MeSH descriptor: [Dehydration] this term only	593
23	{or #20-#22}	2028
24	#19 and #23	8
25	MeSH descriptor: [Female Urogenital Diseases] explode all trees	43972
26	(vulvovagini* or vaginitis):ti,ab	782
27	((vagina? or vulva? or vulvovaginal or vulvo-vaginal or urogenital or genitourinary or genito-urinary) near/4 (atroph* or dry* or prurit* or sore* or irrita* or itch* or inflam* or pain* or burn or dyspareuni? or dysuri? or discharge? or discomfort* or uncomfortable* or erosion or eroded or thin*)):ti,ab	2663
28	(VVA):ti,ab	175
29	(labia* near/4 (adhesi* or fus*)):ti,ab	8
30	((vagina? or vulvovagina* or vulvo-vagina* or urogenital or genitourinary or genito-urinary) near/4 (syndrome? or symptom? or indication? or issue? or problem? or condition?)):ti,ab	1855
31	(GSM):ti,ab	213
32	MeSH descriptor: [Dyspareunia] this term only	227
33	MeSH descriptor: [Sexual Dysfunction, Physiological] this term only	525
34	((sex* or intercourse) near/4 (pain* or discomfort* or bleed* or blood* or disorder* or function* or dysfunction* or uncomfortable* or alter* or chang* or differ* or reduc*)):ti,ab	13862
35	{or #24-#34}	60093
36	MeSH descriptor: [Estrogens] explode all trees	1954
37	MeSH descriptor: [Estrogen Replacement Therapy] this term only	2124
38	(estrogen* or oestrogen*):ti,ab	12608
39	MeSH descriptor: [Estradiol] this term only	4455
40	MeSH descriptor: [Estriol] this term only	222
41	(estradiol or estriol or oestradiol or oestriol):ti,ab	9690
42	MeSH descriptor: [Estrogens, Conjugated (USP)] this term only	1017
43	MeSH descriptor: [Selective Estrogen Receptor Modulators] explode all trees	415
44	(selective near (oestrogen or estrogen) near receptor? modulator?):ti,ab	530
45	SERM?:ti,ab	311
46	{or #36-#45}	20708
47	MeSH descriptor: [Administration, Intravaginal] this term only	1523
48	MeSH descriptor: [Administration, Topical] this term only	6570
49	MeSH descriptor: [Vaginal Creams, Foams, and Jellies] this term only	419
50	MeSH descriptor: [Gels] this term only	2419
51	MeSH descriptor: [Pessaries] this term only	207
52	MeSH descriptor: [Suppositories] this term only	620
53	(local* or topical* or intravaginal* or intra-vaginal* or vaginal* or low-dose* or low-dosage*):ti,ab	161127
54	(vagina* near/4 (cream? or gel? or pessar* or ring? or tablet? or capsule? or suppositor* or ovule?)):ti,ab	3253
55	vagitori*:ti,ab	8
56	{or #47-#55}	164415
57	#46 and #56	4526
58	(gynest or "ortho-gynest" or ovestin or imvaggis or blissel or vagifem or vagirux or estring or vaginal ring? or femring or estrace or premarin):ti,ab	970
59	MeSH descriptor: [Dienestrol] this term only	4
60	MeSH descriptor: [Estrogens, Non-Steroidal] this term only	71
61	(dienestrol or synestrol or dienoestrol or oestrasid):ti,ab	4
62	(ospemifene or osphena or ophena or senshio):ti,ab	85
63	{or #58-#62}	1131
64	MeSH descriptor: [Dehydroepiandrosterone] explode all trees	701
65	(DHEA?):ti,ab	1300
66	(prasterone or dehydroepiandrosterone or dehydroisoandrosterone or androstenolone or dha sulfate or intrarosa):ti,ab	1209
67	{or #64-#66}	1790
68	MeSH descriptor: [Lasers] this term only	687
69	MeSH descriptor: [Lasers, Gas] this term only	294

#	Searches	
70	MeSH descriptor: [Lasers, Solid-State] this term only	763
71	MeSH descriptor: [Low-Level Light Therapy] this term only	1162
72	MeSH descriptor: [Laser Therapy] this term only	2153
73	((treatment* or device* or therap* or appl* or fractional or surg* or scapel* or carbon dioxide* or non-ablative or transvaginal* or endovaginal* or vagina* or procedure*) near/4 (laser* or lazer*)):ti,ab	9740
74	((CO2 or YAG or ER?YAG or erbium?) near/4 (laser? or lazer?)):ti,ab	2821
75	(SMARTXIDE* or IntimaLase* or RenovaLase* or Incontilase* or Fotana*):ti,ab	20
76	{or #68-#75}	12140
77	#57 or #63 or #67 or #76	19031
78	#16 and #35 and #77	119
79	"conference":pt or (clinicaltrials or trialsearch):so	608941
80	#78 not #79 in Trials	49

Database: CRD HTA

Date of last search: 26/08/2022

#	Searches	
1	MeSH DESCRIPTOR climacteric	9
2	MeSH DESCRIPTOR menopause	117
3	MeSH DESCRIPTOR perimenopause	7
4	MeSH DESCRIPTOR postmenopause	209
5	((menopau* or postmenopau* or perimenopau* or climacteri*))	957
6	(("change of life" or "life change" or "life changes"))	38
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	994
8	MeSH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES	65
9	MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES	1798
10	MeSH DESCRIPTOR Hereditary Breast and Ovarian Cancer Syndrome	0
11	((breast* or mammar*) AND (cancer* or neoplas* or carcino* or malignan* or tumour* or tumor* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*))	2497
12	MeSH DESCRIPTOR genes, brca1	44
13	MeSH DESCRIPTOR genes, brca2	31
14	(BRCA*)	93
15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	2532
16	#7 AND #15	270
17	MeSH DESCRIPTOR vagina	83
18	MeSH DESCRIPTOR vulva	6
19	MeSH DESCRIPTOR Atrophy	17
20	MeSH DESCRIPTOR Pruritus	34
21	MeSH DESCRIPTOR Pruritus Vulvae	0
22	MeSH DESCRIPTOR Dehydration	19
23	#17 OR #18	87
24	#19 OR #20 OR #21 OR #22	70
25	#23 AND #24	1
26	MeSH DESCRIPTOR Female Urogenital Diseases EXPLODE ALL TREES	4650
27	((vulvovagini* or vaginitis))	31
28	(((vagina* or vulva* or vulvovaginal or (vulvo-vaginal) or urogenital or genitourinary or (genito-urinary)) AND (atroph* or dry* or prurit* or sore* or irrita* or itch* or inflam* or pain* or burn or dyspareunia or dysuria or discharge* or discomfort* or uncomfortable* or erosion or eroded or thin*)))	334
29	(VVA)	0
30	((labia* AND (adhesi* or fus*)))	1
31	(((vagina* or vulvovagina* or (vulvo-vagina*) or urogenital or genitourinary or (genito-urinary)) AND (syndrome* or symptom* or indication* or issue* or problem* or condition*)))	723
32	(GSM)	2

#	Searches	
33	(((sex* or intercourse) AND (pain* or discomfort* or bleed* or blood* or disorder* or function* or dysfunction* or uncomfortable* or alter* or chang* or differ* or reduc*)))	2053
34	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	6795
35	#16 AND #34	38
36	(#16 AND #34) IN HTA	6

Database: INAHTA

Date of last search: 26/08/2022

#	Searches	
1	"Climacteric"[mh] or "Menopause"[mh] or "Perimenopause"[mh] or "Postmenopause"[mh]	56
2	(menopau* or postmenopau* or perimenopau* or climacteri*)	159
3	("change of life" or "life change" or "life changes")	1
4	#3 OR #2 OR #1	163
5	"Neoplasms, Ductal, Lobular, and Medullary"[mhe]	14
6	"Breast Neoplasms"[mhe]	563
7	"Hereditary Breast and Ovarian Cancer Syndrome"[mh]	0
8	((breast* or mammar*) AND (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)	728
9	"Genes, BRCA1"[mh] or "Genes, BRCA2"[mh]	14
10	BRCA*	39
11	#10 OR #9 OR #8 OR #7 OR #6 OR #5	789
12	#11 AND #4	92
13	"Vagina"[mh] or "Vulva"[mh]	17
14	"Atrophy"[mh]	16
15	"Pruritus"[mh] or "Pruritus Vulvae"[mh]	0
16	"Dehydration"[mh]	2
17	#16 OR #15 OR #14	18
18	#17 AND #13	0
19	"Female Urogenital Diseases"[mhe] or "Dyspareunia"[mh] or "Sexual Dysfunction, Physiological"[mh]	1144
20	(vulvovagini* or vaginitis)	1
21	((vagina* or vulva* or vulvovaginal or vulvo-vaginal or urogenital or genitourinary or genito-urinary) AND (atroph* or dry* or prurit* or sore* or irrita* or itch* or inflam* or pain* or burn or dyspareunia or dysuria or discharge* or discomfort* or uncomfortable* or erosion or eroded or thin*))	66
22	VVA	0
23	(labia* AND (adhesi* or fus*))	0
24	((vagina* or vulvovagina* or vulvo-vagina* or urogenital or genitourinary or genito-urinary) AND (syndrome* or symptom* or indication* or issue* or problem* or condition*))	167
25	GSM	0
26	((sex* or intercourse) AND (pain* or discomfort* or bleed* or blood* or disorder* or function* or dysfunction* or uncomfortable* or alter* or chang* or differ* or reduc*))	188
27	#26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18	1367
28	#27 AND #12	92
29	Limit to English language	73

Database: Epistemonikos

Date of last search: 26/08/2022

#	Searches	
1	((menopau* OR postmenopau* OR perimenopau* OR climacteri* OR "change of life" OR "life change" OR "life changes") AND ((breast* OR mammar*) AND (cancer* OR neoplas* OR carcino* OR malignan* OR tumor* OR tumour* OR adenocarcinoma* OR sarcoma* OR angiosarcoma* OR lymphoma* OR leiomyosarcoma* OR dcis OR ductal OR infiltrat* OR intraductal* OR lobular OR medullary OR metasta*) OR BRCA*))	

#	Searches	
2	((vulvovagin* OR vaginitis OR VVA OR GSM OR (labia* AND (adhesi* or fus*))) OR ((vagina* OR vulva* OR (vulvo-vagina*) OR urogenital or genitourinary OR (genito-urinary)) AND (atroph* OR dry* OR prurit* OR sore* OR irrita* OR itch* OR inflam* OR pain* OR burn OR dyspareunia OR dysuria OR discharge* OR discomfort* OR uncomfortable* OR erosion OR eroded OR thin* OR syndrome* OR symptom* OR indication* OR issue* OR problem* OR condition*)) OR ((sex* OR intercourse) AND (pain* OR discomfort* OR bleed* OR blood* OR disorder* OR function* OR dysfunction* OR uncomfortable* OR alter* OR chang* OR differ* OR reduc*)))	
3	((estrogen* OR oestrogen* OR estradiol OR estriol OR oestradiol OR oestriol OR SERM* OR vagitori* OR gynest OR "ortho-gynest" or ovestin OR imvaggis OR blissel OR vagifem OR vagirux OR estring OR "vaginal ring" OR "vaginal rings" OR femring OR estrace OR premarin OR dienestrol OR synestrol OR dienoestrol OR oestrasid OR ospemifene OR osphena OR ophena OR senshio) OR (vagina* AND (cream* OR gel* OR pessar* OR ring* OR tablet* OR capsule* OR suppositor* OR ovule*)) OR (prasterone OR dehydroepiandrosterone OR dehydroisoandrosterone OR androstenolone OR (dha sulfate) OR intrarosa OR DHEA OR SMARTXIDE* OR IntimaLase* OR RenovaLase* OR Incontilase* OR Fotana*) OR ((treatment* OR device* OR therap* OR appl* OR fractional OR surg* OR scapel* OR (carbon dioxide*) OR (non-ablative) OR transvaginal* OR endovaginal* OR vagina* OR procedure* OR CO2 OR ERYAG OR "ER YAG" OR erbium*) AND (laser* OR lazer*)))	
4	1 AND 2 AND 3	261

Economic searches

Database: Ovid MEDLINE(R) ALL <1946 to July 27, 2022>

Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	4935
2	Menopause/ or Perimenopause/ or Postmenopause/	55972
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	102310
4	("change of life" or life change?).tw.	3141
5	or/1-4	116452
6	limit 5 to english language	103660
7	limit 6 to yr="2012 -Current"	41579
8	letter/	1188475
9	editorial/	613156
10	news/	213557
11	exp historical article/	408665
12	Anecdotes as Topic/	4746
13	comment/	973045
14	case report/	2282504
15	(letter or comment*).ti.	179095
16	or/8-15	4782431
17	randomized controlled trial/ or random*.ti,ab.	1466248
18	16 not 17	4751747
19	animals/ not humans/	4997958
20	exp Animals, Laboratory/	942090
21	exp Animal Experimentation/	10205
22	exp Models, Animal/	631246
23	exp Rodentia/	3472512
24	(rat or rats or mouse or mice).ti.	1407073
25	or/18-24	10620565
26	7 not 25	34368
27	Economics/	27455
28	Value of life/	5793
29	exp "Costs and Cost Analysis"/	259348
30	exp Economics, Hospital/	25612
31	exp Economics, Medical/	14359

#	Searches	
32	Economics, Nursing/	4013
33	Economics, Pharmaceutical/	3074
34	exp "Fees and Charges"/	31172
35	exp Budgets/	14034
36	budget*.ti,ab.	33535
37	cost*.ti.	136425
38	(economic* or pharmaco?economic*).ti.	56592
39	(price* or pricing*).ti,ab.	48567
40	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	191586
41	(financ* or fee or fees).ti,ab.	145674
42	(value adj2 (money or monetary)).ti,ab.	2817
43	or/27-42	689907
44	exp models, economic/	16130
45	*Models, Theoretical/	64214
46	*Models, Organizational/	6490
47	markov chains/	15758
48	monte carlo method/	31445
49	exp Decision Theory/	12940
50	(markov* or monte carlo).ti,ab.	79077
51	econom* model*.ti,ab.	4760
52	(decision* adj2 (tree* or analy* or model*)).ti,ab.	31806
53	or/44-52	210296
54	43 or 53	865352
55	26 and 54	849

Database: Embase <1974 to 2022 July 27>

Date of last search: 28/07/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8930
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	133601
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	147803
4	("change of life" or life change?).tw.	4239
5	or/1-4	183218
6	limit 5 to english language	163179
7	limit 6 to yr="2012 -Current"	81270
8	letter.pt. or letter/	1241876
9	note.pt.	901797
10	editorial.pt.	733613
11	case report/ or case study/	2836641
12	(letter or comment*).ti.	224206
13	or/8-12	5462442
14	randomized controlled trial/ or random*.ti,ab.	1928915
15	13 not 14	5407726
16	animal/ not human/	1159758
17	nonhuman/	6983755
18	exp Animal Experiment/	2874637
19	exp Experimental Animal/	770091
20	animal model/	1570755
21	exp Rodent/	3850325
22	(rat or rats or mouse or mice).ti.	1557060
23	or/15-22	14181910
24	7 not 23	61890

#	Searches	
25	health economics/	34559
26	exp economic evaluation/	337213
27	exp health care cost/	322230
28	exp fee/	42496
29	budget/	32003
30	funding/	67739
31	budget*.ti,ab.	44183
32	cost*.ti.	181970
33	(economic* or pharmaco?economic*).ti.	70774
34	(price* or pricing*).ti,ab.	67140
35	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	264737
36	(financ* or fee or fees).ti,ab.	200470
37	(value adj2 (money or monetary)).ti,ab.	3792
38	or/25-37	1085390
39	statistical model/	171255
40	exp economic aspect/	2251504
41	39 and 40	27469
42	*theoretical model/	30994
43	*nonbiological model/	5065
44	stochastic model/	19388
45	decision theory/	1802
46	decision tree/	18095
47	monte carlo method/	46995
48	(markov* or monte carlo).ti,ab.	87061
49	econom* model*.ti,ab.	7134
50	(decision* adj2 (tree* or analy* or model*)).ti,ab.	43807
51	or/41-50	225433
52	38 or 51	1266430
53	24 and 52	2248

Database: Cochrane Database of Systematic Reviews (CDSR) Issue 7 of 12, July 2022

Date of last search: 01/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	444
7	{or #1-#6}	28529
8	MeSH descriptor: [Economics] this term only	45
9	MeSH descriptor: [Value of Life] this term only	32
10	MeSH descriptor: [Costs and Cost Analysis] explode all trees	11515
11	MeSH descriptor: [Economics, Hospital] explode all trees	736
12	MeSH descriptor: [Economics, Medical] explode all trees	62
13	MeSH descriptor: [Economics, Nursing] explode all trees	13
14	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65
15	MeSH descriptor: [Fees and Charges] explode all trees	259
16	MeSH descriptor: [Budgets] explode all trees	32
17	budget*:ti,ab	1284
18	cost*:ti,ab	75603
19	(economic* or pharmaco?economic*):ti,ab	21792

#	Searches	
20	(price* or pricing*):ti,ab	2632
21	(financ* or fee or fees or expenditure* or saving*):ti,ab	22897
22	(value near/2 (money or monetary)):ti,ab	347
23	resourc* allocat*:ti,ab	4633
24	(fund or funds or funding* or funded):ti,ab	20420
25	(ration or rations or rationing* or rationed):ti,ab	713
26	{or #8-#25}	120278
27	MeSH descriptor: [Models, Economic] explode all trees	371
28	MeSH descriptor: [Models, Theoretical] this term only	744
29	MeSH descriptor: [Models, Organizational] this term only	180
30	MeSH descriptor: [Markov Chains] this term only	288
31	MeSH descriptor: [Monte Carlo Method] this term only	203
32	MeSH descriptor: [Decision Theory] explode all trees	174
33	(markov* or monte carlo):ti,ab	2214
34	econom* model*:ti,ab	7061
35	(decision* near/2 (tree* or analy* or model*)):ti,ab	2140
36	{or #27-#35}	11044
37	#26 or #36	123649
38	#7 and #37	1179
39	#7 and #37 with Cochrane Library publication date Between Jan 2012 and Aug 2022, in Cochrane Reviews	37

Database: Cochrane Central Register of Controlled Trials (CENTRAL) Issue 7 of 12, July 2022

Date of last search: 01/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	444
7	{or #1-#6}	28529
8	MeSH descriptor: [Economics] this term only	45
9	MeSH descriptor: [Value of Life] this term only	32
10	MeSH descriptor: [Costs and Cost Analysis] explode all trees	11515
11	MeSH descriptor: [Economics, Hospital] explode all trees	736
12	MeSH descriptor: [Economics, Medical] explode all trees	62
13	MeSH descriptor: [Economics, Nursing] explode all trees	13
14	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65
15	MeSH descriptor: [Fees and Charges] explode all trees	259
16	MeSH descriptor: [Budgets] explode all trees	32
17	budget*:ti,ab	1284
18	cost*:ti,ab	75603
19	(economic* or pharmaco?economic*):ti,ab	21792
20	(price* or pricing*):ti,ab	2632
21	(financ* or fee or fees or expenditure* or saving*):ti,ab	22897
22	(value near/2 (money or monetary)):ti,ab	347
23	resourc* allocat*:ti,ab	4633
24	(fund or funds or funding* or funded):ti,ab	20420
25	(ration or rations or rationing* or rationed):ti,ab	713
26	{or #8-#25}	120278

#	Searches	
27	MeSH descriptor: [Models, Economic] explode all trees	371
28	MeSH descriptor: [Models, Theoretical] this term only	744
29	MeSH descriptor: [Models, Organizational] this term only	180
30	MeSH descriptor: [Markov Chains] this term only	288
31	MeSH descriptor: [Monte Carlo Method] this term only	203
32	MeSH descriptor: [Decision Theory] explode all trees	174
33	(markov* or monte carlo):ti,ab	2214
34	econom* model*:ti,ab	7061
35	(decision* near/2 (tree* or analy* or model*)):ti,ab	2140
36	{or #27-#35}	11044
37	#26 or #36	123649
38	#7 and #37	1179
39	"conference":pt or (clinicaltrials or trialsearch):so	608941
40	#38 not #39 with Publication Year from 2012 to 2022, in Trials	326

Database: EconLit <1886 to July 21, 2022>

Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	0
2	Menopause/ or Perimenopause/ or Postmenopause/ or exp Menopause Related Disorder/	0
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	70
4	("change of life" or life change?).tw.	92
5	or/1-4	162
6	limit 5 to yr="2012 -Current"	69

Database: CRD HTA

Date of last search: 28/07/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR postmenopause	209
5	(((menopau* or postmenopau* or perimenopau* or climacteri*)))	957
6	((("change of life" or "life change" or "life changes")))	38
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6) IN HTA FROM 2012 TO 2022	42

Database: INAHTA

Date of last search: 28/07/2022

#	Searches	
1	"Climacteric"[mh]	2
2	"Menopause"[mh]	28
3	"Perimenopause"[mh]	1
4	"Postmenopause"[mh]	31
5	(menopau* or postmenopau* or perimenopau* or climacteri*)	159
6	("change of life" or "life change" or "life changes")	1
7	#6 OR #5 OR #4 OR #3 OR #2 OR #1	163
8	Limit to English Language	134

Database: EED

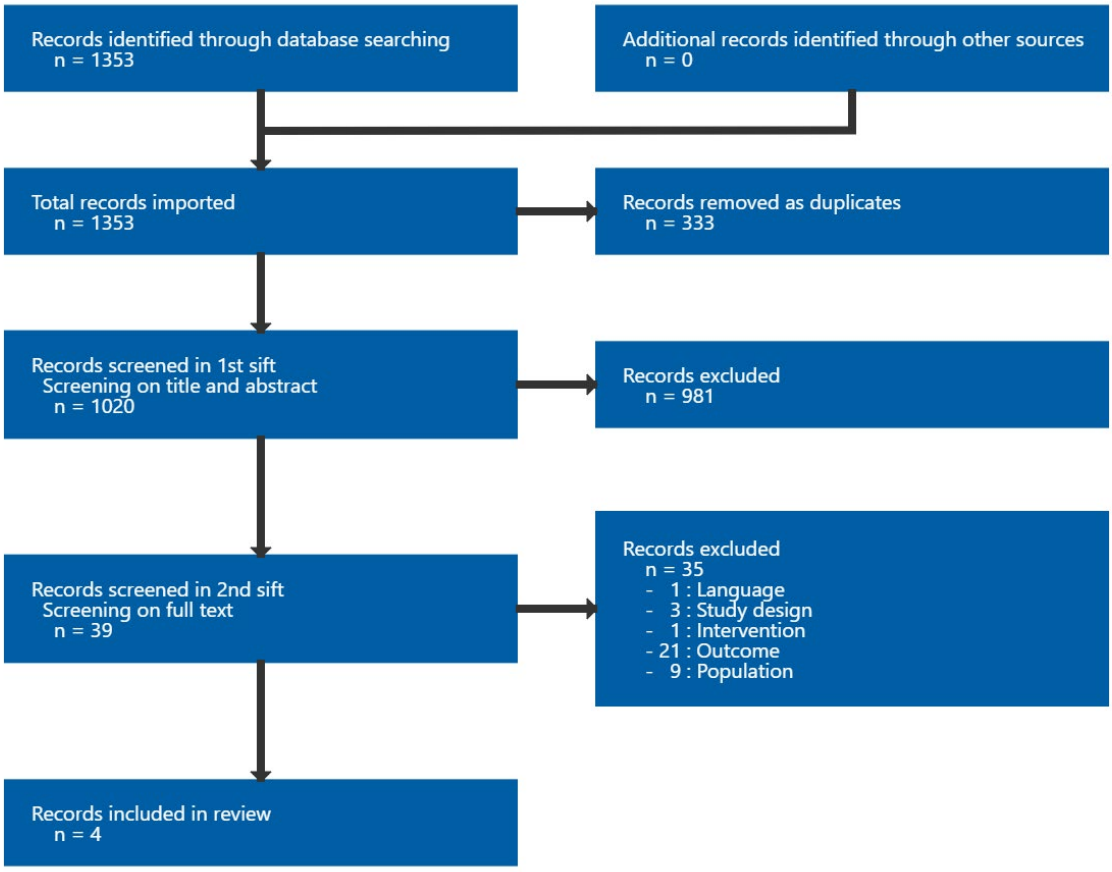
Date of last search: 28/07/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR postmenopause	209
5	(((menopau* or postmenopau* or perimenopau* or climacteri*)))	957
6	((("change of life" or "life change" or "life changes")))	38
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6) IN NHSEED FROM 2012 TO 2022	33

Appendix C Effectiveness evidence study selection

Study selection for: Are treatments for managing genitourinary symptoms associated with the menopause safe for women with a personal history or high inherited risk of breast cancer?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: Are treatments for managing genitourinary symptoms associated with the menopause safe for women with a personal history or high inherited risk of breast cancer?

Table 4: Evidence tables

Cold, 2022

Bibliographic Reference	Cold, Soren; Cold, Frederik; Jensen, Maj-Britt; Cronin-Fenton, Deirdre; Christiansen, Peer; Ejlertsen, Bent; Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study.; Journal of the National Cancer Institute; 2022

Study details

Country/ies where study was carried out	Denmark
Study type	Prospective cohort study
Study dates	January 1997 to December 2004
Inclusion criteria	• Postmenopausal women aged 35-95 • diagnosed with invasive early stage nonmetastatic, oestrogen receptor positive breast cancer • diagnosed between 1997 to 2004 • did not receive chemotherapy • all women were allocated either to 5 years of tamoxifen, an aromatase inhibitor, or both treatments in sequence, or to no endocrine treatment
Exclusion criteria	• Use of vaginal oestrogen therapy or menopausal hormonal therapy pre-diagnosis of breast cancer - use classified as any prescription before breast cancer diagnosis up to 2 years before diagnosis.
Patient characteristics	**Age <65 years - number (%):** Vaginal oestrogen therapy (VET): 1327 (68%) Never-users: 4047 (64%)

	Age ≥65 years - number (%): VET: 630 (32%) Never-users: 2297 (36%) Adjuvant endocrine therapy: **None - number (%):** VET: 790 (40%) Never-users: 2259 (35%) **Tamoxifen - number (%):** VET: 345 (18%) Never-users: 1629 (26%) **Aromatase inhibitors (AI) - number (%):** VET: 93 (5%) Never-users: 302 (5%) **Sequence of tamoxifen and AI - number (%):** VET: 729 (37%) Never-users: 2181 (34%)
Intervention(s)/control	Intervention: Prescribed vaginal oestrogen therapy (VET) post breast cancer diagnosis only. Not prescribed menopausal hormone therapy (MHT). Control: Not prescribed VET or MHT post breast cancer diagnosis.
Duration of follow-up	10-year maximum follow-up, or until recurrence of breast cancer, diagnosis of a secondary malignancy, or death. Estimated median time for risk of recurrence was 9.8 years.
Sources of funding	Not industry funded

Sample size	Total, N=8328 (8461 including menopausal hormonal treatment) Vaginal oestrogen therapy: n=1957 Never users: n=6371 n=133 used menopausal hormonal treatment - this group is not part of the protocol so data will not be extracted from this group
Other information	Confounders adjusted for: • Age at surgery • Tumour size • nodal status • histological type and grade • oestrogen receptor • progesterone receptor • lymphovascular invasion • loco-regional therapy • Charlson Comorbidity Index As time-dependent variables: • use of tamoxifen • use of aromatase inhibitors • non-compliance for endocrine therapy

Outcomes

Outcome	**Vaginal oestrogen therapy vs Never users**
Risk of recurrence of breast cancer (with or without adjuvant endocrine therapy) Adjusted HR Hazard ratio/95% CI	 1.08 (0.89 to 1.32)
Not using adjuvant treatment	

Outcome	Vaginal oestrogen therapy vs Never users
Hazard ratio/95% CI	1.04 (0.75 to 1.46)
Using Tamoxifen only Hazard ratio/95% CI	 0.64 (0.39 to 1.06)
Using aromatase inhibitors or aromatase inhibitors and tamoxifen in sequence Hazard ratio/95% CI	 1.39 (1.04 to 1.85)

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(BMI and age at menopause were not adjusted for)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(All participants who would have been eligible for the target trial were included in the study, and the start of follow up and start of intervention coincided.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(The intervention is well defined, and the definition is based on the information collected at the time of the intervention (data collected from a clinical database))*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Not enough information on possible co-interventions that may affect breast cancer recurrence. The intervention is assumed to have been implemented successfully, however it is based on the assumption that received a prescription for vaginal oestrogen therapy would mean the use of the therapy - it is not possible to know this.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data was reasonably complete)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Method of outcome assessment were comparable across intervention groups and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants.)*

Section	Question	Answer
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(All reported results correspond to intended outcomes and are available to view on the clinical database. Multiple adjusted analyses reported.)*
Overall bias	Risk of bias judgement	Moderate *(Most domains are low risk of bias, however potential for bias due to confounding as not all potential confounders were adjusted for.)*
Overall bias	Directness	Directly applicable

Dew, 2003

Bibliographic Reference	Dew, J E; Wren, B G; Eden, J A; A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer.; Climacteric : the journal of the International Menopause Society; 2003; vol. 6 (no. 1); 45-52

Study details

Country/ies where study was carried out	Australia
Study type	Retrospective cohort study
Study dates	Not specified
Inclusion criteria	• Women with histologically confirmed breast cancer
Exclusion criteria	none specified
Patient characteristics	**Age at diagnosis of breast cancer - mean years (range):** Vaginal oestrogen users: 53.8 (22-83) All other subjects: 55.6 (21-96) **Total mastectomy - n (%):** Vaginal oestrogen users: 43 (62%) All other subjects: 772 (55%)

	Tamoxifen usage - n (%): Vaginal oestrogen users: 33 (48%) All other subjects: 701 (47%) *342 of the total group used a form of hormonal therapy. 69 of this group used low-dose topical vaginal oestrogen cream. Therefore, in the comparison group 18% used a hormonal therapy to manage their menopausal symptoms other than low-dose topical vaginal oestrogen.
Intervention(s)/control	Vaginal oestrogen: • Women with histologically confirmed breast cancer who had only bothersome vaginal symptoms used low-dose topical vaginal oestrogen cream or tablet. • Low dose vaginal oestrogens used were: estriol cream and pessaries (Ovestin), or estradiol 25microgram tablets (vaginal insert) (Vagifem). Comparison: • Women with histologically confirmed breast cancer not using vaginal oestrogen.
Duration of follow-up	Median follow-up was 5.5 years, range 0.5 to 29 years
Sources of funding	Not specified
Sample size	N=1472 total Vaginal oestrogen users, n=69 Comparison group, n=1403
Other information	Comparison group did not necessarily have genitourinary symptoms - not specified in the text. Confounders adjusted for: • Known prognostic variables of tumour size • axillary node status • age at diagnosis • age at menarche • parity.

Outcomes

Outcome	Vaginal oestrogen therapy vs Comparison
Tumour recurrence adjusted HR Hazard ratio/95% CI	 0.57 (0.2 to 1.58)

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(BMI and age at menopause were not adjusted for)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(All participants who would have been eligible for the target trial were included in the study, and the start of follow up and start of intervention coincided.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(The intervention is well defined, and the definition is based on the information collected at the time of the intervention (data collected from medical records))*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Not enough information on possible co-interventions that may affect breast cancer recurrence. The intervention is assumed to have been implemented successfully but there is not enough information on the use of the vaginal oestrogen cream or tablets.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data was available for most participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Method of outcome assessment were comparable across intervention groups and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(All reported results correspond to intended outcomes. Unadjusted and adjusted results reported.)*

Section	Question	Answer
Overall bias	Risk of bias judgement	Moderate *(Most domains are low risk of bias, however potential for bias due to confounding as not all potential confounders were adjusted for.)*
Overall bias	Directness	Directly applicable

Le Ray, 2012

Bibliographic Reference	Le Ray, Isabelle; Dell'Aniello, Sophie; Bonnetain, Franck; Azoulay, Laurent; Suissa, Samy; Local estrogen therapy and risk of breast cancer recurrence among; Breast Cancer Res. Treat.; 2012; vol. 135 (no. 2); 603-609

Study details

Country/ies where study was carried out	UK
Study type	Retrospective cohort study
Study dates	January 1998 to June 2008
Inclusion criteria	• Female, at least 18 years old. • diagnosed with breast cancer for the first time and prescribed either tamoxifen or aromatase inhibitors (or both) between Jan 1998 and June 2008. • At least 1 year of follow up after first prescription of anti-oestrogen.
Exclusion criteria	• Less than 1 year of up-to-standard medical history in the General Practice Research Database prior to cohort entry, • Prescribed tamoxifen or aromatase inhibitors (AI) before January 1, 1998. • Prescribed tamoxifen or AI more than 3 months before primary diagnosis of breast cancer. • Prescribed the 1st tamoxifen or AI more than 12 months after the primary diagnosis.
Patient characteristics	**Age, years - mean (SD):** Overall cohort: 63.1 (13.7)

	AI treated patients: 70.4 (12.4) Tamoxifen treated patients: 61.7 (13.5) **BMI <30 - n (%):** Overall cohort: 7578 (69.3) AI treated patients: 1133 (65.7) Tamoxifen treated patients: 6445 (70) **BMI ≥30 - n (%):** Overall cohort: 1574 (14.4) AI treated patients: 340 (19.7) Tamoxifen treated patients: 1234 (13.4) **Previous use of HRT - n (%):** Overall cohort: 2038 (18.6) AI treated patients: 166 (9.6) Tamoxifen treated patients: 1872 (20.3)
Intervention(s)/control	Intervention: Concurrent users - defined as those who were ever prescribed a local hormone treatment during their tamoxifen or AI treatment. Local hormonal treatments include: • estrogenic cream • vaginal tablet • vaginal pessary Non-concurrent users were those who were ever prescribed a hormonal treatment after their endocrine therapy (never during). Comparison: Patients with breast cancer who never used local treatment.

Duration of follow-up	From date of first tamoxifen or AI until breast cancer recurrence, death from any cause, end of registration with the general practice, or the end of the study period (June 30, 2008) - whichever came first. Duration of follow up, years - mean (SD): Overall cohort: 4.2 (2.4) AI treated patients: 2.6 (1.3) Tamoxifen treated patients: 4.5 (2.5)
Sources of funding	Not reported
Sample size	N=10933 total women followed up >1 year Cases: n=917 women with breast cancer recurrence Matched controls: n=8885 The date of each breast cancer recurrence was defined as index date. Analysis based on 917 women with a breast cancer recurrence matched to 8885 controls. For each case of breast cancer recurrence, up to 10 controls were randomly selected from the case's risk set. They were matched on year of birth (+- 1year), date of cohort entry (+- 1year), initial endocrine treatment received and duration of follow up. Concurrent local hormonal treatment, n=271 No local hormonal treatment, n=9507
Other information	Cases seemed to have been more likely to be obese, smokers, and prescribed antipsychotics and benzodiazepines. Rate ratios adjusted for: • obesity • smoking • excessive alcohol use • history of oophorectomy • previous use of HRT

	• anti-depressants (other than CYP2D6 substrates) • antidiabetic agents • NSAIDS (other than CYP2D6 substrates) • benzodiazepines • antipsychotic drugs (other than CYP2D6 substrates) • CYP2D6 inhibitors and statins

Outcomes

Outcome	**Local hormonal treatment vs No local hormonal treatment**
Breast cancer recurrence Concurrent use of tamoxifen or AI with LHT Rate ratio/95% CI	 0.78 (0.48 to 1.25)
Breast cancer recurrence LHT use after end of tamoxifen or AI use Rate ratio/95% CI	 0.97 (0.22 to 4.18)
Breast cancer recurrence Concurrent use of tamoxifen with LHT Rate ratio/95% CI	 0.83 (0.51 to 1.34)
Breast cancer recurrence LHT use after end of tamoxifen use Rate ratio/95% CI	 0.95 (0.22 to 4.14)

Critical appraisal

Section	**Question**	**Answer**
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(Age at menopause, tumour grade, lymph node status, or lymphatic/vascular invasion not controlled for)*

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(All participants who would have been eligible for the target trial were included in the study, and the start of follow up and start of intervention coincided.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(The intervention is well defined, and the definition is based on the information collected at the time of the intervention (data collected from a clinical database)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Not enough information on possible co-interventions that may affect breast cancer recurrence. The intervention is assumed to have been implemented successfully, however it is based on the assumption that received a prescription for local hormonal treatments would mean the use of the therapy - it is not possible to know this.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data was reasonably complete)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Method of outcome assessment were comparable across intervention groups and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(All reported results correspond to intended outcomes and are available to view on the clinical database. Multiple adjusted analyses reported.)*
Overall bias	Risk of bias judgement	Moderate *(Most domains are low risk of bias, however potential for bias due to confounding as not all potential confounders were adjusted for.)*
Overall bias	Directness	Directly applicable

AI: aromatase inhibitors; CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; LHT: local hormonal treatment; MHT: menopausal hormone therapy; SD: standard deviation; VET: vaginal (o)estrogen therapy

O'Meara, 2001

Bibliographic Reference	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.; Journal of the National Cancer Institute; 2001; vol. 93 (no. 10)

Study details

Country/ies where study was carried out	US
Study type	Retrospective cohort study
Study dates	1997-1994
Inclusion criteria	Diagnosis of invasive carcinoma of the breast Aged 35-74 years
Exclusion criteria	Distant metastatic disease at diagnosis Prior diagnosis of in situ or invasive breast cancer
Patient characteristics	**Age at diagnosis, years - range (n):** Users: 35-44: 20 45-54: 36 55-64: 54 65-74: 64 Non-users: 35-44: 80 45-54: 144 55-64: 216 65-74: 255 **Age at reference, years - range (n):** Users: <50: 20 50-59: 42 60-69: 54 ≥70: 58

	Non-users: <50: 88 50-59: 159 60-69: 212 ≥70: 236 **Time from diagnosis to reference, years (n):** Users: <1: 47 1-2: 46 3-7: 44 ≥8: 37 Non-users: <1: 188 1-2: 184 3-7: 175 ≥8: 148 **Age at natural menopause, years (n):** Users: <47: 25 47-51: 30 ≥51: 25 Missing data: 2 Non-users: <47: 88 47-51: 148 ≥51: 122 Missing data: 4 **Age at induced menopause, years (n):** Users: <47: 20

	47-51: 11 ≥51: 7 Non-users: <47: 73 47-51: 29 ≥51: 13 **HRT use before diagnosis, years (n):** Users: 119 Non-users: 337 **Duration of HRT use before diagnosis, years (n):** Users: 0: 45 >0-5: 30 6-10: 24 >10: 40 Missing data: 35 Non-users: 0: 327 >0-5: 173 6-10: 55 >10: 66 Missing data: 74 **Age at first use if HRT used before diagnosis, years (n):** Users: 45: 33 45-54: 45 ≥55: 15 Missing data: 26 Non-users: 45: 87 45-54: 152

	≥55: 50 Missing data: 74
Intervention(s)/control	Intervention: Vaginal HRT: Required to have at least 2 prescriptions for HRT containing oestrogen in last 6-month interval, any time after initial diagnosis and before diagnosed recurrence Control: No HRT: Recurrence-free interval at least as long as the interval from diagnosis to HRT initiation in the matched user.
Duration of follow-up	Median follow-up of 3.7 years for recurrence and 4.6 years for mortality.
Sources of funding	National Cancer Institute National Institutes of Health Department of Health and Human Services
Sample size	N= 869 with diagnosis of breast cancer n= 174 users n= 695 non-users

Outcomes

Outcome	**Vaginal oestrogen vs Non-users**
Risk of recurrence of breast cancer (with or without adjuvant endocrine therapy)	
Hazard ratio/95% CI	0.46 (0.21 to 1.01)

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(All important confounders were controlled for.)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low (All participants who would have been eligible for the target trial were included in the study, and the start of follow up and start of intervention coincided.)
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(The intervention is well defined, and the definition is based on the information collected at the time of the intervention (data collected from a clinical database).)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate (Not enough information on possible co-interventions that may affect breast cancer recurrence. The intervention is assumed to have been implemented successfully but there is not enough information on the use of the vaginal estrogen cream or tablets.)
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data was available for most participants.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low (Method of outcome assessment were comparable across intervention groups and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants.)
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(All reported results correspond to intended outcomes and are available to view on the clinical database. Unadjusted and adjusted analyses reported.)*
Overall bias	Risk of bias judgement	Moderate (Most domains are low risk of bias, however potential for bias due to lack of information about potential deviations from the intended intervention.)
Overall bias	Directness	Directly applicable

Appendix E Forest plots

Forest plots for review question: Are treatments for managing genitourinary symptoms associated with the menopause safe for women with a personal history or high inherited risk of breast cancer?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in Appendix F.

Comparison 1: vaginal oestrogens versus no treatment

Figure 2: Breast cancer recurrence; with or without adjuvant treatment

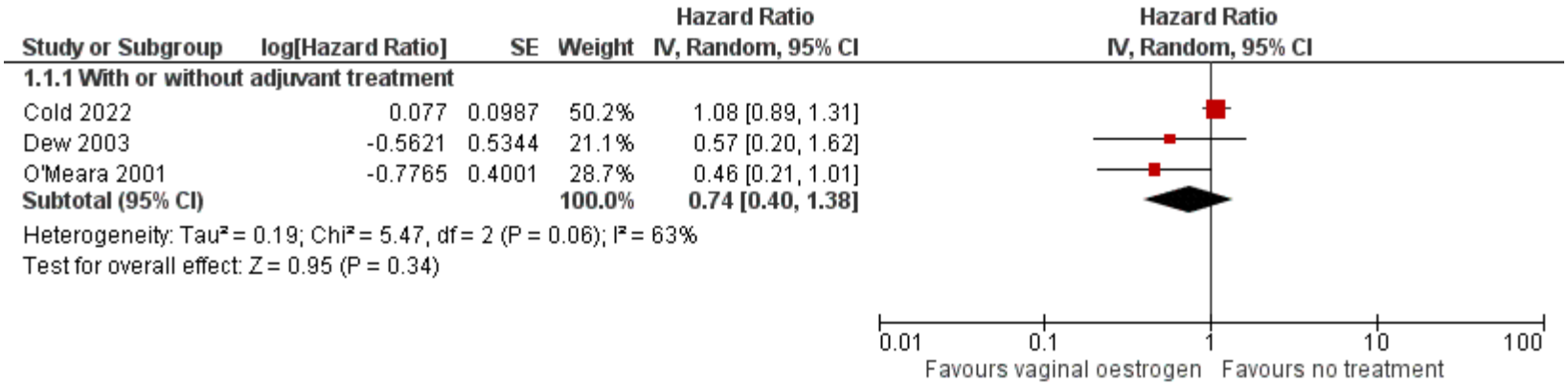
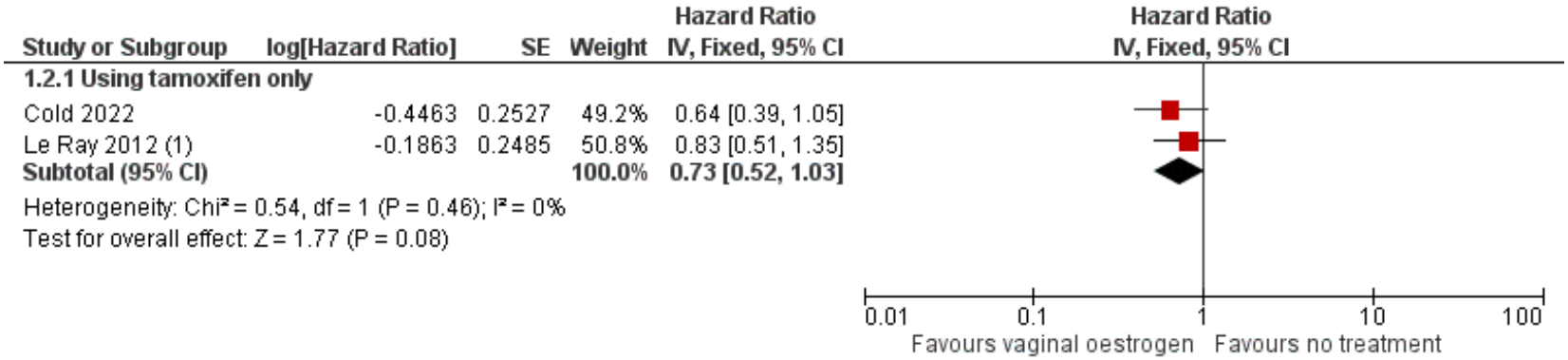


Figure 3: Breast cancer recurrence; tamoxifen use only



Footnotes

(1) Incidence rate ratio

Appendix F GRADE tables

GRADE tables for review question: Are treatments for managing genitourinary symptoms associated with the menopause safe for women with a personal history or high inherited risk of breast cancer?

Table 5: Evidence profile for comparison 1: vaginal oestrogens versus no treatment

Quality assessment							No of patients		Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal oestrogen	No treatment	Relative (95% CI)	Absolute 5 year recurrence[1]	Absolute 10 year recurrence[1]		
Incidence or recurrence of breast cancer - With or without adjuvant treatment													
3[2]	observational studies	serious[3]	serious[4]	no serious indirectness	very serious[5]	none	2101	7849	HR 0.74 (0.40 to 1.38)	Not calculable	46 fewer per 1000 (from 109 fewer to 62 more)	VERY LOW	CRITICAL
Incidence or recurrence of breast cancer - Not using adjuvant treatment													
Cold 2022	observational studies	serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	790	2259	HR 1.04 (0.75 to 1.44)	Not calculable	7 more per 1000 (from 44 fewer to 72 more)	VERY LOW	CRITICAL
Incidence or recurrence of breast cancer - Using tamoxifen only													
2[7]	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[6]	none	604	10107	HR 0.73 (0.52 to 1.03)	Not calculable	47 fewer per 1000 (from 86 fewer to 5 more)	LOW	CRITICAL
Incidence or recurrence of breast cancer – AI or AI and tamoxifen in sequence													
Cold 2022	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[6]	none	729	2181	HR 1.39 (1.04 to 1.86)	Not calculable	64 more per 1000 (from 7 to 134 more)	LOW	CRITICAL
Incidence or recurrence of breast cancer - Using either tamoxifen or AI													
Le Ray 2012	observational studies	serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	271	9507	Rate Ratio 0.78 (0.48 to 1.27)	23 fewer per 1000 (from 56 fewer to 28 more)	38 fewer per 1000 (from 94 fewer to 45 more)	VERY LOW	CRITICAL

AI: aromatase inhibitors; CI: confidence interval; HR: Hazard ratio; RR: risk ratio
1. Absolute numbers were calculated using the hazard ratio combined with the 5- and 10-years recurrence free survival rates of the no HRT or VET group in Cold 2022
2. Cold 2022, Dew 2003, O'Meara 2001
3. Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I
4. Serious heterogeneity unexplained by subgroup analysis
5. 95% CI crosses 2 MIDs
6. 95% CI crosses 1 MID
7. Cold 2022; Le Ray 2012

Appendix G Economic evidence study selection

Study selection for review question: Are treatments for managing genitourinary symptoms associated with the menopause safe for women with a personal history or high inherited risk of breast cancer?

A single economic search was undertaken for all topics included in the scope of this guideline. See Supplement 2 for further information.

Appendix H Economic evidence tables

Economic evidence tables for review question: Are treatments for managing genitourinary symptoms associated with the menopause safe for women with a personal history or high inherited risk of breast cancer?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: Are treatments for managing genitourinary symptoms associated with the menopause safe for women with a personal history or high inherited risk of breast cancer?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: Are treatments for managing genitourinary symptoms associated with the menopause safe for women with a personal history or high inherited risk of breast cancer?

Excluded effectiveness studies

Table 6: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Areas, Fernanda, Valadares, Ana L R, Conde, Delio Marques et al. (2019) The effect of vaginal erbium laser treatment on sexual function and vaginal health in women with a history of breast cancer and symptoms of the genitourinary syndrome of menopause: a prospective study. Menopause (New York, N.Y.) 26(9): 1052-1058	- Outcome *Reported outcomes do not match the review protocol*
Barton, Debra L, Shuster, Lynne T, Dockter, Travis et al. (2018) Systemic and local effects of vaginal dehydroepiandrosterone (DHEA): NCCTG N10C1 (Alliance). Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 26(4): 1335-1343	- Outcome *Reported outcomes do not match the review protocol*
Barton, Debra L, Sloan, Jeff A, Shuster, Lynne T et al. (2018) Evaluating the efficacy of vaginal dehydroepiandosterone for vaginal symptoms in postmenopausal cancer survivors: NCCTG N10C1 (Alliance). Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 26(2): 643-650	- Outcome *Reported outcomes do not match the review protocol*
Becorpi, Angelamaria, Campisciano, Giuseppina, Zanotta, Nunzia et al. (2018) Fractional CO2 laser for genitourinary syndrome of menopause in breast cancer survivors: clinical, immunological, and microbiological aspects. Lasers in medical science 33(5): 1047-1054	- Outcome *Reported outcomes do not match the review protocol*
Biglia, Nicoletta, Peano, Elisa, Sgandurra, Paola et al. (2010) Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: a preliminary study. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 26(6): 404-12	- Outcome *Reported outcomes do not match the review protocol*
Bruyniks, N, Biglia, N, Palacios, S et al. (2017) Systematic indirect comparison of ospemifene versus local estrogens for vulvar and vaginal atrophy. Climacteric : the journal of the International Menopause Society 20(3): 195-204	- Population *Not breast cancer or high risk population*
Chambers, Laura M, Herrmann, Alyssa, Michener, Chad M et al. (2020) Vaginal estrogen use for genitourinary symptoms in women with a history of uterine, cervical, or ovarian carcinoma. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society 30(4): 515-524	- Population *Women had a previous history of cervical, endometrial or ovarian cancer - not breast cancer. Less than 33%*

Study	Code [Reason]
	(18%) had a history of ovarian cancer.
Crandall, Carolyn J; Diamant, Allison; Santoro, Nanette (2020) Safety of vaginal estrogens: a systematic review. Menopause (New York, N.Y.) 27(3): 339-360	- Population *Systematic review - no included studies in women with/at risk of breast cancer*
Crandall, Carolyn J, Hovey, Kathleen M, Andrews, Christopher A et al. (2018) Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. Menopause (New York, N.Y.) 25(1): 11-20	- Population *Not women with breast cancer or at high risk*
Di Donato, Violante, Schiavi, Michele Carlo, Iacobelli, Valentina et al. (2019) Ospemifene for the treatment of vulvar and vaginal atrophy: A meta-analysis of randomized trials. Part II: Evaluation of tolerability and safety. Maturitas 121: 93-100	- Population *Not breast cancer or high-risk population*
Gambacciani, Marco and Levancini, Marco (2017) Vaginal erbium laser as second-generation thermotherapy for the genitourinary syndrome of menopause: a pilot study in breast cancer survivors. Menopause (New York, N.Y.) 24(3): 316-319	- Outcome *Reported outcomes do not match the review protocol*
Gardner, Alyssa N and Aschkenazi, Sarit O (2021) The short-term efficacy and safety of fractional CO2 laser therapy for vulvovaginal symptoms in menopause, breast cancer, and lichen sclerosus. Menopause (New York, N.Y.) 28(5): 511-516	- Outcome *Reported outcomes do not match the review protocol*
Gittens, Paul and Mullen, Gregory (2019) The effects of fractional microablative CO2 laser therapy on sexual function in postmenopausal women and women with a history of breast cancer treated with endocrine therapy. Journal of cosmetic and laser therapy : official publication of the European Society for Laser Dermatology 21(3): 127-131	- Outcome *Reported outcomes do not match the review protocol*
Harris, Benjamin S, Bishop, Katherine C, Kuller, Jeffrey A et al. (2020) Hormonal management of menopausal symptoms in women with a history of gynecologic malignancy. Menopause (New York, N.Y.) 27(2): 243-248	- Study design *Systematic review checked for relevant studies*
Hirschberg, Angelica Linden, Sanchez-Rovira, Pedro, Presa-Lorite, Jesus et al. (2020) Efficacy and safety of ultra-low dose 0.005% estriol vaginal gel for the treatment of vulvovaginal atrophy in postmenopausal women with early breast cancer treated with nonsteroidal aromatase inhibitors: a phase II, randomized, double-blind, placebo-controlled trial. Menopause (New York, N.Y.) 27(5): 526-534	- Outcome *Reported outcomes do not match the review protocol*

Study	Code [Reason]
Hocke, C, Diaz, M, Bernard, V et al. (2021) [Genitourinary Menopause Syndrome. CNGOF and GEMVi clinical practice guidelines]. Gynecologie, obstetrique, fertilite & senologie	- Language *Not English language*
Jha, Swati; Wyld, Lynda; Krishnaswamy, Priyanka H (2019) The Impact of Vaginal Laser Treatment for Genitourinary Syndrome of Menopause in Breast Cancer Survivors: A Systematic Review and Meta-analysis. Clinical breast cancer 19(4): e556-e562	- Outcome *Reported outcomes do not match the review protocol*
Knight, Charity; Logan, Vera; Fenlon, Deborah (2019) A systematic review of laser therapy for vulvovaginal atrophy/genitourinary syndrome of menopause in breast cancer survivors. Ecancermedicalscience 13: 988	- Outcome *Reported outcomes do not match the review protocol*
Lethaby, Anne; Ayeleke, Reuben Olugbenga; Roberts, Helen (2016) Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews 8(8): cd001500	- Population *Not breast cancer or high risk*
Li, Bohan, Duan, Hua, Chang, Yanan et al. (2021) Efficacy and safety of current therapies for genitourinary syndrome of menopause: A Bayesian network analysis of 29 randomized trials and 8311 patients. Pharmacological research 164: 105360	- Outcome *Reported outcomes do not match the review protocol*
Lyytinen, H.; Pukkala, E.; Ylikorkala, O. (2006) Breast cancer risk in postmenopausal women using estrogen-only therapy. Obstetrics and Gynecology 108(6): 1354-1360	- Population *Not women with/ at risk of breast cancer*
Mension, Eduard; Alonso, Inmaculada; Castelo-Branco, Camil (2021) Genitourinary Syndrome of Menopause: Current Treatment Options in Breast Cancer Survivors - Systematic Review. Maturitas 143: 47-58	- Study design *Systematic review checked for relevant studies*
Moegele, M, Buchholz, S, Seitz, S et al. (2012) Vaginal estrogen therapy in postmenopausal breast cancer patients treated with aromatase inhibitors. Archives of gynecology and obstetrics 285(5): 1397-402	- Study design *Systematic review checked for relevant studies*
Mothes, A R; Runnebaum, M; Runnebaum, I B (2018) Ablative dual-phase Erbium:YAG laser treatment of atrophy-related vaginal symptoms in post-menopausal breast cancer survivors omitting hormonal treatment. Journal of cancer research and clinical oncology 144(5): 955-960	- Outcome *Reported outcomes do not match the review protocol*
Pagano, Tiziana, De Rosa, Pasquale, Vallone, Roberta et al. (2018) Fractional microablative CO2 laser in breast cancer survivors affected by iatrogenic vulvovaginal atrophy after failure of nonestrogenic local treatments: a retrospective study. Menopause (New York, N.Y.) 25(6): 657-662	- Outcome *Reported outcomes do not match the review protocol*

Study	Code [Reason]
Pavlovic, R T, Jankovic, S M, Milovanovic, J R et al. (2019) 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. Clinical breast cancer 19(6): e731-e740	- Outcome *Reported outcomes do not match the review protocol*
Pearson, Antonia, Booker, Andrew, Tio, Martin et al. (2019) Vaginal CO2 laser for the treatment of vulvovaginal atrophy in women with breast cancer: LAAVA pilot study. Breast cancer research and treatment 178(1): 135-140	- Outcome *Reported outcomes do not match the review protocol*
Pieralli, Annalisa, Fallani, Maria Grazia, Becorpi, Angelamaria et al. (2016) Fractional CO2 laser for vulvovaginal atrophy (VVA) dyspareunia relief in breast cancer survivors. Archives of gynecology and obstetrics 294(4): 841-6	- Outcome *Reported outcomes do not match the review protocol*
Quick, Allison M, Hundley, Andrew, Evans, Cynthia et al. (2022) Long-Term Follow-Up of Fractional CO2 Laser Therapy for Genitourinary Syndrome of Menopause in Breast Cancer Survivors. Journal of clinical medicine 11(3)	- Outcome *Reported outcomes do not match the review protocol*
Saeaib, Nungrutai, Peeyananjarassri, Krantarat, Liabsuetrakul, Tippawan et al. (2020) Hormone replacement therapy after surgery for epithelial ovarian cancer. The Cochrane database of systematic reviews 1: cd012559	- Intervention *No relevant interventions*
Sanchez-Rovira, Pedro, Hirschberg, Angelica Linden, Gil-Gil, Miguel et al. (2020) A Phase II Prospective, Randomized, Double-Blind, Placebo-Controlled and Multicenter Clinical Trial to Assess the Safety of 0.005% Estriol Vaginal Gel in Hormone Receptor-Positive Postmenopausal Women with Early Stage Breast Cancer in Treatment with Aromatase Inhibitor in the Adjuvant Setting. The oncologist 25(12): e1846-1854	- Outcome *Reported outcomes do not match the review protocol*
Simon, James A, Altomare, Corrado, Cort, Susannah et al. (2018) Overall Safety of Ospemifene in Postmenopausal Women from Placebo-Controlled Phase 2 and 3 Trials. Journal of women's health (2002) 27(1): 14-23	- Population *Not breast cancer or high risk*
Tranoulis, Anastasios; Georgiou, Dimitra; Michala, Lina (2019) Laser treatment for the management of genitourinary syndrome of menopause after breast cancer. Hope or hype?. International urogynecology journal 30(11): 1879-1886	- Outcome *Reported outcomes do not match the review protocol*
Wills, S;Ravipati, A;Venuturumilli, P. et al. (2012) 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. Journal of Oncology Practice 8(3): 144-149	- Outcome *Reported outcomes do not match the review protocol*

Study	Code [Reason]
Zuo, Stephanie Wang; Wu, Harold; Shen, Wen (2018) Vaginal estrogen and mammogram results: case series and review of literature on treatment of genitourinary syndrome of menopause (GSM) in breast cancer survivors. Menopause (New York, N.Y.) 25(7): 828-836	- Population *The case series excluded women with history of breast cancer*

Excluded economic studies

No economic evidence was identified for this review. See Supplement 2 for further information.

Appendix K Research recommendations – full details

Research recommendations for review question: Are treatments for managing genitourinary symptoms associated with the menopause safe for women with a personal history or high inherited risk of breast cancer?

K.1.1 Research recommendation

After breast cancer, or for people at high familial or genetic risk of breast cancer, does vaginal oestrogen increase the risk of recurrence of or new breast cancer?

Why this is important

Genitourinary symptoms are common after treatment for breast cancer and due to the medications used to treat breast cancer, genitourinary symptoms can be quite severe. Vaginal oestrogens are currently used in practice for the treatment of genitourinary symptoms associated with menopause. However, it is uncertain whether vaginal oestrogens increase the risk of recurrence of breast cancer, or a new breast cancer, and the efficacy of vaginal oestrogens after breast cancer is uncertain. It is important to investigate the safety and efficacy of vaginal oestrogens after breast cancer.

Rationale for research recommendation

Table 7: Research recommendation rationale

Importance to 'patients' or the population	Understanding the safety of using vaginal oestrogens following a breast cancer diagnosis will have a considerable impact on the way women are counselled prior to being prescribed vaginal oestrogens and the shared decision making between women and their doctor about treating this condition. Research in this area would allow oncologists and women with a personal history of breast cancer, or at high familial or genetic risk of breast cancer, to have more confidence about the safety and efficacy of vaginal oestrogens after breast cancer.
Relevance to NICE guidance	There was limited evidence on the effectiveness and safety of vaginal oestrogens for genitourinary symptoms in menopausal women with a personal history of breast cancer, or at high familial or genetic risk of breast cancer, and research in this area is essential to inform future updates of key recommendations in the guidance.
Relevance to the NHS	This research would provide an evidence base on the use of vaginal oestrogens in women with a personal history of breast cancer, or at high familial or genetic risk of breast cancer, which could impact the types of treatments provided to menopausal women for managing genitourinary symptoms by the NHS. The research may also aid in predicting the future healthcare needs for women who have had breast cancer.
National priorities	This research is relevant to the government's women's health strategy which aims to improve the health of women everywhere over the next

	10-years, and specifically addresses the following sections on menopause: • healthcare professionals in primary care are well informed about the menopause, and able to offer women evidence-based advice and treatment options, including HRT and alternatives • other healthcare professionals – for example cardiologists or neurologists – have a basic understanding of menopause, including awareness of symptoms and future health risks associated with menopause, and can signpost women to appropriate support • there is increased research into the menopause, including different treatment options and impacts of menopause or menopause treatment on future health risks And the following section on cancer: • research enables us to better understand the causes, identification of and treatments – including side effects of treatment – for poorly understood cancers to reduce risk, improve early diagnosis, and subsequent health outcomes and quality of life
Current evidence base	There was minimal evidence available of low to very low quality from observational studies only. Many of the studies did not appropriately adjust for confounders, specifically regarding the prognostic variables of breast cancer and this would impact on the risk of recurrence.
Equality considerations	Further research would address equality considerations particularly in the following groups, people: • with disabilities • from diverse races and ethnicities • from diverse socio-economic backgrounds

NHS: national health service

Modified PICO table

Table 8: Research recommendation modified PICO table

Population	Women, trans men, and non-binary people registered female at birth (who are not taking cross sex hormones as gender affirming therapy) with genitourinary symptoms associated with menopause (including perimenopause and post-menopause) who have a personal history of breast cancer or are at high familial or genetic risk of breast cancer. The committee further recommends research that would address equality considerations in the equality impact assessment form, particularly in the following groups, people: • with disabilities • across a range of race / ethnicities

	• from a wider range of socio-economic backgrounds
Intervention	Vaginal oestrogen o Estriol cream o Estriol pessary o Estriol gel o Oestradiol vaginal tablet o Oestradiol Ring
Comparator	• Placebo treatment (including non-hormonal treatment such as moisturisers and lubricants) • No treatment • Sham treatment
Outcome	• Incidence of breast cancer (including recurrence or a new breast cancer) • Mortality from breast cancer
Study design	Randomised controlled trials and non-randomised comparative studies
Timeframe	5 years
Additional information	None

NHS: national health service; PICO: population, intervention, comparator, outcome.