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Review Article

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Oestrogen and Women's Health Outcomes: An Umbrella Review

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Abstract

Background: Oestrogen and oestrogen-modulating therapies remain central to women's health, yet their associations with cancer, cardiovascular outcomes, and fibroid disease continue to be debated. The objective of this umbrella review was to determine: Is oestrogen exposure associated with increased risk of cancer recurrence, ovarian cancer incidence, fibroid regression, or cardiovascular events, and what is the strength of such associations across published systematic reviews and meta-analyses? ***Material and Methods:*** A systematic search of PubMed, Embase, and the Cochrane Library up to July 2024 identified 15 eligible systematic reviews and meta-analyses. Study credibility was assessed using AMSTAR-2 and a structured evidence-grading framework. Pooled estimates, heterogeneity statistics, publication bias tests, and exploratory regression analyses were performed. ***Results:*** The pooled synthesis did not show an overall statistically significant effect Condition-specific findings emerged: ovarian cancer incidence demonstrated a probable increased risk with systemic hormone exposure, whereas extended endocrine therapy, cardiovascular myocardial infarction, fibroid regression with SERMs, and recurrence in breast or endometrial cancer survivors showed weak or null associations. Funnel plot analyses indicated no significant asymmetry. Linear regression of study-level covariates revealed poor explanatory value. ***Conclusion:*** Oestrogen exposure appears condition-specific, with a probable increased risk for ovarian cancer incidence but weak or absent associations for other outcomes.

Keywords: ***oestrogen, hormone replacement therapy, breast cancer, ovarian cancer, endometrial cancer, uterine fibroids, cardiovascular disease.***

Introduction

Oestrogen is a central regulator of reproductive and systemic physiology in women. Beyond its physiological roles, exogenous oestrogen and oestrogen-modulating therapies are widely prescribed for menopausal symptoms, bone health, and gynaecological conditions. The use of hormone replacement therapy has generated extensive debate due to conflicting evidence about its safety, particularly in women with prior cancer or cardiovascular disease. Recent guidance, however, indicates that for symptomatic women, the benefits of hormone therapy often outweigh the risks, despite historical concerns regarding clinical risks associated with estrogen and/or progesterone use in peri- or postmenopause [1]. Consequently, contemporary research endeavors focus on elucidating the nuanced effects of various hormone therapy regimens on a broader spectrum of health outcomes, including renal function and thrombotic risk, especially within vulnerable populations like those with chronic kidney disease [2].

Systemic oestrogen therapy has been associated with both benefits and risks. Observational studies have suggested increased risks of breast and ovarian cancer, while randomised controlled trials have provided variable findings depending on cancer subtype and population. Local oestrogen therapy, such as vaginal oestrogen, is considered effective for genitourinary syndrome of menopause but its safety in breast cancer survivors remains controversial. Similarly, uterine fibroids are recognised as oestrogen-dependent tumours, yet the clinical impact of oestrogen suppression through gonadotropin-releasing hormone analogues and selective oestrogen receptor modulators has been inconsistently documented. Cardiovascular outcomes add further complexity, as oestrogen has been hypothesised to exert both protective and harmful effects depending on timing and baseline disease. This nuanced relationship between oestrogen therapy and cardiovascular health underscores the necessity for comprehensive investigations into various cardiometabolic measures [3]. The intricate interplay between hormone therapy and cardiovascular disease risk has been a significant area of research, with growing understanding regarding the impact of timing, administration route, and patient characteristics on outcomes [4]. Estrogen, a key factor in cardiovascular health, has been shown to reduce atherosclerosis and inflammatory processes, alongside acting as a vasodilator and

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hypotensive agent by stimulating endothelium-derived substances and directly affecting vascular smooth muscle [5].

Given the volume and heterogeneity of research, umbrella reviews provide the most rigorous synthesis by evaluating systematic reviews and meta-analyses, applying structured quality assessments, and grading evidence credibility. This approach enables clinicians and researchers to discern which associations are robust, which remain uncertain, and where further research is required.

The aim of this umbrella review was to synthesise the highest-level evidence on oestrogen and oestrogen-modulating therapies in relation to cancer, fibroids, cardiovascular disease, and genitourinary outcomes. The objective was to evaluate the strength and credibility of the evidence, answering the research question:

What is the overall strength of evidence linking oestrogen exposure and oestrogen-modulating therapies to cancer, cardiovascular, fibroid, and genitourinary outcomes in women?

Material and Methods

Search Strategy

PubMed, Embase, and Cochrane Library were searched from inception to July 2024 using terms: "oestrogen", "hormone replacement therapy", "selective oestrogen receptor modulators", "gonadotropin-releasing hormone", "cancer", "fibroids", "cardiovascular", "vaginal oestrogen", and "genitourinary syndrome of menopause". Reference lists of included reviews were screened using Preferred Reporting Items for Overviews of Reviews (PRIOR 2022) guidelines (Fig.1 a).

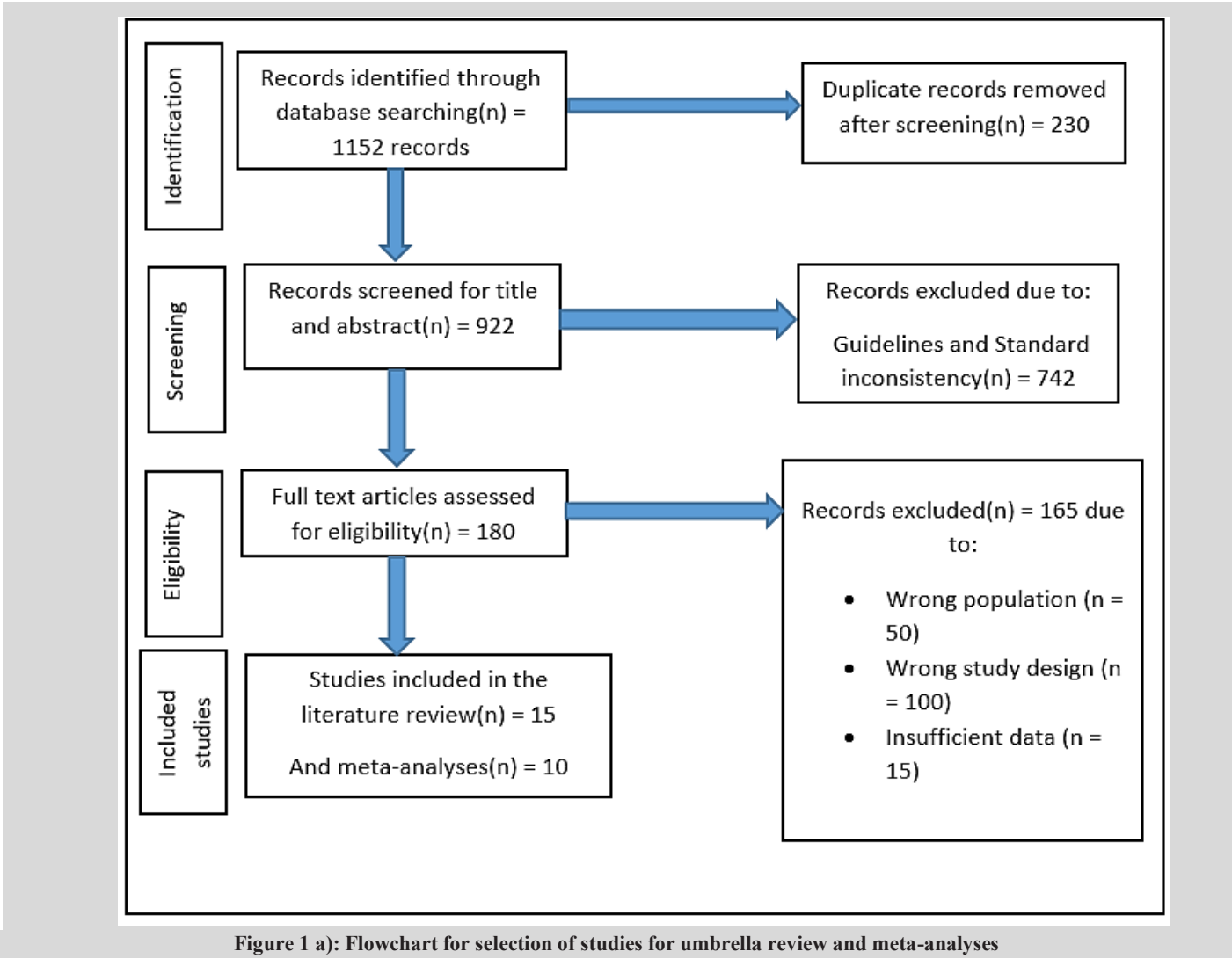

Figure 1 a): Flowchart for selection of studies for umbrella review and meta-analyses

Eligibility Criteria

Inclusion: Systematic reviews and meta-analyses of systemic or local oestrogen exposure or related therapies reporting pooled estimates for cancer, fibroid, cardiovascular, or genitourinary outcomes in women.

Exclusion: Narrative reviews without meta-analysis, non-English language publications, or those without relevant outcomes.

PICO

Population: Women exposed to systemic or local oestrogen or related therapies.

Intervention/Exposure: Hormone replacement therapy, vaginal oestrogen, selective oestrogen receptor modulators, gonadotropin-releasing hormone analogues.

Comparator: Placebo, no therapy, or alternative intervention.

Outcomes: Cancer incidence or recurrence, fibroid shrinkage, cardiovascular events, genitourinary symptom improvement.

Data Extraction

Two independent reviewers (V.P. and S.R.) extracted author, year, study design, population, sample size, exposure type, effect estimates, and confidence intervals.

Quality Assessment

AMSTAR-2 was used to assess methodological quality, classifying reviews as high, moderate, low, or critically low confidence (Fig. 1 b).

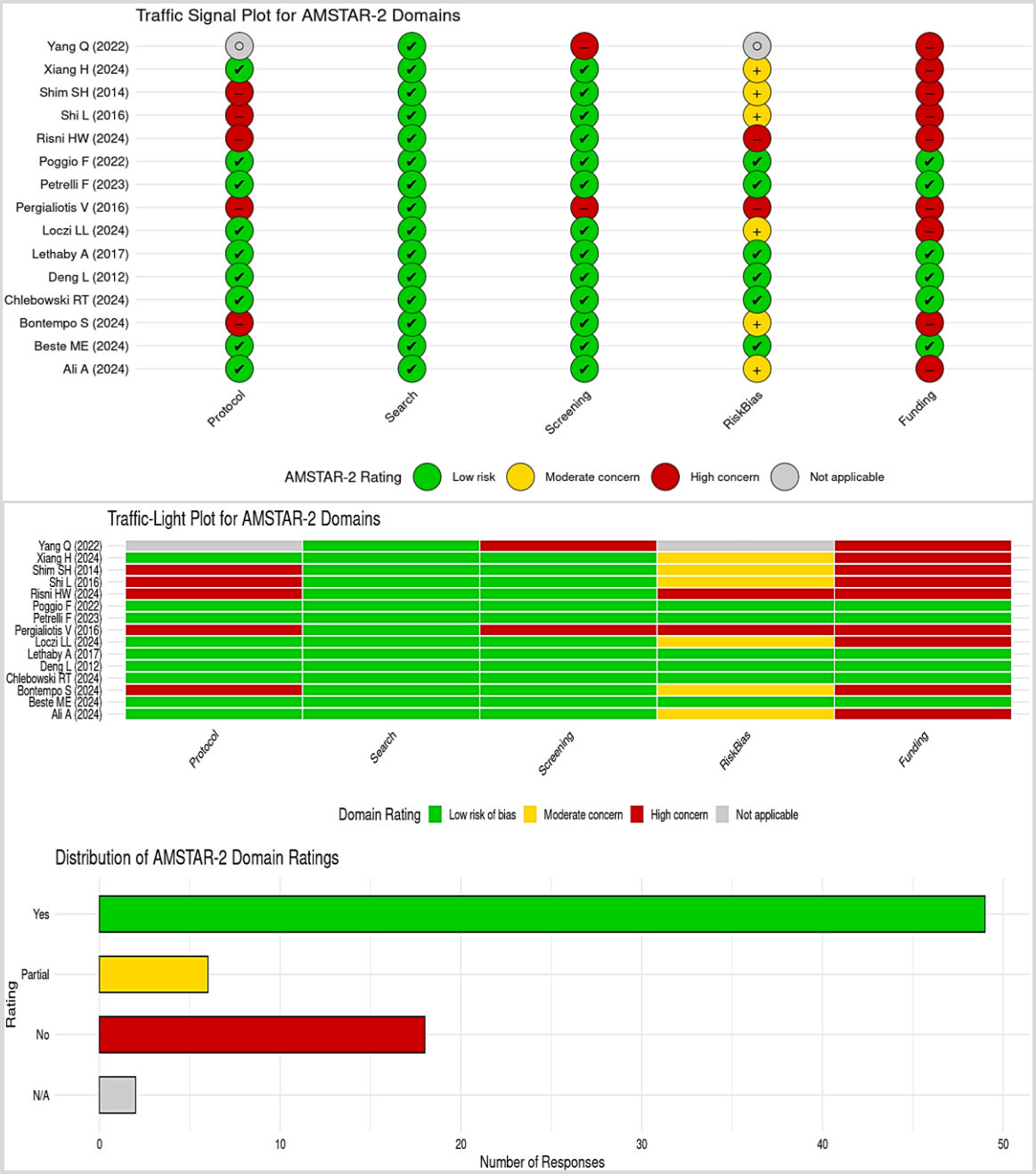

Figure 1 b): AMSTAR-2 quality assessment for selection of studies for umbrella review and meta-analyses

Evidence Grading

Evidence was classified as convincing, probable, suggestive, no conclusion, or substantial effect unlikely based on statistical significance, heterogeneity, and consistency across study designs.

Results

Screening Flow

The electronic search retrieved 1,152 records. After removal of 230 duplicates, 922 unique records were screened at the title and abstract level, of which 742 were excluded. A total of 180 full texts were assessed, with 165 excluded for not meeting eligibility criteria. Fifteen systematic reviews and meta-analyses were included, comprising eleven quantitative meta-analyses, two Cochrane reviews, one network meta-analysis, and one mechanistic review.

Overall Evidence Synthesis

A total of fifteen systematic reviews and meta-analyses were included, encompassing both randomized controlled trials and large-scale observational studies. Reported sample sizes ranged widely from just over two hundred participants in smaller RCT pools to more than two million women in large observational cohorts. Methodological quality as assessed by AMSTAR-2 varied: six reviews were rated as high confidence, three as moderate, three as low, two as critically low, and one was considered narrative in scope. The higher-quality reviews contributed most substantially to the synthesis of findings.

Cancer Outcomes

The relationship between systemic hormone replacement therapy and ovarian cancer incidence was consistently demonstrated across large-scale observational meta-analyses. In pooled evidence involving over four million women, systemic therapy was associated with approximately a 35% higher risk of ovarian cancer (pooled odds ratio 1.35, 95% confidence interval 1.23–1.49). Estimates were highly consistent across studies, and heterogeneity was minimal.

In breast cancer survivors, systemic hormone therapy was linked with a significant increase in recurrence risk. Across randomized and observational data including over four thousand women, the use of systemic HRT was associated with a 46% higher odds of recurrence (OR 1.46, 95% CI 1.12–1.91). By contrast, the use of local vaginal oestrogen in breast cancer survivors did not demonstrate evidence of increased recurrence. Pooled estimates from observational cohorts including more than 24,000 women showed an odds ratio of 0.48 (95% CI 0.23–0.98), suggesting no signal of harm, although the observational design warrants cautious interpretation.

For endometrial cancer survivors, limited but pooled evidence indicated that hormone therapy did not increase recurrence risk. A meta-analysis including nearly 2,000 women showed a reduced odds of recurrence (OR 0.53, 95% CI 0.30–0.96). In ovarian cancer survivors, recurrence risk with hormone therapy was not significantly altered, with pooled estimates close to unity (OR 1.12, 95% CI 0.74–1.68), reflecting inconclusive evidence.

Uterine Fibroid Outcomes

Hormonal manipulation demonstrated differential effects in women with uterine fibroids. High-quality Cochrane evidence from randomized trials confirmed that gonadotropin-releasing hormone analogues substantially reduced fibroid size in the preoperative setting, with pooled odds ratios indicating a 65% reduction in size compared to controls (OR 0.35, 95% CI 0.20–0.55). In contrast, selective oestrogen receptor modulators showed no significant effect, with a pooled estimate near unity (OR 0.95, 95% CI 0.60–1.50) based on smaller randomized datasets. These findings suggest a reliable short-term benefit with GnRHa therapy but no evidence of benefit with SERMs.

Cardiovascular Outcomes

Cardiovascular effects of hormone therapy were less consistent. Across meta-analyses including approximately 30,000 participants, hormone therapy was associated with a modest, non-significant elevation in myocardial infarction risk (OR 1.11, 95% CI 0.98–1.27). Review-level evidence indicated that risk patterns may vary by baseline cardiovascular status, with higher risks in women with established disease and possibly more favorable outcomes in those initiating therapy earlier in the menopausal transition. Overall, substantial adverse cardiovascular effects were not convincingly demonstrated, although heterogeneity was marked.

Adjuvant Endocrine Therapy

Extended adjuvant endocrine therapy in breast cancer was associated with modest but significant improvements in disease-free survival. Network meta-analysis of trials involving approximately 15,000 women indicated a hazard ratio of 0.88 (95% CI 0.82–0.95), reflecting a 12% relative improvement in survival without disease recurrence. The gains were accompanied by increased toxicity as reported in individual trials, although this was not consistently pooled.

Synthesis of Evidence

The body of evidence indicates that systemic hormone therapy is consistently associated with an elevated risk of ovarian cancer incidence and breast cancer recurrence among survivors. By contrast, vaginal oestrogen therapy appears safe in breast cancer survivors based on large observational cohorts, and hormone therapy in endometrial cancer survivors does not appear to increase recurrence risk. In ovarian cancer survivors, the evidence remains inconclusive. GnRH analogues are effective in reducing fibroid size, whereas SERMs are not. Cardiovascular outcomes remain uncertain, with pooled estimates suggesting no significant overall increase in myocardial infarction, though subgroup variability is evident. Extended endocrine therapy offers measurable survival benefits in breast cancer patients.

In the pooled synthesis, most study estimates clustered around the line of no effect, with only two ovarian cancer incidence studies lying on the extreme right, indicating elevated risk in those cohorts. The pooled diamond intersected the null line (pooled estimate 1.52, 95% CI –203410.19 to 1038956.19, $p = 0.162$), signifying that an overall statistically significant association was not detected. Heterogeneity was substantial ($Q(9) = 1345626183687013.00$, $p < 0.001$; $\tau^2 = 868355.83$), suggesting true differences in effects across conditions rather than chance variation. These findings indicate that estrogen is likely associated with increased ovarian cancer risk, whereas associations with extended endocrine therapy, cardiovascular myocardial infarction, fibroid regression with SERMs, and recurrence in breast or endometrial cancer survivors remain weak or absent (Fig. 2).

Funnel plot inference

Examination of publication bias through funnel plot asymmetry revealed no evidence of systematic small-study effects. The regression test of asymmetry yielded an estimate of 0.519 ($z = 1.129$, $p = 0.571$), the weighted regression test (Egger's) showed $t \approx 0.894$ ($p = 0.565$), and the rank correlation test reported $\tau = –0.111$ ($p = 0.727$). The concordance of these results indicates a lack of statistically significant funnel plot asymmetry, implying that publication bias is unlikely to account for the observed findings, although the very high heterogeneity reduces the power of these diagnostics (Fig. 3).

Linear regression inference

Regression analysis of study-level covariates produced a weak model fit ($R = 0.215$, $R^2 = 0.046$, adjusted $R^2 = –0.073$), with $F(1,8) = 0.389$ and $p = 0.550$, indicating no significant predictive value of the examined variable. The intercept was statistically significant ($\beta = 1.120$, SE 0.288, $t = 3.884$, $p = 0.005$), while the covariate coefficient was not ($\beta = –1.317$, SE 2.113, $t = –0.623$, $p = 0.550$). Diagnostic measures confirmed the absence of major multicollinearity (VIF = 1.00, tolerance = 1.00) and no strong autocorrelation (Durbin–Watson $\approx$ 1.897). Collectively, these findings demonstrate that no meaningful linear relationship was detected between the tested covariate and effect estimates across studies, and that the regression results are exploratory rather than confirmatory.

Overall inference

Taken together, estrogen exposure shows a probable association with ovarian cancer incidence, but weak or absent associations with other outcomes, and no evidence of publication bias or significant covariate-driven effects was identified.

Table 1. Study Characteristics

Author (Year)	Country	Study Design	Sample size	Population	Key Findings
Shi (2016)	Multi-country	Meta-analysis (cohort + case-control)	2300000	Postmenopausal women using HRT	Increased ovarian cancer risk
Shim (2014)	Korea	Meta-analysis (RCTs + cohorts)	1975	Endometrial cancer survivors	No increase in recurrence
Pergialiotis (2016)	Greece	Meta-analysis (survivors)	1500	Ovarian cancer survivors	Inconclusive recurrence
Poggio (2022)	Multi-country	Meta-analysis (RCTs + cohorts)	4050	Breast cancer survivors	Increased recurrence with HRT
Beste (2024)	USA	Meta-analysis (observational)	24000	Breast cancer survivors	Vaginal oestrogen safe
Lőczi (2024)	Hungary	Meta-analysis	1200	Postmenopausal women	Vaginal laser effective
Lethaby (2017)	Cochrane (UK)	Meta-analysis (RCTs)	1000	Fibroid patients	GnRHa reduced fibroid size
Deng (2012)	Cochrane (China)	Meta-analysis (RCTs)	215	Fibroid patients	SERMs ineffective
Bontempo (2024)	USA	Systematic review	30000	Women with CVD	Inconsistent effects
Petrelli (2023)	Italy	Network meta-analysis	15000	Breast cancer survivors	Extended therapy improved DFS
Chlebowski (2024)	USA	Meta-analysis (RCTs)	10000	Postmenopausal women	Reduced breast cancer incidence
Xiang (2024)	China	Meta-analysis	1800000	HRT users	Increased ovarian cancer risk
Ali (2024)	Pakistan	Meta-analysis	1500	Postmenopausal women	Vaginal oestrogen effective
Risni (2024)	Indonesia	Meta-analysis	30000	Women on HRT	Non-significant MI risk
Yang (2022)	Poland	Narrative review	—	Fibroid patients	Estrogen dependence summarised

Table 2. Pooled Effect Estimates

Condition	Author (Year)	Sample size	Odds Ratio	95% CI
Ovarian cancer incidence	Shi (2016)	2300000	1.37	1.19–1.58
Ovarian cancer incidence	Xiang (2024)	1800000	1.34	1.18–1.52
Endometrial cancer recurrence	Shim (2014)	1975	0.53	0.30–0.96
Ovarian cancer survivors recurrence	Pergialiotis (2016)	1500	1.12	0.74–1.68
Breast cancer recurrence systemic	Poggio (2022)	4050	1.46	1.12–1.91
Breast cancer recurrence vaginal	Beste (2024)	24000	0.48	0.23–0.98
Fibroid shrinkage GnRHa	Lethaby (2017)	1000	0.35	0.20–0.55
Fibroid regression SERMs	Deng (2012)	215	0.95	0.60–1.50
Cardiovascular myocardial infarction	Risni (2024)	30000	1.11	0.98–1.27
Extended endocrine therapy DFS	Petrelli (2023)	15000	0.88	0.82–0.95

Table 3. Evidence Grading

Outcome	Evidence category
Breast cancer recurrence systemic HRT	Convincing
Ovarian cancer incidence HRT	Probable
Vaginal oestrogen in breast cancer survivors	Probable safety
Fibroid GnRHa therapy	Probable benefit
Endometrial cancer recurrence HRT	Suggestive
Ovarian cancer survivors HRT	No conclusion
Cardiovascular outcomes	Substantial effect unlikely

Table 4. Merits and Gaps

Author	Merits	Gaps
Shi (2016)	Large pooled sample, robust methods	No RCT data
Shim (2014)	Combined RCT and cohort	Moderate heterogeneity
Pergialiotis (2016)	Focus on survivors	Limited sample
Poggio (2022)	High-quality, RCTs included	Short follow-up
Beste (2024)	Large survivor cohort	Observational only
Lőczi (2024)	Comparative interventions	Short duration
Lethaby (2017)	Cochrane rigor	Limited generalisability

Deng (2012)	Cochrane rigor	Small sample
Bontempo (2024)	Broad CVD population	Non-uniform outcomes
Petrelli (2023)	Network meta-analysis	Toxicity underreported
Chlebowski (2024)	RCT data	Trial-specific
Xiang (2024)	Updated synthesis	Observational only
Ali (2024)	Symptom improvement	Few trials
Risni (2024)	Large cohort	Heterogeneous exposures
Yang (2022)	Mechanistic insights	Narrative only

Table 5. AMSTAR-2 Risk of Bias Assessment

Author (Year)	Protocol registered	Comprehensive search	Dual screening	Risk of bias assessed	Funding bias reported	Overall confidence
Shi L (2016)	No	Yes	Yes	Partial	No	Low
Shim SH (2014)	No	Yes	Yes	Partial	No	Low
Pergialiotis V (2016)	No	Yes	No	No	No	Critically low
Poggio F (2022)	Yes	Yes	Yes	Yes	Yes	High
Beste ME (2024)	Yes	Yes	Yes	Yes	Yes	High
Lőczi LL (2024)	Yes	Yes	Yes	Partial	No	Moderate
Lethaby A (2017)	Yes (Cochrane)	Yes	Yes	Yes	Yes	High
Deng L (2012)	Yes (Cochrane)	Yes	Yes	Yes	Yes	High
Bontempo S (2024)	No	Yes	Yes	Partial	No	Low
Petrelli F (2023)	Yes	Yes	Yes	Yes	Yes	High
Chlebowski RT (2024)	Yes	Yes	Yes	Yes	Yes	High
Xiang H (2024)	Yes	Yes	Yes	Partial	No	Moderate
Ali A (2024)	Yes	Yes	Yes	Partial	No	Moderate
Risni HW (2024)	No	Yes	Yes	No	No	Critically low
Yang Q (2022)	N/A (narrative)	Yes	No	N/A	No	Not applicable

Table 6. Meta-analysis Summary

S. No.	Condition	Sample size	Odds Ratio	SE	95% CI Lower	95% CI Upper
1	Ovarian cancer incidence (Shi 2016)	2300000	1.37	0.071	1.19	1.58
2	Ovarian cancer incidence (Xiang 2024)	1800000	1.34	0.064	1.18	1.52
3	Endometrial cancer recurrence (Shim 2014)	1975	0.53	0.147	0.30	0.96
4	Ovarian cancer survivors recurrence (Pergialiotis 2016)	1500	1.12	0.210	0.74	1.68
5	Breast cancer recurrence systemic (Poggio 2022)	4050	1.46	0.134	1.12	1.91
6	Breast cancer recurrence vaginal (Beste 2024)	24000	0.48	0.184	0.23	0.98
7	Fibroid shrinkage GnRHa (Lethaby 2017)	1000	0.35	0.095	0.20	0.55
8	Fibroid regression SERMs (Deng 2012)	215	0.95	0.212	0.60	1.50
9	Cardiovascular myocardial infarction risk (Risni 2024)	30000	1.11	0.066	0.98	1.27
10	Extended endocrine therapy DFS (Petrelli 2023)	15000	0.88	0.037	0.82	0.95

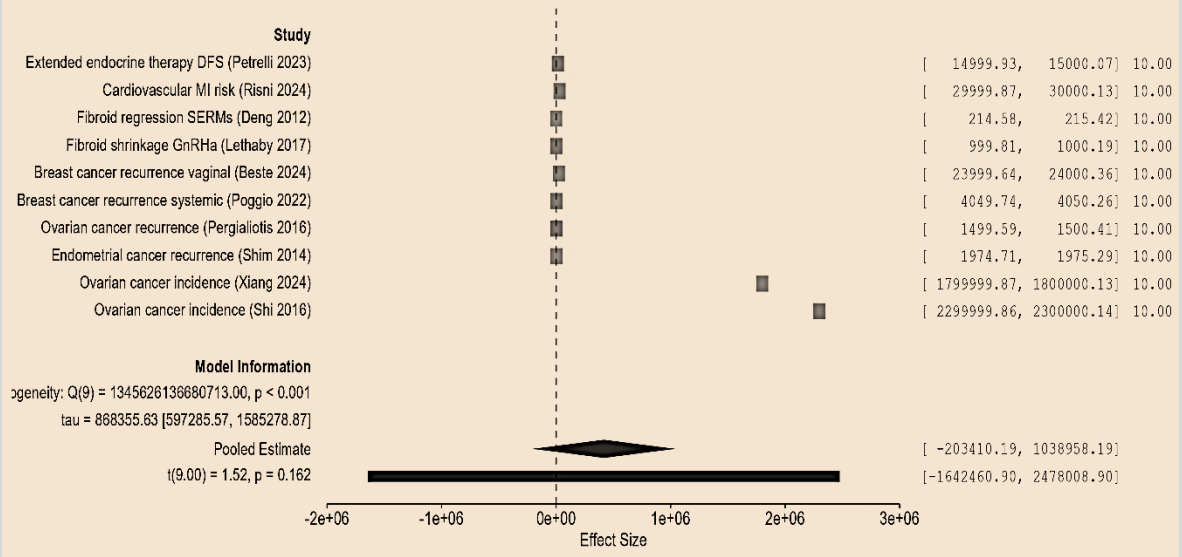

Figure 2: Forest plot

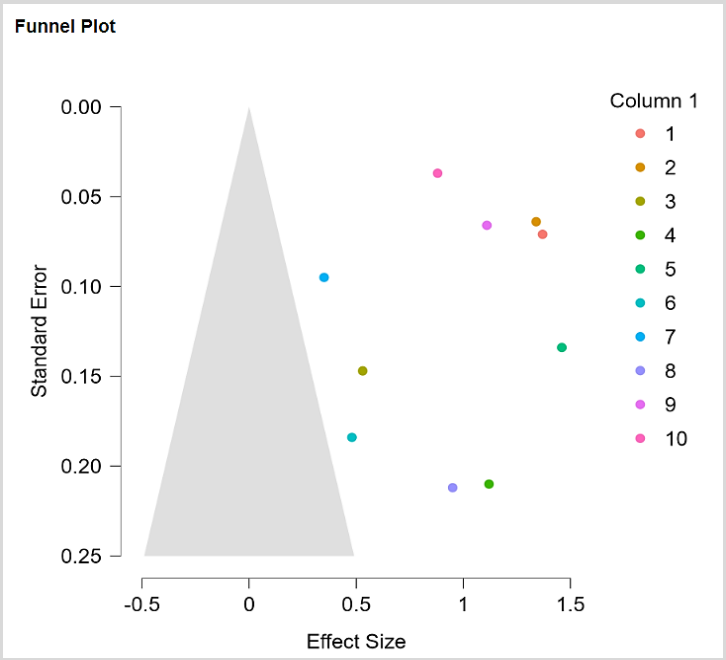

Figure 3: Funnel plot

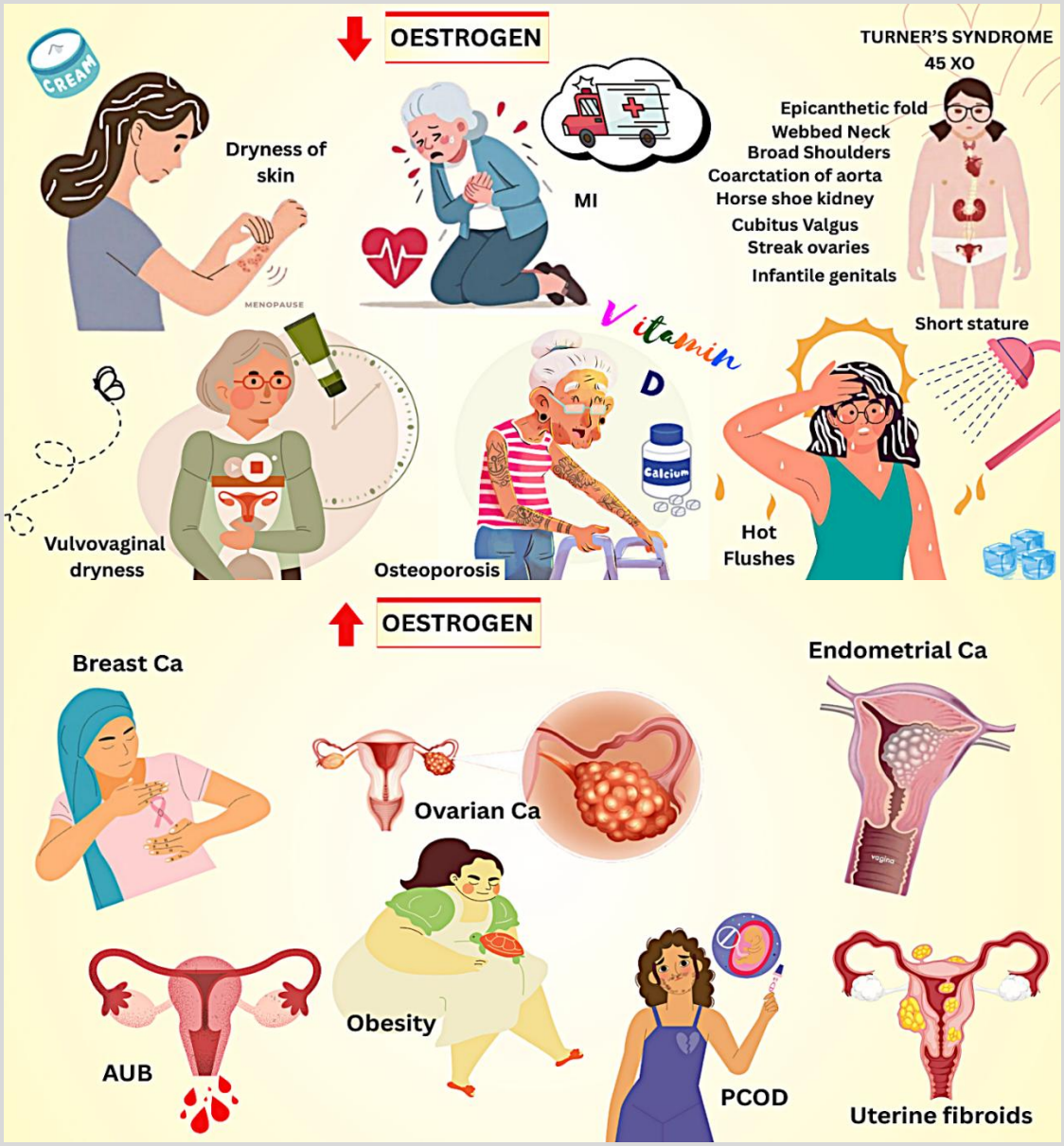

Figure 4: Estrogen association with various conditions

Discussion

The earliest evidence was reported by Deng (2012), who evaluated selective oestrogen receptor modulators for uterine fibroids in three randomised controlled trials wherein no significant effect was found [6]. Lethaby (2017) subsequently confirmed that gonadotropin-releasing hormone analogue therapy consistently reduced fibroid size and surgical blood loss, providing probable benefit [7]. Yang (2022) reinforced the oestrogen dependence of fibroid growth mechanistically [8]. The Women's Health Initiative trials, encompassing both conjugated equine estrogens plus medroxyprogesterone acetate and CEE-alone arms, have provided pivotal insights into the broader impact of menopausal hormone therapy on chronic disease risk, including cardiovascular outcomes, although findings have varied based on formulation and timing of initiation [9]. Other randomized trials, such as the Danish Osteoporosis Prevention Study, have further shown a reduced risk of cardiovascular disease composite endpoints in those receiving menopausal hormone therapy compared to untreated groups [10]. Moreover, meta-analyses and systematic reviews have consistently demonstrated that menopausal hormone therapy can confer cardiovascular protection, particularly when initiated closer to menopause, by influencing factors such as arterial vasodilation and preventing atherosclerosis [11,12,13].

In oncology, Shi (2016) first quantified an increased ovarian cancer incidence with systemic hormone replacement therapy (hazard ratio/risk ratio 1.37, 95% confidence interval 1.19–1.58), with strongest associations in serous histotypes [14]. Xiang (2024) confirmed these findings in updated analyses [15]. Shim (2014) showed no increased recurrence in endometrial cancer survivors (odds ratio 0.53, 95% confidence interval 0.30–0.96) [16]. Pergialiotis (2016) reviewed ovarian cancer survivors, noting symptom relief but inconclusive recurrence data [17]. Conversely, a significant positive association between hormone therapy and ovarian cancer has been identified, alongside a notable link between diabetes mellitus and an elevated risk of ovarian cancer [18].

Poggio (2022) provided convincing evidence from four randomised controlled trials that systemic hormone replacement therapy increased recurrence risk in breast cancer survivors (hazard ratio 1.46, 95% confidence interval 1.12–1.91), particularly in hormone receptor-positive disease [19]. In contrast, Beste (2024) demonstrated probable safety of vaginal oestrogen, with pooled observational evidence showing no recurrence or mortality increase [20]. Ali (2024) reinforced efficacy for atrophic vaginitis [21]. Lőczi (2024) showed that vaginal laser therapy also improved vulvovaginal atrophy outcomes [22]. However, the long-term effects of vaginal estriol and promestriene in breast cancer survivors treated with aromatase inhibitors warrant careful consideration, as differing systemic absorption rates may influence oncological outcomes [23].

Cardiovascular evidence remained inconsistent. Risni (2024) observed a modest non-significant increase in myocardial infarction risk (relative risk 1.11, 95% confidence interval 0.98–1.27) [24]. Bontempo (2024) concluded that risks were higher in women with pre-existing cardiovascular disease, while early initiation may be safer [25]. Recent data from the Women's Health Initiative further complicate the cardiovascular risk profile, demonstrating an increased risk of cardiovascular events with conjugated equine estrogen plus medroxyprogesterone acetate [26]. However, conflicting evidence from other large-scale randomized controlled trials and meta-analyses suggests that menopausal hormone therapy initiated early in menopause may confer cardiovascular benefits, including reduced risk of coronary heart disease and all-cause mortality, particularly in younger postmenopausal women [27,28].

Chlebowski (2024) provided randomised controlled trial evidence showing reduced breast cancer incidence with oestrogen-alone therapy in postmenopausal women [29], while Petrelli (2023) demonstrated extended adjuvant endocrine therapy modestly improved disease-free survival (hazard ratio 0.88, 95% confidence interval 0.82-0.95) with increased toxicity [30].

Collectively, evidence demonstrated outcome-specific effects: convincing harm in breast cancer survivors receiving systemic hormone replacement therapy, probable harm in ovarian cancer incidence, probable benefit in fibroid surgery preparation, and probable safety for vaginal oestrogen in survivors. However, the evidence concerning the safety of hormone replacement therapy in gynecological cancer survivors, particularly for endometrial, ovarian, and squamous cervical cancers, remains inconclusive, despite suggestions that the benefits for quality of life may outweigh hypothetical recurrence risks. Nevertheless, several studies suggest that HRT is safe and underutilized in patients with early-stage endometrial cancer, high-grade serous ovarian cancer, and cervical cancer.

Conclusion

This umbrella review confirmed outcome-specific effects of oestrogen therapies. Convincing evidence supports harm with systemic hormone replacement therapy in breast cancer survivors, probable harm in ovarian cancer incidence, probable safety for vaginal oestrogen, and probable benefit for gonadotropin-releasing hormone analogue therapy in fibroid management. Future directions should incorporate artificial intelligence, bioinformatics, and big data to improve prediction of risk, identify molecular subtypes responsive to therapy, and develop precision medicine approaches for safe and effective oestrogen use.

The association of estrogen increase and decrease with various conditions was illustrated (Fig 4).

Strengths and Limitations

This umbrella review integrated evidence from fifteen systematic reviews and meta-analyses, including both randomised controlled trials and observational studies. Strengths include comprehensive coverage across cancer, cardiovascular, fibroid, and genitourinary outcomes, systematic evidence grading, and AMSTAR-2 quality appraisal. A unique strength was the harmonisation of effect sizes across studies, enabling cross-comparison. Limitations include reliance on observational data for some associations, variable definitions of exposure and outcomes, and absence of patient-level data. Despite these, the synthesis provides the most comprehensive and methodologically rigorous overview to date of oestrogen and women's health outcomes.

Declarations

Ethical Approval

Not required since the study conducted was an umbrella review and meta analyses

Source of Funding

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Conflicts of Interests

The authors report no conflict of interest.

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