Review Article

Mechanistic and Clinical Insights into Menopausal Hormone Therapy-Associated Breast Carcinogenesis

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ABSTRACT

Objective: To synthesize clinical, epidemiological, and molecular evidence on the association between menopausal hormone therapy (MHT) and breast cancer risk, with emphasis on formulation-specific effects and mechanistic pathways. **Data Sources:** A narrative literature review was conducted using PubMed, Scopus, and Web of Science databases. Search terms included menopausal hormone therapy, estrogen-only therapy, estrogen–progestin therapy, breast cancer risk, mammographic density, and progesterone receptor signaling. Studies published in English from 1995 to 2024 were prioritized. **Data Summary:** Evidence from randomized controlled trials, including the Women's Health Initiative, and large cohort studies demonstrates divergent breast cancer risk profiles for estrogen-only therapy (ET) and estrogen–progestin therapy (EPT). ET using conjugated equine estrogen is associated with neutral or reduced breast cancer incidence, whereas EPT significantly increases risk, particularly for estrogen receptor–positive tumors. Mechanistically, estrogen and progestogens influence carcinogenesis through receptor-mediated transcription, non-genomic kinase signaling, altered steroid metabolism, epigenetic remodeling, expansion of mammary progenitor cells, and tumor microenvironment changes. Synthetic progestins promote tumor progression via RANKL, STAT, PI3K/Akt, and MAPK pathways. MHT also increases mammographic density, contributing to increased carcinogenic susceptibility and reduced screening sensitivity. **Conclusions:** Breast cancer risk associated with MHT is heterogeneous and strongly dependent on hormone composition, duration of exposure, and individual patient factors. Estrogen-only regimens appear biologically and clinically safer than combined estrogen–progestin therapy. Improved mechanistic understanding and molecular risk stratification are essential for individualized menopausal symptom management with reduced oncologic risk.

Key words: Menopausal hormone therapy, Breast cancer risk, Estrogen-only therapy, Estrogen–progestin therapy, Mammographic density, Progesterone receptor, Carcinogenesis

Menopausal hormone therapy (MHT) is widely used for the management of vasomotor symptoms and the prevention of osteoporosis in postmenopausal women; however, evidence from observational studies and randomized clinical trials has produced discordant findings regarding its association with breast cancer risk and mortality, making this an ongoing clinical controversy [1]. The Women's Health Initiative (WHI), which enrolled more than 27,000 postmenopausal women, revealed contrasting Outcomes, estrogen-only therapy (ET) with conjugated equine estrogen (CEE) in women with prior hysterectomy was associated with a significantly lower incidence of breast cancer and reduced disease-specific mortality, whereas combined Estrogen-progestin therapy (EPT) in women with an intact uterus significantly increased breast cancer incidence, with adverse effects persisting long after treatment discontinuation [2]. Mechanistic hypotheses suggest that progestogens may counteract estrogen-induced apoptosis in occult tumor cells that arise during estrogen-deprived states, providing biological plausibility for these divergent effects [3,4]. Epidemiological studies consistently demonstrate higher excess risk with EPT than with ET, with risk varying by tumor estrogen receptor status, administration route, specific hormone compounds, duration of exposure, and body mass index, which tends to inversely correlate with risk [2,5,6]. This narrative review integrates clinical and mechanistic evidence to clarify

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formulation-specific heterogeneity in MHT-associated breast carcinogenesis and to inform individualized patient counseling and risk stratification [5-7].

2. OVERVIEW OF MENOPAUSAL HORMONE THERAPY (MHT): PREPARATIONS AND ROUTES

Menopausal hormone therapy (MHT) is not a single uniform intervention but a spectrum of regimens defined by hormone composition and delivery strategy. In routine clinical practice, uterine status remains the primary determinant of regimen selection, as unopposed estrogen increases the risk of endometrial hyperplasia and carcinoma [8]. For this reason, estrogen-only therapy (ET) is reserved for women who have undergone hysterectomy, whereas women with an intact uterus require combined estrogen–progestogen therapy (EPT) to counteract estrogen-driven endometrial stimulation [8,9].

These combined regimens may be administered continuously or sequentially, creating distinct endocrine environments that influence breast tissue biology and potentially modify carcinogenic risk [8,9]. A wide range of estrogen formulations is currently used, including conjugated equine estrogens (CEE), 17β-estradiol, estradiol valerate, estriol, and ethinyl estradiol, delivered through oral, transdermal, intranasal, vaginal, injectable, or implant routes, with varying dose ranges and metabolic profiles [5,8,10]. Oral CEE remains the most extensively studied formulation, as it was the primary estrogen used in the Women's Health Initiative trials [2], whereas bioidentical 17β-estradiol is increasingly favored in modern practice, particularly in transdermal form because it more closely resembles endogenous estrogen and avoids first-pass hepatic metabolism [8,10]. Representative estrogen types, routes of administration, and commonly used dose categories are summarized in Table 1.

Table 1. Estrogen formulations used in menopausal hormone therapy

Estrogen type	Route(s) used	Example dose categories	Notes	Ref
Conjugated equine estrogens	Oral	Moderate: 0.625 mg/day; High: 1.25 mg/day	Primary estrogen in Women's Health Initiative trials; mixture of equine estrogens	[2,8]
17β-Estradiol (E2)	Oral, transdermal, intranasal	Oral: 1 mg/day; Patch: 0.05 mg/day; High: 0.075 mg/day	Widely used; bioidentical structure; avoids first-pass metabolism when transdermal	[8,10]
Estradiol valerate	Oral	Moderate: 2 mg/day	Prodrug converted to estradiol after absorption	[8]
Estriol	Oral, vaginal	No standardized systemic dose	Weak estrogen; evaluated mainly in observational cohort studies	[8]
Ethinyl estradiol	Oral	No standardized dose category	Included as estrogen class in large cohort analyses	[5]

Table 2. Routes of estrogen administration in menopausal hormone therapy

Route	Formulation examples	Dose range studied	Notes	Ref
Oral	CEE tablets, oral E2, estradiol valerate	Low–high	Most RCT data (WHI) involve oral CEE; subject to first-pass hepatic metabolism	[2,8]
Transdermal	Estradiol patches, gels, creams	Ultra-low to high	Avoids hepatic first-pass metabolism; lower venous thromboembolism risk; widely used in modern HT	[8,10]
Vaginal	Creams, tablets, rings	Low–high	Mainly for local genitourinary symptoms; minimal systemic exposure	[8]
Intranasal	Estradiol nasal spray	0.15–0.30 mg/day	Included in long-term eligibility criteria for HT studies	[8]
Subcutaneous	Estradiol implants	Not standardized	Provides continuous estrogen delivery	[8]

Progestogens used in MHT include medroxyprogesterone acetate, norethisterone acetate (norethindrone acetate), dydrogesterone, micronized progesterone, and tibolone, which differ substantially in receptor selectivity, androgenic and glucocorticoid activity, and downstream transcriptional signaling [8,9]. These pharmacologic differences translate into meaningful biological heterogeneity at the level of the breast, with synthetic progestins, particularly medroxyprogesterone acetate, most strongly associated with increased breast cancer risk in observational studies and randomized trials [2,9]. In contrast, micronized progesterone and dydrogesterone appear to confer a comparatively lower oncologic risk, although long-term randomized data remain limited [9]. Beyond formulation, the route of administration has meaningful biological consequences. Oral estrogens undergo hepatic first-pass metabolism, leading to higher circulating estrone sulfate levels, altered coagulation profiles, and broader systemic metabolic effects [8,10]. Transdermal estrogen, by contrast, delivers

hormone directly into the systemic circulation, producing more stable estradiol levels and lower risks of venous thromboembolism [8,10]. These pharmacokinetic differences are not merely technical details; they likely contribute to heterogeneity in breast cancer risk by shaping local estrogen exposure and downstream signaling within breast tissue [8-12]. The pharmacokinetic and clinical implications of different routes of estrogen administration are outlined in Table 2.

Taken together, the diversity of hormone types, doses, and delivery routes helps explain the wide variation in breast cancer risk reported across epidemiological studies of MHT [2-7]. Each regimen shapes endocrine signaling within the breast microenvironment in a distinct way, modulating pathways such as estrogen and progesterone receptor activation, RANKL signaling, and estrogen-mediated DNA damage [2,13,14]. Treating MHT as a single exposure is therefore biologically naïve and clinically misleading; formulation-specific risk stratification should instead form the basis of patient counseling and future clinical research [5-7].

3. MECHANISMS OF ESTROGEN AND PROGESTERONE ACTION IN BREAST CANCER

Estrogen and progesterone exert their biological effects primarily through estrogen and progesterone receptors (ER and PR), members of the nuclear receptor superfamily characterized by conserved ligand-binding and DNA-binding domains [15,16]. Ligand binding induces receptor dimerization, conformational change, and recruitment of transcriptional coactivators, thereby regulating gene expression programs that control cellular proliferation, differentiation, and survival [15,16]. In breast tissue, estrogen promotes tumor progression by stimulating cell-cycle entry and inhibiting apoptosis, in part through upregulation of anti-apoptotic genes such as BCL2 [17-19]. Progesterone, by contrast, is a key proliferative hormone in the human breast, and synthetic progestins used in hormone therapy have been associated with higher cancer risk than estrogen alone due to their combined stimulation of proliferation and suppression of apoptotic signaling [3,11].

During tumor progression, hormone receptor–positive cells undergo a functional shift from paracrine to autocrine signaling, enabling sustained growth independent of stromal support [13,20-22]. Progesterone-regulated mediators such as amphiregulin and Notch ligands play a central role in this transition by reinforcing proliferative circuits within mammary epithelial cells [13,20-22]. In parallel, progesterone expands mammary progenitor and stem cell populations, thereby increasing susceptibility to malignant transformation, while synthetic progestins may reactivate dormant premalignant cells and further elevate risk during long-term exposure [4,23,24]. These effects provide a biologically coherent explanation for the disproportionate oncogenic risk observed with combined estrogen–progestin therapy relative to estrogen-only regimens.

Alterations in progesterone receptor signaling further shape tumor behavior. Dysregulation of PR isoforms, particularly a predominance of PRA over PRB, is observed in premalignant and malignant lesions and is associated with reduced cell adhesion, increased migration, and invasive behavior [25-29]. This isoform imbalance remodels transcriptional responses to progesterone and shifts the cellular phenotype toward a more aggressive and therapy-resistant state, reinforcing the tumor-promoting effects of progestogen exposure. At the chromatin level, ER and PR signaling is modulated by transcriptional coactivators such as SRC-3 (also known as AIB1), which is frequently amplified or overexpressed in breast cancer and enhances hormone-driven gene transcription [30].

Hormone receptor activation is also accompanied by extensive epigenetic reprogramming, including altered DNA methylation and histone modifications, which disrupt normal transcriptional control and lock cells into oncogenic expression programs [31-33]. Together, these receptor-dependent and epigenetic mechanisms integrate hormonal signaling into stable molecular changes that promote tumor initiation, progression, and resistance to endocrine therapy.

4. MOLECULAR PATHWAYS LINKING MHT TO BREAST CARCINOGENESIS

Menopausal hormone therapy (MHT) influences breast carcinogenesis through interconnected genomic, non-genomic, and metabolic pathways that regulate cellular proliferation, differentiation, DNA repair, and interactions with the tumor microenvironment, with distinct biological effects observed for estrogen-only therapy (ET) and estrogen–progestin therapy (EPT) depending on formulation and route of administration [14]. These pathways do not operate in isolation; instead, they converge to create a permissive molecular landscape for tumor initiation, progression, and therapeutic resistance. The key molecular pathways are summarized in Table 3.

At the genomic and non-genomic levels, estrogen, primarily 17β-estradiol, activates nuclear estrogen receptors ERα and ERβ to induce transcription of growth-promoting genes while simultaneously triggering rapid kinase signaling via membrane-associated estrogen receptors and the G protein–coupled estrogen receptor (GPER) [14]. These non-genomic actions engage mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/Akt, and cyclic adenosine monophosphate (cAMP) pathways, thereby enhancing proliferation, migration, and survival of breast epithelial cells [14]. This dual genomic–non-genomic signaling architecture enables estrogen to sustain oncogenic programs even under fluctuating hormone levels.

Table 3. Key molecular pathways linking MHT to breast carcinogenesis

Pathway/mechanism	Hormone involved	Key molecular effects	Ref
Genomic ER signaling	Estrogen (17β-estradiol)	ERα/ERβ activation → transcription of BCL2, cyclin D1; cell-cycle progression and anti-apoptosis	[14-16]
Non-genomic kinase signaling	Estrogen (membrane ER / GPER)	Rapid activation of MAPK, PI3K/Akt, cAMP → enhanced proliferation and migration	[14]
Estrogen metabolite genotoxicity	Catechol estrogen quinones	ROS generation, DNA adduct formation; NQO2 polymorphisms increase luminal BC risk	[34]
RANKL/RANK/NF-κB	Progesterone / synthetic progestins	Expansion of mammary stem/progenitor cells; upregulation of cyclin D1	[35]
PI3K/Akt and MAPK/ERK	Progestogens	Proliferation, migration; synergy with estrogen signaling	[35]
STAT3/ErbB2/PR complexes	MPA (synthetic progestin)	Receptor promiscuity, fatty acid synthase induction, ROS-mediated DNA damage	[35]
PGRMC1 phosphorylation	Norethindrone + estradiol	Proliferative signaling via PR membrane component 1; synergistic E–P effects	[35]
PR isoform imbalance (PRA > PRB)	Progesterone / synthetic progestins	Reduced cell adhesion, increased migration and invasion; therapy resistance	[25-29]
Epigenetic remodeling	Estrogen + progesterone	DNA methylation/histone modification changes at ESR1, CYP19A1, BRCA1; stable oncogenic programs	[31-33]
Integrin–FAK / ECM signaling	Estrogen (ER-independent)	Type I collagen activates α2β1 integrin → ER-independent growth, endocrine resistance.	[36]

Estrogen metabolism adds a second, genotoxic layer to carcinogenesis. Cytochrome P450–mediated conversion of estrogens generates reactive catechol estrogens that form quinones, produce reactive oxygen species, and create mutagenic DNA adducts [34]. Although detoxification pathways involving catechol-O-methyltransferase (COMT) and NAD(P)H quinone oxidoreductase 2 (NQO2) mitigate this damage, polymorphisms in NQO2 are associated with increased risk of luminal-type breast cancer, underscoring the intrinsic carcinogenic potential of estrogen metabolites themselves [34].

Progestogens further modulate tumor biology through both progesterone receptor (PR)–dependent and non-genomic mechanisms. Activation of RANKL/RANK/NF-κB signaling expands mammary stem and progenitor cell populations and upregulates cyclin D1, while PI3K/Akt and MAPK/ERK pathways promote proliferation and migration [35,36]. Tumor tissue often exhibits a pro-tumorigenic shift toward proliferative progesterone metabolites such as 5α-dihydroprogesterone over apoptotic metabolites like 3α-hydroxyprogesterone, reinforcing survival signaling within the tumor microenvironment [35,36]. These effects provide a mechanistic explanation for the disproportionate oncogenic risk observed with EPT relative to ET. Synthetic progestins display distinct oncogenic signatures that further amplify these effects. Medroxyprogesterone acetate promotes formation of Stat3/ErbB2/PR complexes, exhibits receptor promiscuity, induces fatty acid synthase expression, and generates ROS-mediated DNA damage [35]. In parallel, norethindrone can stimulate proliferation via phosphorylation of progesterone receptor membrane component 1 (PGRMC1), particularly in the presence of estradiol, highlighting synergistic estrogen–progestin interactions at the molecular level [35]. These compound-specific effects underscore why treating all progestogens as biologically equivalent is mechanistically indefensible. Gene expression profiling provides additional support for formulation-specific differences in oncogenic signaling. EPT more strongly activates cell-cycle and DNA repair programs than ET, upregulating genes such as cyclin E2 (CCNE2) and radiation-sensitive protein 51 (RAD51), which drive replication stress and chromosomal instability [14]. These transcriptional changes intersect with oncogenic networks involving AKT1, KRAS, TP53, and PTEN, collectively promoting genomic instability and tumor progression [14].

Hormone signaling is further shaped by microenvironmental cross-talk. Fibroblast growth factor (FGF), ribosomal protein S6 kinase A3 (RSK2)–mediated PR phosphorylation promotes aggressive phenotypes, while prolactin–signal transducer and activator of transcription 5A (STAT5), ErbB signaling enhances proliferation [36-38]. Extracellular matrix components, particularly type I collagen, promote estrogen receptor–independent growth and endocrine resistance through integrin–focal adhesion kinase (FAK) pathways, thereby enabling tumor persistence under hormone-

deprived conditions [36-38]. Obesity amplifies these effects by enhancing inflammatory signaling, extracellular matrix remodeling, epithelial–mesenchymal transition, and proliferative gene signatures, leading to increased invasiveness and therapeutic resistance, particularly in estrogen receptor–positive disease [35] (Figure 1).

5. INFLUENCE OF HORMONE TYPE ON THE BREAST TISSUE MICROENVIRONMENT

Hormone therapy reshapes the breast tissue microenvironment in ways that directly influence carcinogenic susceptibility, primarily by altering mammographic density (MD), local hormone metabolism, stromal cell composition, and extracellular matrix (ECM) architecture [39-41]. These changes are not merely imaging artifacts but reflect biologically meaningful remodeling of the breast that modifies both intrinsic cancer risk and the effectiveness of screening strategies. Mammographic density is a strong independent risk factor for breast cancer and is consistently increased by combined estrogen-progestin therapy, whereas estrogen-only regimens exert minimal or no significant effects [39]. Quantitative analyses indicate that MD mediates approximately 10–11% of the total hormone replacement therapy-associated breast cancer risk, with the magnitude of change varying according to hormone composition, dose, and duration of exposure [39]. Clinically, this density increase not only reflects heightened epithelial and stromal proliferation but also reduces the sensitivity of mammographic screening, thereby increasing the likelihood of interval cancers and delayed diagnosis in current users of combined regimens [39,40]. The formulation-specific effects of hormone therapy on mammographic density and their implications for breast cancer risk are summarized in Table 4

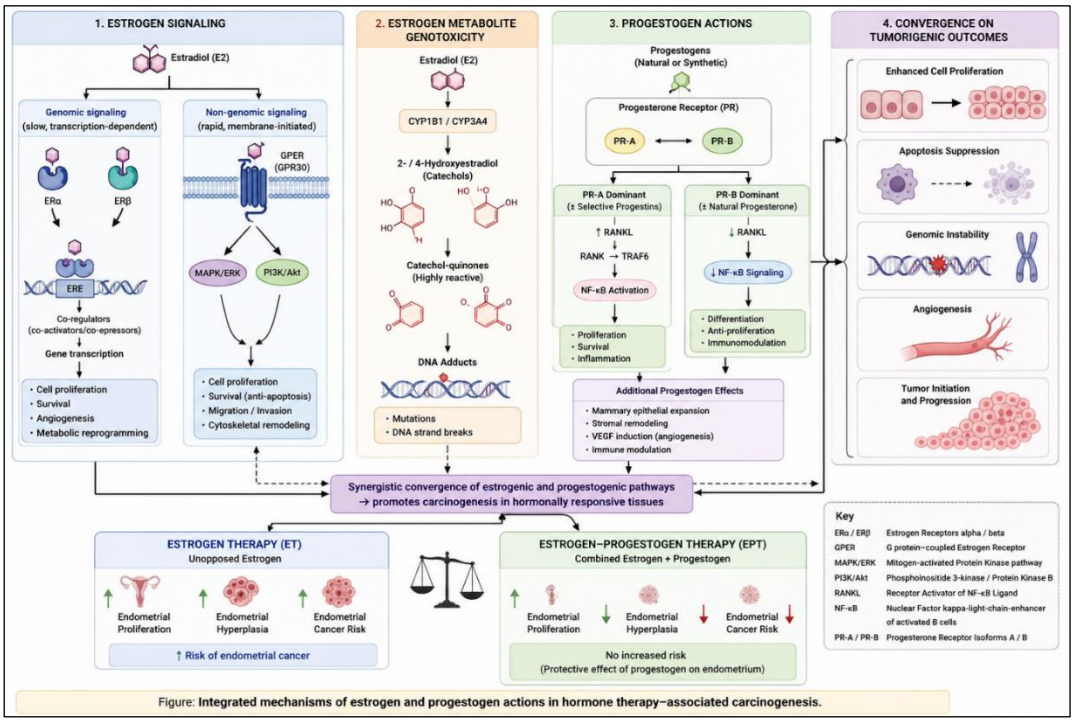


Figure 1. Schematic overview of molecular pathways linking MHT to breast carcinogenesis.

Table 4. Impact of hormone therapy type on mammographic density and breast cancer risk

Hormone therapy type	Finding on mammographic density (MD)	Implications for breast cancer risk	Ref
Estrogen + progestin (E+P)	Mean MD increase of ~6.0% at year 1 vs. 0.9% decrease in placebo; effect attenuated but sustained (~4.9% at year 2)	Strongly associated with increased breast density and higher breast cancer risk.	[3,39]
Sequential/continuous E+P regimens	Highest proportion of women with mixed/dense breasts (~75%) showed MD increase.	Sequential and continuous regimens carry the greatest risk elevation	[3,39]
Estrogen-only (E)	Minor or no significant increase in MD	Lower risk association compared with combined regimens	[39]
CEE-containing therapy	Estrone sulfate levels increased; each 1 nmol/L rise correlated with ~1.3% higher MD	Suggests local estrogen activation contributes to density changes	[12]
Current HT users (any type)	MD mediates ~10–11% of total HT-related breast cancer risk	MD acts as a partial mediator of hormone-related carcinogenic effects	[39]

Formulation-specific effects further shape density-related risk. Conjugated equine estrogen (CEE) therapy increases circulating estrone sulfate levels, and each incremental rise correlates with higher MD, reflecting enhanced local conversion to active estrogens via steroid sulfatase within breast tissue [11,12]. This localized estrogenic amplification provides a mechanistic bridge between systemic hormone exposure and microenvironmental remodeling, reinforcing why oral CEE-containing regimens are disproportionately associated with density changes and, by extension, elevated cancer risk [11,12]. Hormone exposure also remodels stromal cell populations within the breast. MHT has been shown to enrich mesenchymal stem-like cells and alter benign epithelial phenotypes, suggesting a role in priming the tissue for malignant transformation by expanding cell populations with enhanced proliferative and migratory potential [41]. These stromal shifts contribute to a permissive niche that facilitates tumor initiation and progression, particularly in the context of sustained hormonal stimulation.

Beyond cellular composition, hormonal influences extend to the extracellular matrix. Type I collagen, a dominant ECM component, promotes estrogen receptor–positive tumor cell proliferation even under hormone-deprived conditions by activating α2β1 integrin signaling, thereby facilitating a shift toward estrogen receptor–independent growth and contributing to endocrine resistance [36]. This matrix-driven signaling axis underscores how microenvironmental remodeling can stabilize oncogenic behavior even when systemic hormone levels decline, helping to explain the persistence of elevated breast cancer risk after discontinuation of combined hormone therapy [36] (Figure 2).

6. GENETIC AND RECEPTOR CONTEXT IN HORMONE-DRIVEN CARCINOGENESIS

The biological impact of menopausal hormone therapy on breast cancer risk and progression is strongly shaped by genetic background, receptor context, and interindividual variability in hormone metabolism [42-44]. Elevated circulating levels of estradiol, testosterone, and dehydroepiandrosterone sulfate (DHEAS) are associated with increased risk of estrogen receptor (ER)–positive breast cancer, particularly luminal A– and B–like subtypes [42]. Prognosis is further influenced by cholesterol-derived metabolites such as 27-hydroxycholesterol, an endogenous selective estrogen receptor modulator whose adverse effects are most evident in low-estradiol states, thereby amplifying estrogenic signaling under conditions of systemic hormone deprivation [43].

Genetic variation in estrogen metabolism and signaling pathways modifies both risk and disease behavior. Polymorphisms in detoxification and aromatase-related genes, including NQO2, CYP19A1, and UGT2B17, alter estrogen bioavailability and have been linked to differences in breast cancer susceptibility and clinical outcomes [34,44]. Estrogen signaling also contributes to metastatic behavior, with ERα–Src pathway activation promoting bone dissemination in ER-positive tumors [44]. Pharmacogenomic studies have identified variants near ZNF423 and MIR2052HG that influence response to endocrine therapies, although large interaction analyses

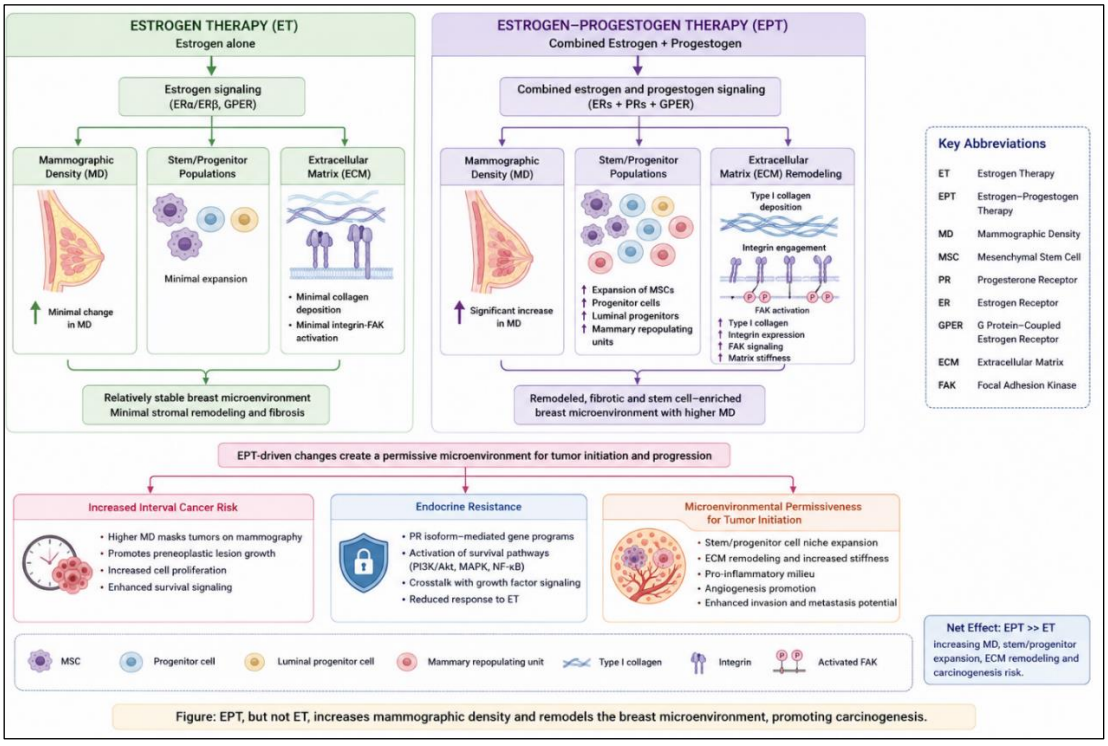


Figure 2. Effects of MHT on the breast tissue microenvironment.

suggest only limited genetic modification of MHT-associated risk in European populations [45]. Inherited mutations such as BRCA1 further shape disease biology by expanding aldehyde dehydrogenase 1 (ALDH1) positive stem cell populations linked to tumor initiation and therapy resistance [46]. Finally, dynamic crosstalk among estrogen, progesterone, and androgen receptors regulates ERα activity. It contributes to endocrine resistance, while epigenetic modifications of key genes including ESR1, CYP19A1, and BRCA1 alter receptor expression and hormone sensitivity, integrating chromatin-level regulation into hormone-driven carcinogenesis [45,46].

7. INTERACTIONS WITH ENDOCRINE AND METABOLIC PATHWAYS

Endocrine and metabolic factors interact closely with hormone exposure to shape breast cancer risk and therapeutic response. Alcohol consumption is consistently associated with increased breast cancer incidence in postmenopausal women, even at moderate intake, and is accompanied by elevations in estrone sulfate and dehydroepiandrosterone sulfate (DHEAS), reflecting stimulation of adrenal steroidogenesis and increased peripheral aromatization of androgens to estrogens after menopause [47]. This metabolic amplification of estrogenic signaling provides a plausible mechanistic link between lifestyle factors and hormone-driven carcinogenesis.

Evidence from the Women's Health Initiative highlights formulation-specific endocrine effects of MHT. Combined conjugated equine estrogen (CEE) plus medroxyprogesterone acetate significantly increases breast cancer incidence independently of baseline hormone levels, suggesting dominant direct progestin effects on breast epithelial proliferation [48]. In contrast, estrogen-only therapy reduces breast cancer incidence, an effect partly mediated by increased sex hormone–binding globulin, which lowers bioavailable estrogen and attenuates downstream receptor signaling [49]. These divergent endocrine profiles reinforce the biological non-equivalence of ET and EPT. At the molecular level, interactions between hormone receptors and growth factor pathways drive endocrine resistance. In tamoxifen-resistant ER-positive tumors, loss of Rho guanine nucleotide dissociation inhibitor (Rho GDI) leads to upregulation of androgen receptor and epidermal growth factor receptor (EGFR) signaling, enabling tamoxifen to function as an agonist through ERα phosphorylation and sustained proliferative signaling [50]. This receptor cross-talk provides a mechanistic bridge between metabolic context, hormone therapy exposure, and treatment failure.

8. CLINICAL CORRELATIONS AND MOLECULAR PHENOTYPES OF MHT-ASSOCIATED BREAST CANCER

Clinical evidence consistently supports biologically distinct effects of estrogen-only therapy and combined estrogen–progestin therapy on breast cancer risk and tumor phenotype. The Women's Health Initiative trials demonstrated that CEE plus medroxyprogesterone acetate increases breast cancer incidence, with effects persisting long after discontinuation, whereas CEE alone reduces risk in women with prior hysterectomy, reinforcing the mechanistic role of progestins in tumor promotion [2,51]. These divergent outcomes provide the strongest causal evidence for formulation-specific oncogenic effects of MHT. Large cohort studies and meta-analyses confirm that any hormone therapy increases breast cancer risk, with EPT conferring substantially higher risk than ET, particularly with long durations of use and continuous regimens that can nearly double incidence rates [5,52]. Risk is strongly linked to estrogen receptor–positive tumors and both ductal and lobular histologies with EPT, while ET shows a preferential association with lobular cancers [5,53]. Molecular profiling further connects MHT exposure with luminal A phenotypes, and risk is modified by body mass index, ethnicity, and mode of cancer detection [5,6,53]. These formulation-specific clinical risk profiles are summarized in Table 5.

Table 5. Formulation-specific breast cancer risk profiles associated with MHT: clinical summary

MHT type	Tumor phenotype	Relative risk (approximate)	Key modifying factors	Ref
ET (CEE only)	Lobular histology (preferential)	Neutral to reduced (RR <1.0)	Prior hysterectomy; BMI inversely correlates with risk	[2,5,49,51]
EPT (CEE+MPA)	ER+/PR+ ductal and lobular	Increased (RR ~1.24–2.0 with >5 yr use)	Continuous > sequential regimens; longer duration; higher BMI	[2,5,49,51]
EPT with dydrogesterone / micronized P	ER+ tumors	Lower vs. MPA-based EPT	Observational data; limited randomized trial evidence	[9]
Any current HT use	All subtypes	Elevated vs. never use	Reduced screening sensitivity due to increased MD; interval cancer risk	[40,52]
ET (post-discontinuation)	ER+ tumors	Risk attenuates over time	Persistent effect ≥5 yr post-cessation for EPT; less for ET	[51]

Current users, especially of combined regimens, exhibit the greatest increases in mammographic density, reducing screening sensitivity and increasing the likelihood of interval cancers, thereby supporting the need for enhanced imaging strategies such as tomosynthesis or magnetic resonance imaging [40]. In breast cancer survivors, evidence regarding the safety of systemic MHT remains mixed, with some trials reporting increased recurrence and others showing no significant risk; however, vaginal estrogen use alongside aromatase inhibitors appears to increase recurrence, underscoring the need for individualized risk–benefit decision-making [54]. Finally, emerging therapies such as high-dose estetrol (E4) have shown favorable safety profiles and early signals of efficacy in heavily pretreated ER-positive/HER2-negative metastatic disease, suggesting potential utility in endocrine-resistant settings and future hormone replacement strategies [55].

9. FUTURE MECHANISTIC AND THERAPEUTIC DIRECTIONS

Future research in MHT-associated breast carcinogenesis should prioritize the development of safer hormonal formulations, refined risk stratification, and personalized therapeutic strategies informed by molecular profiling [56,57]. Novel agents such as estetrol (E4) show promise in delivering anti-tumor activity with improved tolerability, offering potential options for endocrine-resistant estrogen receptor–positive disease while preserving quality of life [55-57]. Clinically, combination strategies integrating endocrine therapy with targeted agents, including CDK4/6 inhibitors and PI3K–Akt–mTOR inhibitors, are reshaping management, with biomarkers such as the PEPI score, DNA damage indicators, and genomic signatures like PAM50 guiding treatment selection [56]. Mechanistically, the field is moving toward multi-omics integration and deep-learning–based modeling to unravel tumor heterogeneity and resistance, while metabolic dependencies such as fatty acid oxidation and glycolysis offer emerging therapeutic targets [56,57]. Despite significant progress, key biological questions, particularly the mechanisms underlying estrogen-induced apoptosis and differential progestin effects, remain unresolved and require further investigation before full clinical translation can be achieved [56,57].

CONCLUSION

Menopausal hormone therapy is associated with breast cancer risk in a formulation-dependent manner that reflects both clinical outcomes and underlying molecular mechanisms. Evidence from randomized trials and large observational studies consistently demonstrates that estrogen-only therapy confers a neutral or reduced breast cancer risk in women with prior hysterectomy, whereas combined estrogen–progestin therapy significantly increases risk, particularly for estrogen receptor–positive tumors. Mechanistic data support these findings by implicating progestogen-driven proliferative signaling, estrogen-mediated genotoxicity, expansion of mammary progenitor cell populations, and remodeling of the breast tissue microenvironment, including increased mammographic density.

Importantly, MHT-associated risk is further modified by individual factors such as body mass index, genetic susceptibility, baseline breast density, and hormone metabolism. Emerging hormonal formulations with improved biological safety profiles, together with advances in molecular risk stratification and biomarker-guided therapy, offer a pathway toward more individualized menopausal symptom management with reduced oncologic risk. Nonetheless, sustained mechanistic and clinical research is essential to refine formulation-specific risk estimates and support evidence-based counseling for women considering hormone therapy.

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