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MENOPAUSAL HORMONE THERAPY AND BREAST CANCER RISK

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ABSTRACT

Introduction. Menopausal hormone therapy (MHT) is widely used for the relief of menopausal symptoms and for the prevention of osteoporosis. However, its use remains controversial due to the potential increased risk of breast cancer, especially with combined estrogen-progestin therapy (EPT).
Aim. This review aims to critically evaluate the current evidence on the relationship between MHT and breast cancer risk, with a focus on formulation-specific effects, timing of initiation, duration of use, and risk among breast cancer survivors.
Material and methods. A structured literature review was conducted using PubMed, MED-LINE, and EMBASE databases from January 2018 to June 2025. Inclusion criteria covered randomized controlled trials, cohort and case-control studies, systematic reviews, and meta-analyses involving > 600 breast cancer cases. Studies examining systemic MHT and breast cancer incidence, subtype-specific risk, and recurrence in survivors were included. A total of 30 high-quality references were selected.
Results. Combined EPT consistently increases breast cancer risk (RR/HR~1.5-2.5), with high-er risk for long-duration use and early initiation after menopause (<3 years). Estrogen-only therapy (ET) shows a modest risk increase in observational studies, but RCT data (e.g., WHI) suggest reduced incidence and mortality. Bioidentical progesterone appears less harmful than synthetic progestins. Transdermal MHT may carry lower risk than oral formulations. Vaginal estrogen shows no significant increase in breast cancer risk. Among breast cancer survivors, systemic MHT is associated with a significantly increased risk of recurrence (HR~1.46).
Conclusions. MHT use, particularly EPT, is associated with an elevated breast cancer risk. Risk varies by formulation, duration, timing, and patient profile. Clinicians should tailor MHT decisions individually, favoring the lowest effective dose and shortest duration, while considering non-hormonal alternatives when appropriate. Systemic MHT is generally contraindicated in breast cancer survivors.

KEYWORDS

Menopausal Hormone Therapy; Breast Cancer; Estrogen-Progestin Therapy; Estrogen-Only Therapy; Hormone Replacement Therapy; Recurrence Risk; Transdermal Hormones; Bioidentical Progesterone; WHI; Breast Cancer Survivors

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Abbreviations

- MHT - menopausal hormone therapy
- ET - estrogen - only therapy
- EPT - combined estrogen - progestin therapy
- HR - hazard ratio
- RR/OR - relative risk/odds ratio
- RCT - randomized controlled trial
- CEE - conjugated equine estrogens
- MPA - medroxyprogesterone acetate

Introduction

Menopausal hormone therapy is widely used for relief of vasomotor and urogenital symptoms and for prevention of osteoporosis. However, concerns persist regarding its role in breast cancer development. The seminal Women's Health Initiative (WHI) trials in early 2000s linked combined EPT to increased breast cancer risk, prompting a shift in prescribing practices. Subsequent observational and randomized studies have further investigated the impact of MHT formulation, dosage, timing, duration, and patient characteristics (e.g., BMI, cancer history). This review evaluates current evidence to inform clinical decision-making.

Methods

A targeted literature search in PubMed, MEDLINE, Cochrane Library, EMBASE and ClinicalTrials.gov was conducted through mid-2025. Inclusion criteria: RCTs, cohort or case-control studies, meta-analyses with >600 breast cancer cases, as well as systematic reviews on MHT and breast cancer risk. Excluded were studies focusing exclusively on non-systemic MHT (e.g., vaginal estrogen). PRISMA guidelines were followed; extracted data included HRs or ORs for EPT and ET, stratified by duration (>5 years), timing of initiation (gap hypothesis), histological or receptor subtype, mortality, and recurrence in survivors. The final analysis included 30 references, prioritizing large-scale or recent high-quality studies.

Results

1. Overall breast cancer risk

The Collaborative Group's meta-analysis of individual data from 51 studies (n=160 000 cases) found increased risk for combined EPT (every year of use, RR~1.08) and modestly elevated risk with ET. The Million Women Study (n>1million) reported RR~2.0 for current EPT users and ~1.3 for ET users. WHI RCTs confirmed increased breast cancer incidence with EPT (HR~1.28) and a surprising decrease with ET alone (HR~0.78).

2. Formulation-, route-, and dosage-specifics risks

A large Norwegian cohort (1.27 million women; 2004-2018) reported highest risk for oral estradiol + norethisterone acetate (NETA), with HR up to 2.67, and increased risk also for transdermal estradiol (HR~1.48); vaginal estrogen carried no significant BC risk. A Finnish study (1994-2019) showed modestly elevated ORs: ET 1.61 for 5-9 years, tibolone ~1.30, and EPT~1.82. Notably, bioidentical progesterone appears safer than synthetic progestogens.

3. Timing of initiation (gap hypothesis)

Data from the French E3N cohort revealed that EPT initiates within 3 years post-menopause increased risk even for short-duration (<2 years) use (HR~1.54), whereas delayed initiation showed no early risk.

4. Histological subtypes & receptor status

Combined MHT is most strongly linked to hormone receptor-positive (ER+) cancers, including luminal A (HR~1.97). There is evidence for increased ductal and lobular tumors with EPT.

5. Mortality & recurrence

Observational analyses suggest ET increases breast cancer mortality, while EPT is linked to higher incidence. WHI follow-up showed no increased all-cause mortality with MHT use. In breast cancer survivors, a meta-analysis of four RCTs (n=4050) reported increased recurrence with systemic HRT (HR~1.46); no significant increase in death (HR~0.91).

6. Effect modifiers

Risk is heightened in low-BMI women. Family history significantly increases absolute but not relative risk, with combined EPT raising absolute BC incidence slightly (e.g., from 9.8% to 11.0% over 30 years).

Discussion

Summary

Evidence indicates:

- **EPT** markedly increases breast cancer risk (RR~1.5-2.5); risk rises with duration and persists post-cessation.
- **ET** also increases risk in observational studies (RR~1.3-1.6), though WHI showed reduced incidence and mortality.
- **Route matters**: oral estradiol + synthetic progestin poses highest risk, transdermal slightly lower; vaginal ET appears safe.
- **Timing** plays a role: early initiation (<3 years post-menopause) increases risk even for short use.

- **Bioidentical progesterone** may be safer than synthetic progestins.
- **Survivor data** show elevated recurrence risk; systemic MHT is generally discouraged in these women.

Clinical implications

Risk-benefit assessments must be individualized. Estrogen-only transdermal therapy, especially post-hysterectomy, may be preferable for symptomatic women. If the uterus is intact, consider EPT using micronized progesterone with the lowest effective dose and duration (<5 years) while monitoring risk modulators (e.g, BMI, family history). Non-hormonal alternatives should be considered in higher-risk individuals.

Limitations

- RCTs (e.g., WHI) often involved older initiation age and CEE+MPA rather than contemporary regimens.
- Observational studies may be affected by confounding and detection bias.
- Survivor trials are limited in size and duration, and largely pertain to systemic therapy.

Conclusions

Combined estrogen-progestin MHT is clearly associated with increased breast cancer risk; absolute risk varies based on formulation, duration, initiation timing, and patient factors. Estrogen-only therapy may pose a lower risk, but safety remains context-dependent. Clinicians should customize MHT based on individual risk profiles, using the lowest effective dose, shortest duration, and safer regiments, especially among women with elevated baseline risk. Shared decision-making and close monitoring are essential.

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