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Review

Menopausal Hormone Therapy: Its Role in the Prevention of Cardiovascular Diseases and the Risk of Breast Cancer in Women

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Abstract

Objective: This review was conducted to explain how menopausal hormone therapy (MHT) benefits cardiovascular diseases (CVDs) and how to control the risk of breast cancer. **Mechanism**: Estrogen deficiency, altered energy homeostasis, adipocyte changes, inflammation, and insulin resistance are responsible for the development of metabolic syndrome and CVDs. Estrogen influences hypothalamic function and maintains the energy balance, protecting menopausal women from these cardiovascular risk factors. However, estrogen metabolism plays a crucial role in the genotoxic pathway that leads to breast cancer. Moreover, MHT is associated with cell proliferation and mutation signaling pathways in breast cancer, as well as the process of growing the breast cancer stem cell. **Findings in Brief**: While MHT may have favorable effects when started early, introducing it later in the course of atherosclerosis may pose major dangers, underlining the importance of timing in hormone therapy. Estrogen-only therapy has a greater favorable effect on CVDs than the estrogen-progesterone combination. Although the connection between MHT and breast cancer is well-documented, significant knowledge gaps remain, especially regarding the long-term effects of newer MHT formulations. Current studies support using the lowest effective dose for the shortest possible duration, with a focus on tailoring therapy to individual risk factors, such as obesity, smoking, and alcohol consumption. Thus, MHT should be customized due to the intricacy of individual risk factors and differences in responses to therapy. **Conclusions**: Although MHT is effective for controlling CVDs in women entering menopause, it must be used with caution, especially in women at high risk of breast cancer.

Keywords: atherosclerosis; cardiovascular risk factors; menopausal women; obesity; estradiol; cell proliferation; mutation

1. Introduction

As individuals approach the average retirement age, typically between 50 and 70 years, they become more susceptible to a range of diseases, both mild and severe. In women, this period coincides with menopause—a natural biological transition marked by the cessation of ovarian hormone production, particularly estrogen and progesterone. The decline in these hormones is a significant contributor to the increased incidence of cardiovascular diseases (CVDs) among women over 55 years. Common cardiovascular conditions in this demographic include coronary heart disease (CHD), myocardial infarction (MI), heart failure, venous thromboembolism (VTE), and deep vein thrombosis [1–5].

Menopausal hormone therapy (MHT) has been proposed as a potential intervention to address the rising prevalence of CVDs among menopausal women. It is primarily used to relieve menopausal symptoms, such as hot flashes, night sweats, and vaginal dryness. It involves the administration of estrogen, and sometimes progesterone or progestin, to restore hormonal balance. While MHT can improve quality of life and prevent bone loss, it is not without risks, including an increased risk of blood clots, breast cancer, and heart disease—particularly for women who begin therapy after age 60 years or use it long-term. These risks have led to the cautious prescription of MHT, tailoring it to individual health needs and recommending the shortest effective duration [1,6,7]. Historically, MHT was widely used; however, after the Women's Health Initiative (WHI) found an increased risk of CVDs, breast cancer, and stroke associated with MHT in 2004, its use declined significantly. More recent research, including several meta-analyses, has highlighted the potential protective effects of estrogen against CVDs, although the evidence remains controversial [8–10].

MHT impacts cardiovascular health by affecting lipid profiles, blood pressure, and glucose metabolism. Reduced estrogen levels during menopause increase low-density lipoprotein (LDL) cholesterol and triglycerides, reduce high-density lipoprotein (HDL) cholesterol, and elevate blood pressure, collectively raising the risk of atheroscle-

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rosis, MI, and stroke. Estrogen deficiency also impairs glucose tolerance and insulin sensitivity, increasing the risk of type 2 diabetes and cardiovascular complications. Research suggests that starting MHT within 10 years of menopause onset may mitigate these risks, but its safety in women over 60 years remains uncertain [5,8–10].

In parallel, breast cancer risk has become a prominent concern associated with MHT. Epidemiological studies consistently demonstrate that the prolonged use of combined estrogen-progesterone therapy increases the risk of breast cancer, especially when therapy exceeds 3 to 5 years. Estrogen's role in breast tissue involves stimulating cell proliferation and activating genotoxic pathways, which may contribute to malignancy. These findings emphasize the need to carefully balance the benefits of MHT for symptom relief and cardiovascular protection against its potential to elevate breast cancer risk [1,11,12].

While CVDs and breast cancer have distinct etiologies, estrogen deficiency emerges as a shared factor that links these conditions. Estrogen's protective effects on cardiovascular health are diminished post-menopause, while altered estrogen metabolism contributes to carcinogenesis in breast tissue. This dual role underscores the complexity of prescribing MHT, which must consider individual risk profiles to optimize its benefits while minimizing harm.

This review aims to explore the impact of MHT on CVDs in menopausal women, focusing on its effects on lipid levels, blood pressure, glucose tolerance, and metabolic syndrome, particularly obesity. It also examines the mechanisms through which MHT may influence breast cancer risk. By addressing these areas, the review seeks to provide a nuanced understanding of how MHT can be used effectively and safely to manage menopausal health.

2. Understanding Menopause, MHT, and CVDs in Menopausal Women

Menopause marks a critical transition in a woman's life. It is characterized by the cessation of menstrual cycles and a significant decline in estrogen levels. This hormonal shift has profound effects on cardiovascular health, leading to both primary and secondary outcomes that heighten cardiovascular risk [5,13–15]. Estrogen is integral in maintaining cardiovascular health through its influence on lipid metabolism, blood pressure regulation, and glucose tolerance. As estrogen levels decrease during menopause, these protective mechanisms weaken, resulting in notable adverse changes in cardiovascular risk factors [9,10,16–18]. One primary outcome of menopause is the alteration in lipid concentrations. Estrogen benefits lipid profiles by increasing HDL cholesterol, often referred to as good cholesterol, and decreasing LDL cholesterol, known as bad cholesterol. With reduced estrogen levels, women experience an unfavorable shift in lipid concentrations, characterized by an increase in LDL cholesterol and a decrease in HDL cholesterol [8,15,19]. This dyslipidemia accelerates the development of atherosclerosis, a condition in which plaque builds up in the arterial walls, leading to a higher risk of coronary artery disease and other cardiovascular events. Another frequent primary outcome of menopause is an increase in blood pressure [5,14,19,20]. Estrogen contributes to blood pressure regulation through its effects on vascular function and sodium balance. As estrogen levels decline, systolic and diastolic blood pressure tend to rise. Elevated blood pressure, or hypertension, further contributes to the risk of CVDs such as heart attack, stroke, and heart failure [2,10,13,21,22]. The combination of increased blood pressure and adverse changes in lipid profiles creates a compounded risk for women during and after menopause. This heightened risk is partly due to the declining levels of estrogen, a hormone that plays a vital role in maintaining glucose metabolism. Estrogen enhances insulin sensitivity and supports glucose uptake in peripheral tissues, thereby helping to regulate blood sugar levels. During menopause, reduced estrogen levels can lead to insulin resistance, which increases the risk of impaired glucose metabolism and type 2 diabetes. Women undergoing menopause are more likely to experience severe cardiovascular conditions due to the cumulative effects of dyslipidemia, hypertension, and impaired glucose metabolism [19,23–25]. The incidence of heart disease, which is lower in premenopausal women than in men, increases after menopause and can surpass that in men. To address these heightened risks, effective management strategies are crucial. Regular monitoring of lipid levels, blood pressure, and glucose tolerance is essential for early detection and intervention. Lifestyle modifications, such as adopting a heart-healthy diet, engaging in regular physical activity, and maintaining a healthy weight, are beneficial. Additionally, pharmacological treatments may be required to manage dyslipidemia, hypertension, and glucose intolerance [7,23,24,26]. MHT has been considered a means to alleviate some menopausal symptoms and potentially improve cardiovascular outcomes, but its benefits must be weighed against its risks. In summary, menopause induces significant cardiovascular changes, primarily due to reduced estrogen levels, leading to unfavorable shifts in lipid profiles, increased blood pressure, and impaired glucose tolerance. These changes result in a higher risk of CVDs, including coronary artery disease, heart failure, and stroke [7,23,27].

Comprehensive management strategies are essential to address the interconnected risks of menopause, estrogen deficiency, and obesity, which contribute to metabolic syndrome and cardiovascular complications (Fig. 1, Ref. [7,24,26,28]). Menopause leads to a significant drop in estrogen, disrupting energy balance and contributing to altered body weight, fat distribution, and increased androgen levels, which elevate obesity risk [6,7,23,25]. Hormonal changes drive adipocyte hyperplasia and hypertrophy, triggering local inflammation marked by elevated interleukin-6 (IL-6), tumor necrosis factor- α (TNF-α), and

C-reactive protein (CRP), leading to systemic inflammation and insulin resistance [8,23,24,26,29,30]. Dysfunctional adipose tissue further alters adipokine secretion, reducing adiponectin and increasing leptin, thereby worsening metabolic disturbances [7,23,24,26]. As adipose tissue becomes overwhelmed, ectopic fat deposition and lipotoxicity affect organs such as the liver and muscle, increasing insulin resistance—a central component of metabolic syndrome [8,9]. This syndrome, characterized by the interplay of systemic inflammation, insulin resistance, and hormonal imbalances, heightens the risk of CVDs, including atherosclerosis, which involves fatty deposits in arteries and elevates the risk of heart disease and stroke [8,9,15,28]. Fig. 1 (Ref. [7,24,26,28]) underscores how menopause drives these changes through estrogen deficiency, inflammation, and adipose tissue dysfunction, highlighting the need for targeted interventions to manage these risks effectively [8,9,15,23–30].

MHT is commonly administered to alleviate menopausal symptoms, such as hot flashes and vaginal dryness, but its effects on metabolic syndrome and CVDs in postmenopausal women are complex and multifaceted. The clinical evidence regarding MHT's role in managing metabolic syndrome is mixed. On one hand, some studies suggest that MHT, particularly when started around the time of menopause, can improve lipid profiles by increasing HDL cholesterol, decreasing LDL cholesterol, and enhancing insulin sensitivity, which may mitigate the components of metabolic syndrome [23–25,31,32]. Estrogen, the primary hormone used in MHT, has been shown to exert favorable effects on vascular function and glucose metabolism. Conversely, other research has raised concerns about the safety of MHT, particularly regarding its impact on cardiovascular health. Large-scale trials like that by the WHI have revealed that certain forms of MHT may be associated with an increased risk of adverse cardiovascular events, including MI, stroke, and VTE [33–35]. These risks appear to vary depending on the type of hormone used (estrogen alone *vs.* estrogen-progestin combinations), the dose, and the timing of initiation relative to the onset of menopause. For example, estrogen-progesterone combinations have been linked with a higher risk of thrombotic events compared to estrogen alone [1,10,13,14]. The timing hypothesis suggests that initiating MHT close to the onset of menopause may offer cardiovascular benefits, whereas starting it later in life could pose increased risks. This has led to the recommendation that MHT should be individualized, taking into account the woman's overall health, risk factors for CVDs, and the severity of menopausal symptoms [5,8,9]. In summary, while MHT might provide benefits in managing metabolic syndrome and improving certain cardiovascular risk factors, its use must be carefully evaluated on a case-by-case basis. Ongoing research and clinical trials aim to clarify the nuanced effects of MHT, refine treatment guidelines, and ultimately ensure that postmenopausal women receive optimal care based on their specific health needs and risk profiles.

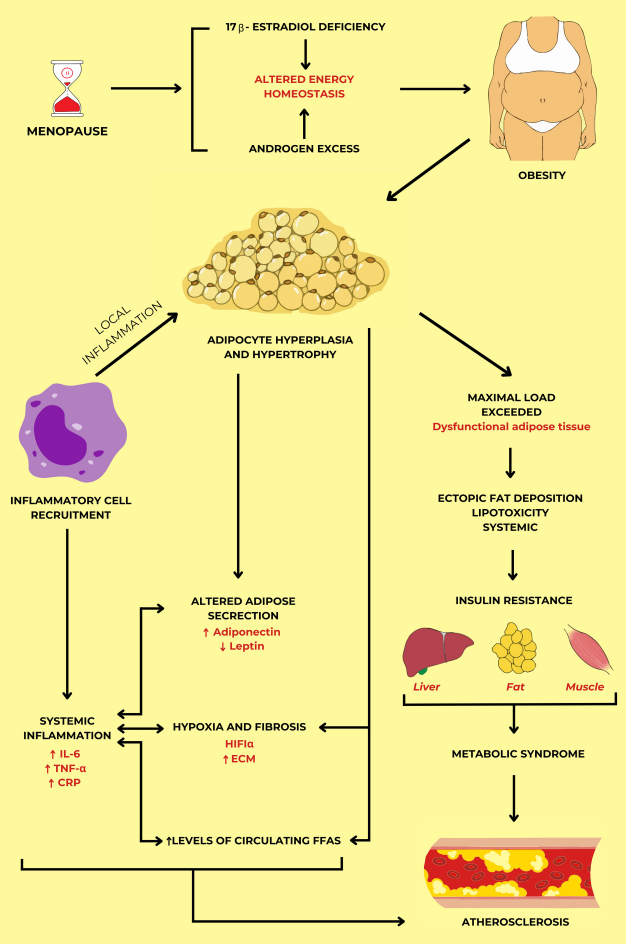

Fig. 1. The mechanism of the development of atherosclerosis in menopausal women through metabolic syndrome and systemic inflammation. Energy metabolism changes associated with sex hormone disorders in postmenopausal women lead to adipose tissue dysfunction in obesity. Due to the insufficient storage capacity of adipocytes, insulin resistance, and metabolic syndrome appear through increased lipolysis, hypoxia, and altered adipokine secretion. As a result, atherosclerosis is established following metabolic syndrome and systemic inflammation. The figure was drawn by summarizing the findings of references [7,24,26,28] with permission under The Creative Commons Attribution 4.0 Licenses and Attribution Non-Commercial License. Abbreviations: IL-6, interleukin-6; TNFα, tumor necrosis factor-α; CRP, C-reactive protein; HIFIα, hypoxia-inducible factor-I α; ECM, extracellular matrix; FFAS, free fatty acids; ↑, increase; ↓, decrease. The figures are created using Canva (https://www.canva.com).

3. The Benefits of MHT in CVDs

The complex network of physiological, neuroendocrine, and metabolic processes that govern energy balance, body weight regulation, and the role of the hypothalamus as a central regulator is illustrated in Fig. 2 (Ref. [25]). At the heart of this system is the hypothalamus, a critical brain region that integrates and processes a variety of signals from different parts of the body to maintain energy homeostasis. The hypothalamus receives metabolic signals, such as leptin and insulin, which are key hormones involved in appetite regulation and energy expenditure. Leptin, secreted by adipose tissue, provides the brain with feedback on the body's energy reserves, while insulin, produced by the pancreas, influences food intake and energy storage [8,23,24,26]. Fig. 2 also highlights the role of gastrointestinal satiety signals, including cholecystokinin and glucagon-like peptide-1, which are released from the stomach and small intestine in response to food intake [22–25]. These hormones communicate with the hypothalamus via the vagal afferent neurons and the paracrine pathway, signaling fullness and reducing food consumption. The nodose ganglion, which contains the cell bodies of these afferent neurons, acts as a relay station, transmitting information from the gut to the brain. The interaction between these signals and the hypothalamus is essential for regulating appetite and preventing overeating. Moreover, Fig. 2 illustrates the influence of 17β-estradiol, an estrogen hormone that modulates hypothalamic function and affects energy balance [15,25,26]. Specifically, it modulates the release of gonadotropin-releasing hormone, crucial for reproductive function, by providing both positive and negative feedback to control the menstrual cycle and ovulation. Additionally, 17β-estradiol influences the hypothalamic-pituitary-adrenal axis, affecting the stress response and cortisol levels. It also plays a role in thermoregulation, which is linked to menopausal symptoms like hot flashes, and regulates appetite and energy balance through its impact on hypothalamic neuropeptides. Beyond these functions, 17β-estradiol contributes to neuroprotection and cognitive functions, potentially reducing the risk of neurodegenerative diseases and supporting memory and learning. Its diverse effects on the hypothalamus make it a key hormone in maintaining various aspects of health, particularly in women [17,36]. Estradiol impacts the hypothalamus by enhancing its sensitivity to satiety signals and promoting pathways that increase energy expenditure. One such pathway involves the activation of brown adipose tissue (BAT), which is specialized in thermogenesis, the process of heat production. BAT thermogenesis, driven by uncoupling protein 1 activity, contributes to increased energy expenditure and helps maintain body temperature. Furthermore, the browning of white adipose tissue (WAT), a process in which white fat cells take on characteristics of brown fat cells, is also promoted, enhancing the body's capacity to burn calories. The combination of a reduction in food intake, increased thermogenesis, and the browning of white fat results in a net decrease in body weight. Fig. 2 underscores the importance of the hypothalamus in coordinating these diverse signals to achieve energy homeostasis. This coordination is crucial for preventing obesity and related metabolic disorders as it ensures that energy intake matches energy expenditure. Disruptions in this delicate balance can lead to weight gain or loss, highlighting the complexity of the body's regulatory mechanisms [23,25,26,37]. Overall, Fig. 2 provides a comprehensive overview of the multifaceted interactions between the peripheral signals and central neural pathways that regulate energy balance and body weight.

Fig. 3 (Ref. [38]) depicts the differential effects of MHT on vascular health during the progression from early to established atherosclerosis in detail. Fig. 3A focuses on early atherogenesis, wherein the endothelium, the thin layer of cells lining the blood vessels, plays a vital role in maintaining vascular homeostasis and preventing the onset of atherosclerosis. In this early stage, nitric oxide (NO) is a key mediator of vascular health, promoting vasodilation, which helps maintain open and flexible blood vessels, thereby reducing blood pressure and improving blood flow. NO also plays a critical role in reducing inflammatory activation [8,9,19,35,39]. Inflammation is a driving factor in atherosclerosis, and by inhibiting inflammatory pathways, NO reduces the adhesion and migration of leukocytes (white blood cells) to endothelial cells. This is important because leukocyte adhesion is among the first steps in atherosclerotic plaque development. NO further contributes to decreasing lesion progression by limiting the activation of platelets, which are involved in blood clot formation, and reducing the adhesion of monocytes to the endothelium. Once adhered, monocytes can migrate into the vessel wall and differentiate into macrophages, which engulf oxidized LDL particles, leading to foam cell formation, which characterizes early atherosclerotic lesions [35]. MHT, when administered during this early stage, can positively modulate these processes. It reduces levels of endothelin and cyclooxygenase-2, which are associated with vasoconstriction and inflammation, respectively [40]. It also decreases the expression of cell adhesion molecules (CAMs) on the endothelial surface, which, in turn, leads to a reduction in macrophage accumulation and the levels of pro-inflammatory cytokines such as monocyte chemoattractant protein-1 and TNF-α [7,8,39]. CAMs are crucial mediators of leukocyte-endothelial interactions, facilitating the binding and transmigration of immune cells like monocytes to and across the endothelial barrier. By downregulating CAM expression, MHT reduces leukocyte adhesion, thereby limiting the infiltration of inflammatory cells into the arterial wall, a key process in early atherogenesis. This reduction in leukocyte adhesion contributes to a lower inflammatory burden within the vasculature, slowing the progression of atherosclerotic lesions. TNF-α, on the other hand, is a potent pro-inflammatory cytokine that

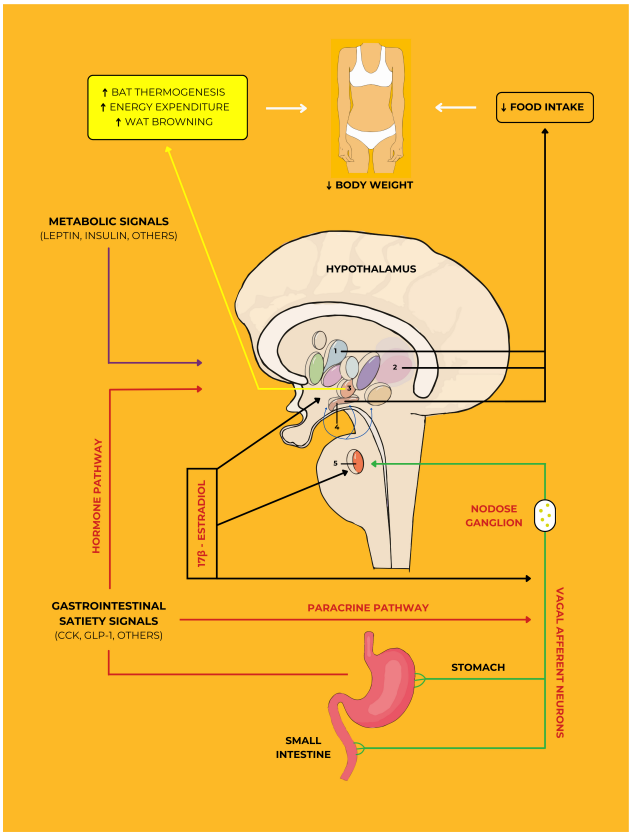

Fig. 2. The essential role of estrogen and meal-related gastrointestinal signals in reducing body weight. The VANs are activated through a paracrine-neuronal pathway and then stimulate secondary neurons located in the NTS (shown in nucleus 5). These signals induce a variety of neurons located in different nuclei that control feeding behavior in the hypothalamus. While circulating estrogens respond to these signals by activating on all levels of the VANs, NTS, and the hypothalamic nuclei such as PVH, LH, VMH, and ARC (shown in nuclei 1, 2, 3, and 4, respectively), gastrointestinal satiety signals through a hormonal pathway, as well as metabolic signals, also act upon these nuclei. Remarkably, estrogens can reduce the levels of AMPK in the VMH. Finally, estrogen activity through the VMH-SNS-BAT pathway and activated hypothalamic nuclei contributes to an increase in BAT thermogenesis, energy expenditure, WAT browning, and a decrease in food intake. This figure was adapted from Vigil *et al.* [25] with permission under The Creative Commons Attribution License. Abbreviations: VANs, vagal afferent neurons; NTS, nucleus of the solitary tract; PVH, paraventricular hypothalamus; LH, lateral hypothalamus; VMH, ventromedial hypothalamus; SNS, sympathetic nervous system; ARC, arcuate nucleus; AMPK, adenosine monophosphate-activated protein kinase; BAT, brown adipose tissue; WAT, white adipose tissue; CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; ↑, increase; ↓, decrease.

plays a central role in the inflammatory cascade associated with atherosclerosis [8,26]. Elevated levels of TNF-α promote the expression of CAMs and other inflammatory mediators, exacerbating vascular inflammation and endothelial dysfunction. By decreasing TNF-α levels, MHT mitigates its deleterious effects on the endothelium, contributing to the preservation of vascular function and a reduction in lesion formation. These effects collectively result in decreased vascular smooth muscle cell proliferation and LDL oxidation [8,19]. Oxidized LDL is more atherogenic (capable of promoting atherosclerosis), so reducing its levels decreases the overall atherogenicity of LDL particles and the likelihood of plaque formation.

In contrast, Fig. 3B illustrates the scenario in established atherosclerosis, where the disease has progressed, and protective endothelial functions have largely been lost. The endothelial cells are now damaged, leading to the development of a fibrous cap that covers a necrotic core composed of lipids, calcium, cellular debris, and proliferating smooth muscle cells [6,26]. These structural changes make the plaque more prone to rupture, which can precipitate a heart attack or stroke. In this advanced stage, the benefits of MHT are diminished, and the therapy may even exacerbate the condition. MHT is associated with reduced vasodilation, partly due to the decreased expression and function of estrogen receptors (ERs) on vascular cells, which play a critical role in mediating the protective effects of estrogen. Increased methylation of the *ER*α gene further reduces ER function. This loss of estrogen signaling is accompanied by increased inflammatory activation, contributing to the chronic inflammatory state seen in established atherosclerosis. Moreover, the expression of matrix metalloproteinase enzymes that degrade the extracellular matrix and weaken the fibrous cap, is increased, leading to increased plaque instability and rupture. The rupture of atherosclerotic plaques is a dangerous event as it can lead to the formation of a blood clot that may obstruct blood flow, resulting in an MI or stroke. The overall effect of MHT in this context is lesion progression and adverse outcomes due to the loss of estrogen's protective effects on the vascular system [41–44]. Consequently, while MHT may have benefits when initiated early, its introduction in the later stages of atherosclerosis may pose significant risks, emphasizing the importance of timing in the therapeutic use of hormones.

MHT plays a significant role in managing various aspects of postmenopausal women's health, particularly cardiovascular health and metabolic syndrome. Clinical trial results allow for several conclusions about MHT's efficacy in addressing these conditions [13]. With global longevity increasing, women aged 50 years and older are projected to number 1.6 billion by 2050, up from 1 billion in 2020. Natural menopause occurs at a mean age of approximately 49 years, with vasomotor symptoms like hot flashes and night sweats affecting around 75% of perimenopausal women [45]. These symptoms can persist for a decade or longer, significantly impacting women's personal, social, and work lives [13]. Furthermore, up to 84% of postmenopausal

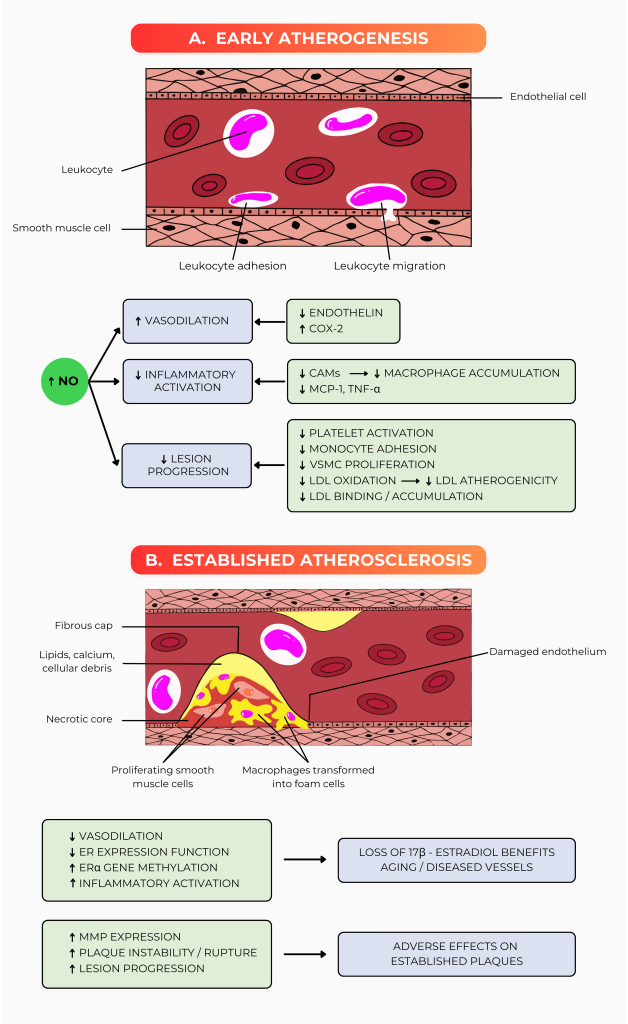

Fig. 3. The benefits of MHT in early atherosclerosis (A) and its altered biology in established atherosclerosis (B). The endothelium's vascular dysfunction is improved by starting MHT early. The delayed onset of MHT in established atherosclerosis is related to decreased vascular function, which induces the vulnerability of the vascular wall to inflammatory disturbances. This figure was adapted from an initiative review [38] with permission from The American Association for the Advancement of Science. Abbreviations: COX-2, cyclooxygenase-2; CAMs, cell adhesion molecules; MCP-1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor-α; NO, nitric oxide; VSMC, vascular smooth muscle cell; LDL, low-density lipoprotein; ER, estrogen receptor; MMP, matrix metalloproteinase; ↑, increase; ↓, decrease.

women experience genitourinary symptoms, including vulvovaginal atrophy and incontinence, underscoring the burden of menopause that MHT aims to alleviate [46]. Clinical guidelines from various medical societies advocate for MHT to effectively manage these symptoms. Despite ongoing debates about its broader health effects, the consensus is that MHT is the most effective treatment available for menopausal symptoms. However, these guidelines often lack consistency regarding outcomes such as CHD and all-cause mortality, highlighting the need for further research to evaluate MHT's health impacts [1]. For instance, the Heart and Estrogen/Progestin Replacement Study, one of the first randomized trials of estrogen-progestin therapy for the secondary prevention of CHD, found no overall cardiovascular benefit and noted an increase in early CHD events with hormone therapy use, raising concerns about the timing and appropriateness of prescribing MHT [47]. The landmark WHI trial further clarified the risks associated with MHT. Enrolling women without CVDs between the ages of 50 and 79 years, the WHI is the largest randomized placebo-controlled trial designed to evaluate systemic hormone therapy. Its initial findings indicated increased risks of CHD, stroke, and VTE among participants taking MHT compared to those on placebo. However, age-stratified analyses revealed that younger women (ages 50–59 years) and those who initiated therapy within a decade of menopause experienced lower absolute risks of adverse events, supporting the timing hypothesis that MHT's cardiovascular risks are influenced by when therapy is initiated relative to menopause [10]. Regarding long-term use, the Nurses' Health Study found a significant 41% increase in breast cancer risk among women over 50 years who used estrogen alone for more than 20 years, with a 77% increase among lean women [48]. These findings highlight the complex relationship between MHT and breast cancer risk, necessitating careful monitoring and individualized treatment approaches. Research from the Nurses' Health Study also indicated that women who began MHT within 4 years of menopause had a significantly reduced risk of CHD, with risk ratios of 0.66 for estrogen alone and 0.72 for estrogen combined with progestin [10]. Another study assessed the effects of two hormone replacement regimens in postmenopausal women, comparing conjugated estrogens with 17β-estradiol and highlighting the importance of specific formulations and dosages in determining health outcomes. For instance, women receiving conjugated estrogens at a dose of 0.625 mg daily combined with medroxyprogesterone acetate (MPA) experienced different effects to those taking 17β-estradiol [19,39]. The choice of estrogen formulation and delivery method significantly impacts the effectiveness and safety profile of MHT. Ultimately, the evolving understanding of MHT highlights the need for personalized treatment approaches. Studies show that women who initiate MHT within 3 years of menopause demonstrate substantial improvements in lipid profiles, including a 15% increase in HDL cholesterol and a 20% reduction in LDL cholesterol levels [49]. This emphasizes the critical role of early intervention in optimizing health outcomes for postmenopausal women. Transdermal estrogen has gained favor over oral forms due to its ability to bypass first-pass metabolism in the liver, reducing thrombotic risks. Evidence suggests that transdermal delivery is associated with

Table 1. Comparative effects of hormone therapies on menopausal symptoms and health outcomes.

Parameter	Estrogen-only therapy	Estrogen-progesterone combination
Timing of initiation	Best benefits when started around menopause (within 5 years)	Optimal when started within 5 years of menopause, particularly effective for women under 60 years
Cardiovascular health	Improved lipid profiles (↑HDL, ↓LDL)	Positive cardiovascular effects when initiated early, especially under 60 years
Lipid profile effects	Significant improvements (e.g., 10% ↑HDL, 15% ↓LDL)	Beneficial changes in lipid profiles, but effects may be less pronounced
Insulin sensitivity	Enhanced insulin sensitivity	Potential improvements, though variable and not as pronounced
Menopausal symptom relief	Effect relief of hot flashes and night sweats	Effective relief of hot flashes, night sweats, and mood swings
Mood and sleep	Improvements in mood and sleep quality	Benefits in mood stabilization and improved sleep quality
Endothelial function	Enhanced endothelial function	Some improvement is beneficial when started early

HDL, high-density lipoprotein; LDL, low-density lipoprotein; ↑, increase; ↓, decrease. The information presented in this table has been synthesized from the references [5,6,9,10,18,23].

a 25% lower risk of adverse thrombotic events compared to oral administration [50]. This advantage is particularly relevant given the heightened risks of VTE and stroke with certain oral formulations identified by the WHI [19]. Thus, the landscape of MHT is complex and multifaceted, influenced by factors such as timing of initiation, type of hormone therapy, dosage, and route of administration. Early initiation, particularly with estrogen-only formulations, is consistently associated with favorable health outcomes, including improved lipid profiles and reduced risks of CVD when therapy is started shortly after menopause. The ongoing evaluation of MHT guidelines and systematic reviews is essential to ensure that women receive the highest standard of care based on the latest evidence.

Table 1 (Ref. [5,6,9,10,18,23]) shows that estrogen-only therapy has notable positive effects on cardiovascular health, improves lipid profiles, enhances insulin sensitivity, and provides overall relief from menopausal symptoms. In contrast, the estrogen-progesterone combination is effective for symptom relief and supports cardiovascular health, although its effects on lipid profiles may be less pronounced. In conclusion, while MHT offers valuable relief from menopausal symptoms and supports cardiovascular health when tailored appropriately, individual health profiles and initiation timing must be considered carefully. The above findings collectively highlight the need for personalized treatment strategies that consider the timing of initiation, type of therapy, appropriate dosing, and route of administration to optimize outcomes and minimize risks. Ongoing research remains essential for refining guidelines and enhancing the safety and efficacy of MHT for postmenopausal women, ultimately contributing to better health outcomes in this population.

4. The Risk of MHT Leading to Breast Cancer

Fig. 4 (Ref. [11,37,42,43]) depicts the signaling pathways and cellular effects mediated by the estrogen hormone 17β-estradiol through its interaction with ERs, outlining its involvement in gene regulation and influence on complex biological pathways and cell development. The major endogenous estrogens are estradiol (E_2), estrone (E_1), and estriol (E_3), among which E_2 is the primary estrogen utilized by women before menopause [51]. Moreover, E_1 and E_2 are interconverted by 17β-hydroxysteroid dehydrogenases 1 and 2 (17β-HSD1 and 2) [52]. Estrogen plays a wide range of physiological roles in mammary organs, uterine tissues, and cardiovascular, musculoskeletal, and central nervous systems through ERs [53]. ERs are categorized into two types, ERα and ERβ. ERα is essential for estrogen movement in the mammary organs [54]. Estrogens have been shown to inhibit breast cancer cells through genomic and non-genomic pathways. In the genomic pathway, estrogens and their receptors bind to estrogen response elements (EREs) in the nuclei of breast cancer cells and recruit cofactors to form initiation complexes; these complexes then activate the expression proliferation-related target genes over a period ranging from hours to days [55–58]. Genomic pathways mediated by ERα/ERβ are located in target cell nuclei, where ligand-bound receptors work as ligand-activated transcription factors to coordinate gene expression by interacting with EREs or other response elements (e.g., specificity protein 1 (SP-1) and activator protein 1 (AP-1) in the promoters of genes synthesizing vasodilators such as endothelial nitric oxide synthase (eNOS) and cystathionine β-synthase (CBS)) [59,60]. In addition to the complex formation by protein-protein interactions between ERs and other transcription factors, coactivators (e.g., Forkhead box protein A1) can aid in making chromatin regions that ERα binds accessible to enhance the physical interaction of ER with chromosomal DNA [61,62].

In some cell types, ERα and ERβ may play different and, in some cases, opposing roles in regulating cellular responses to estrogens [63]. Non-genomic effects have a more rapid onset (from seconds to a few minutes) and might be related to structures in the plasma membrane. These effects are often associated with the induction of diverse protein kinase cascades [64]. In these pathways, E_2 can initiate rapid cellular impacts through the membrane estrogen receptor (mER) or G protein-coupled estrogen receptor (GPER) localized at the plasma membrane [55–57], which is required for rapid downstream signaling in the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) kinase pathway as well as the mitogen-activated protein kinase (MAPK) pathway [65–67]. The GPER (also known as GPR30) is a seven-transmembrane G-protein-coupled receptor (GPCR) embedded in the cell membrane [68]. A recent study [69] highlighted that E_2-induced GPER expression promoted the growth, aggressiveness, and migration of MCF-7 breast cancer cells through the miR-124/CD151 pathway. The miR-124/CD151 pathway involves significant interactions in cellular regulation, particularly in cancer progression. MicroRNA-124 (miR-124) acts as a tumor suppressor, regulating gene expression post-transcriptionally. It directly targets and suppresses CD151, a protein implicated in cell adhesion and migration. Filardo *et al.* [70] found that exposure to 1 nM 17β-estradiol for 5 minutes led to a six-fold increase in extracellular signal-regulated kinase (ERK) phosphorylation in SkBr3 cells that expressed neither ERα nor ERβ. Vivacqua *et al.* [71] reported that E_2 transactivated the early growth response-1 (Egr-1) promoter and induced Egr-1 expression through the GPER/ERK pathway in SkBr3 breast cancer cells. In addition, E_2 might play a role in the *in situ* metastasis of ductal carcinoma in the breast via the GPER signaling pathway [72]. Deng *et al.* [72] showed that E_2 initiated cellar membrane unsettling influence in mammary gland ducts by promoting the production of matrix metalloproteinase 3 (MMP3) and interleukin-1β through the GPER/cAMP/PKA and GPER/PI3K/AKT pathways. In the "GPER" paradigm, estrogen signaling begins within seconds to minutes to activate downstream target proteins and induce common functions independently of nuclear events. Membrane ER-mediated non-genomic signaling can facilitate nuclear ER-mediated gene transcription by inducing the protein kinase-mediated phosphorylation of ER and other ER-interacting transcription factors such as AP-1, SP-1, and cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), thus regulating gene expression in target cells. The discovery of certain anomalies initially appeared to be related to mitochondrial function. Various processes related to mitochondrial energy metabolism, such as oxidative phosphorylation (OXPHOS), the citric acid (TCA) cycle, and fatty acid oxidation, are affected by dysfunction of the energy metabolism processes in mitochondria [73]. According to Villena *et al.* [74], estrogen-related receptor alpha (ERRα) particularly mediates processes fundamental for mitochondrial function, which is why it is essential for regulating thermogenesis. Furthermore, ERRα coordinates muscle recovery and repair [75,76]. Other than that, estrogen-related receptor gamma (ERRγ) has a role in type I muscle fibers and promotes mitochondrial biogenesis and the oxidative assimilation framework [77,78]. ERRγ-regulated pathways allow ERRγ to coordinate the control of type I myosin expression and the high oxidative assimilation framework. This statement is supported by the fact that the gene expression profile induced by ERRγ is similar to that of reddish oxidative muscle fibers and that ERRγ regulates the expression of muscle-related miRNA [79,80]. In conclusion, the figure depicts the multifaceted role of 17β-estradiol in cellular signaling, covering genomic, non-genomic, and mitochondrial pathways, shedding light on how estrogen impacts cellular behavior, particularly concerning nutrient uptake, energy production, and oncogenesis.

Fig. 5 (Ref. [53,54]) depicts 17β-estradiol metabolism and its intricate connection to genotoxic processes involved in breast cancer development, illustrating the pathways occurring primarily in the liver and breast tissue. The liver plays a central role in processing estrogen through three key metabolic pathways: 2-hydroxylation, 4-hydroxylation, and 16-hydroxylation. Estrone (E_1) and 17β-estradiol (E_2), two major forms of estrogen, undergo sequential enzymatic modifications in these pathways [81]. In the 2-hydroxylation pathway, enzymes cytochrome P450 1A1 (CYP1A1) and cytochrome P450 enzyme 1A2 (CYP1A2) convert E_2 into 2-hydroxyestradiol (2-OH E_2), a metabolite known to inhibit proliferation in hormone-dependent breast cancer cell lines such as MCF-7 and T47D [82]. However, 2-OH E_2 can be oxidized within the nucleus to estradiol-2,3-quinone (E_2-2,3-Q), generating reactive oxygen species (ROS) that cause DNA damage through the formation of DNA adducts like 2-OH E_2-6-N3 adenine. Phase II metabolism, mediated by catechol-O-methyltransferase (COMT), transforms 2-OH E_2 into 2-methoxy estradiol, reducing ROS production and minimizing genotoxic effects [83]. In contrast, the 4-hydroxylation pathway involves the enzyme cytochrome P450 1B1 (CYP1B1), which converts E_2 into 4-hydroxyestradiol (4-OH E_2). This metabolite promotes cell proliferation and malignant transformation, as observed in the MCF-10F breast cell line, and has been associated with tumor formation in animal models [84]. Within the nucleus, 4-OH E_2 may oxidize into E_2-3,4-Q, forming DNA adducts such as 4-OH E_2-1-N_3 adenine and 4-OH E_2-1-N7 guanine. These adducts are carcinogenic and lead to DNA damage if phase II detoxification is inhibited or overwhelmed [85]. The 16-hydroxylation pathway involves the conversion of E_1 and E_2 into 16α-hydroxyestrone (16α-OH E_1) via cytochrome P450 3A4 (CYP3A4) [86,87]. This compound exhibits stronger estrogenic activity than E_2 and significantly enhances the expression of cell cycle regulators like cyclin D1 and cyclin-

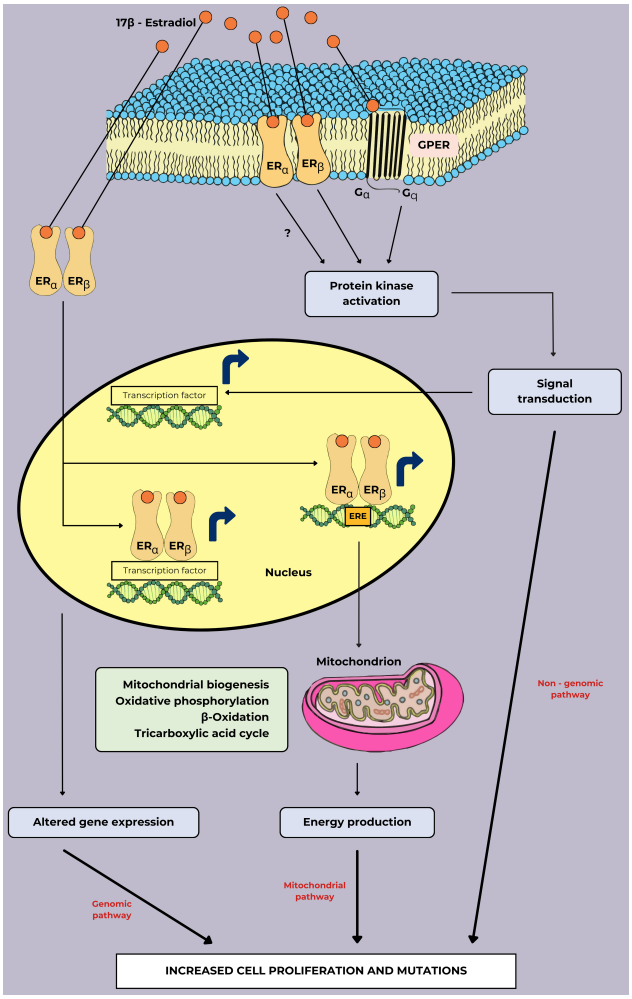

Fig. 4. The signaling pathways of cell proliferation and mutations in breast cancer associated with estrogen treatment. In the genomic pathway, the formation of estrogens and their receptors can induce altered genes that are primarily involved in cell cycle progression, energy metabolism, and survival mechanisms expression by directly binding ERE and transcription factors. In the mitochondrial pathway, essential genes for mitochondrial function are directly activated by the binding of estrogen and ER to ERE. In the non-genomic pathway, estrogen binding to GPER or plasma membrane localization of ER can establish rapid cellular effects by activating several kinase cascades. This figure was adapted from the references [11,37,42,43] with permission under The Creative Commons Attribution 4.0 Licenses. Abbreviations: ER, estrogen receptor; GPER, G protein-coupled estrogen receptor; ERE, estrogen response element.

dependent kinase 2, promoting the proliferation of breast cancer cells [88–90]. Moreover, in breast tissue, the local metabolism of E_2 through CYP1B1 generates 4-OH E_2, contributing to the formation of genotoxic quinone metabolites. These compounds can bind to DNA, induce mutations, and drive carcinogenic processes, even in the absence of ER signaling. Interestingly, 4-OH E_2 has been shown to cause malignant transformation in breast epithelial cells and induce tumor formation in ER-negative animals [84,91,92]. The classical ER-dependent mechanism involves E_2 binding to nuclear ERs, forming ER dimers that interact with EREs in gene promoters, thereby regulating the expression of estrogen-responsive genes. This dual mechanism—ER-dependent and ER-independent—illustrates the complexity of estrogen's role in carcinogenesis [93–95].

Fig. 6 (Ref. [44,96–98]) illustrates the effects of 17β-estradiol on breast cancer stem cell (BCSC), emphasizing both genomic and non-genomic mechanisms that promote their survival, self-renewal, and proliferation. Breast cancer, a hormone-driven disease, is primarily regulated by ERs, particularly ERα and Erβ [99–101]. ERα is present in 75% of breast cancers and serves as the main target of endocrine therapies, while ERβ is associated with improved survival in tamoxifen-treated patients, although its role is less well-defined [58,102,103]. 17β-estradiol influences BCSC through two primary mechanisms. First, traditional ERs, including ERα and ERβ, attach to DNA in EREs within genomic pathways to control gene expression. However, ERα is frequently either absent or expressed at extremely low levels in BCSC, which causes a shift towards non-genomic pathways to control the development and activity of cancer stem cells [48]. In particular, ERα36 has been identified in both ERα-positive and ERα-negative breast cancer cells, and its presence is associated with increased breast cancer aggressiveness [104]. Second, various ERs, specifically ERα36 and GPR30, trigger cytoplasmic signaling pathways in non-genomic processes [105]. The MAPK/ERK pathway is activated by ERα36, a shortened form of ERα, which promotes cell division and tamoxifen resistance [106]. Tafazzin (TAZ), a crucial contributor to BCSC's metastatic characteristics, is stimulated by GPR30, activating the Hippo signaling pathway [107]. 17β-estradiol also affects important developmental pathways, such as Notch, Hedgehog, and Wnt/β-catenin, which increases the number of CD44+/CD24- BCSC and promotes the creation of cancer spheres [96,108,109]. Studies also show that 17β- estradiol can increase the expression of stemness-related genes, such as *ALDH1*, *OCT4*, and *SOX2*, which support the undifferentiated state and self-renewal capabilities of BCSC [12,44,97,110,111]. These mechanisms not only explain 17β-estradiol's role in cancer progression but also highlight why current therapies, although effective in ERα-positive cancers, often fail to eliminate BCSC, leading to recurrence and metastasis. In conclusion, 17β-estradiol significantly impacts BCSC through both genomic and non-genomic mechanisms, underscoring the crucial roles of pathways such as MAPK/ERK, Hippo, and Wnt/β-catenin. These mechanisms reinforce the self-renewal and proliferation of BCSC, contributing to cancer progression and treatment resistance. Thus, targeting atypical receptors like ERα36 or GPR30 or using natural compounds, such as curcumin and soy isoflavon, could provide

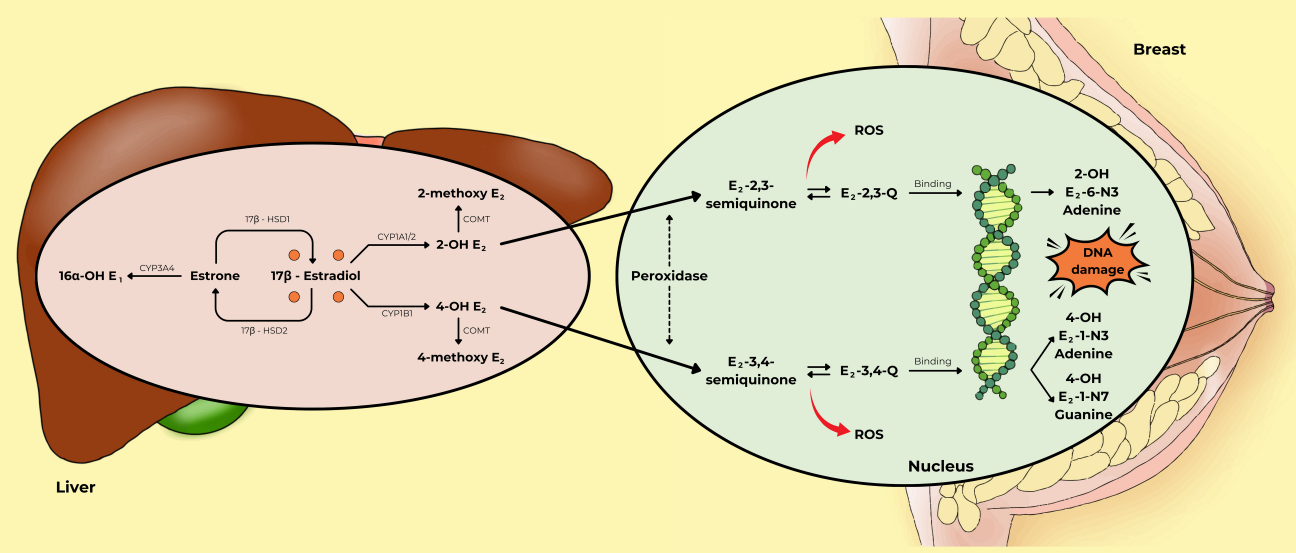

Fig. 5. The metabolism of estrogen plays an important role in the genotoxic pathway of breast cancer development. In the liver, there are three main metabolic pathways for estrogen: the 2-hydroxylation pathway, the 4-hydroxylation pathway, and the 16-hydroxylation pathway. In the nucleus, 2-OH E_2 and 4-OH E_2 are converted into E_2-2,3-Q and E_2-3,4-Q by peroxidase activity. These compounds can bind to DNA to form DNA adducts, such as 2-OH E_2-6-N3 adenine, 4-OH E_2-1-N3 adenine, and 4-OH E_2-1-N7 guanine, which may cause DNA damage in breast cells. This figure was adapted from the references [53,54] with permission under The Creative Commons Attribution 4.0 Licenses. Abbreviations: 16 α-OH E_1, 16α-hydroxyestrone; 17β-HSD1 and 17β-HSD2, 17β-hydroxysteroid dehydrogenase type 1 and type 2; CYP3A4, CYP1A1/2, and CYP1B1 are cytochrome P450 enzymes; COMT, catechol-O-methyltransferase; 2-OH E_2 and 4-OH E_2, 2-hydroxyestradiol and 4-hydroxyestradiol; E_2-2,3-Q and E_2-3,4-Q, estradiol-2,3-quinone and estradiol-3,4-quinone; ROS, reactive oxygen species; DNA, deoxyribonucleic acid.

promising new therapeutic strategies to limit BCSC expansion and reduce the risk of cancer recurrence [112,113].

The WHI trial, with two arms, generated significant evidence regarding the breast cancer risk associated with MHT. The first arm, focusing on estrogen-plus-progestin therapy, included 16,608 postmenopausal women with an intact uterus who received either 0.625 mg of conjugated equine estrogens (CEE) plus 2.5 mg of MPA daily or a placebo. After a mean follow-up of 5.2 years, the hazard ratio (HR) for invasive breast cancer was 1.26 (95% confidence interval (95% CI), 1.00–1.59), leading to the premature termination of this arm due to the elevated breast cancer risk. The second arm, involving 10,739 postmenopausal women with a prior hysterectomy, investigated the effects of daily CEE alone versus a placebo. After an average follow-up of 7.1 years, the HR for invasive breast cancer was 0.77 (95% CI, 0.59–1.01), suggesting a potential, though statistically non-significant, decrease in breast cancer risk [114,115]. The Million Women Study, a large observational study in the United Kingdom involving 1,084,110 postmenopausal women aged 50–64 years, found that current users of MHT had a relative risk (RR) of 1.66 (95% CI, 1.58–1.75) for developing breast cancer compared to never-users. The risk was notably higher for those using combined estrogen-progestin therapy (RR: 2.00; 95% CI, 1.88–2.12) than for those using estrogen-only therapy (RR: 1.30; 95% CI, 1.21–1.40) and increased with the duration of use [116]. The Collaborative Group on Hormonal Factors in Breast Cancer (2019) analyzed data from 58 studies, including 108,647 postmenopausal women who developed breast cancer. They found that all types of MHT except vaginal estrogens were associated with an increased risk of breast cancer. Specifically, for women using estrogen-progestin therapy for 5–14 years, the RR was 2.08 (95% CI, 2.02–2.15), while for those using estrogen-only therapy for the same duration, the RR was 1.33 (95% CI, 1.28–1.37) [117]. In a Cochrane Review by Marjoribanks *et al.* (2017) [118], 22 studies involving 43,637 women were analyzed. The review found that combined continuous MHT was associated with an increased risk of breast cancer, with an RR of 1.26 (95% CI, 1.06–1.51). The absolute risk increase was calculated to be nine additional cases per 1000 women over 5.6 years [118].

MHT remains a critical therapeutic option for menopausal symptoms, but its association with breast cancer risk is a subject of intense study and debate. Varying results from major clinical trials, including the WHI trial and the Million Women Study, underscore the complexity of balancing symptom relief with long-term health outcomes. This discussion focuses on the timing, dose, duration, and types of MHT, followed by insights into future research directions to better understand the risks associated

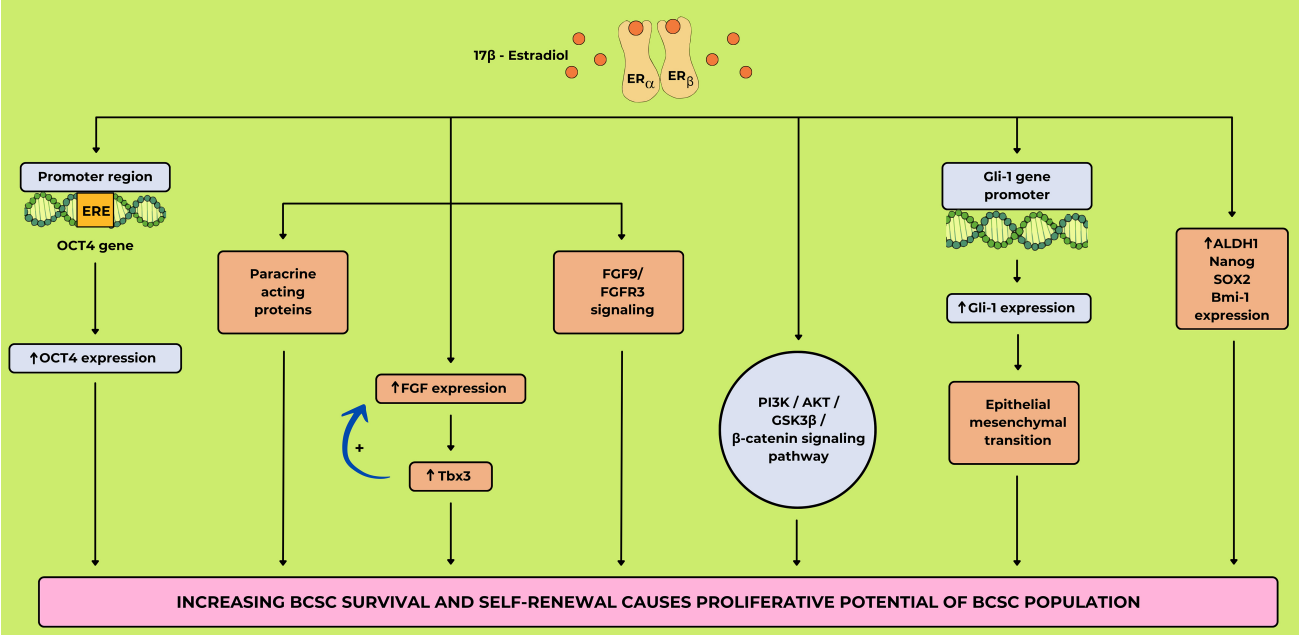

Fig. 6. The mechanism of breast cancer stem cell (BCSC) expansion through17β-estrogen signaling pathways. Estrogen-induced BCSC survival and self-renewal are mediated by the expression of OCT4, paracrine-acting proteins, Gli-1, ALDH1, Nanog, SOX2, and Bmi-1. Moreover, some potential signaling pathways are also responsible for the development of BCSC populations, such as FGF/Tbx3, FGF9/FGFR3, and PI3K/AKT/GSK3β/β-catenin. This figure was drawn by summarizing the findings of the references [44,96–98] with permission under The Creative Commons Attribution 4.0 Licenses. Abbreviations: ER, estrogen receptor; ERE, estrogen response element; SOX2, sex determining region Y-box 2; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; AKT, protein kinase B; GSK3β, glycogen synthase kinase-3 beta; Tbx3, T-box transcription factor 3; ALDH1, aldehyde dehydrogenase 1; ↑, increase; ↓, decrease; OCT4, octamer-binding transcription factor 4; Gli-1, glioma-associated oncogene homolog 1; Bmi-1, B lymphoma Mo-MLV insertion region 1 homolog.

with different MHT regimens. First, the timing of MHT initiation plays a significant role in determining its associated breast cancer risk. Evidence suggests that starting MHT close to the onset of menopause may reduce certain cardiovascular risks while minimizing adverse effects on breast tissue. On the other hand, women who start combined estrogen-progestin therapy shortly after menopause appear to have a slightly higher risk of breast cancer compared to those who initiate therapy later in life, especially after 10 years post-menopause [118]. In addition, according to the British Menopause Society, early initiation of MHT is advised when menopausal symptoms are severe and quality of life is significantly affected. Second, the dose and duration of treatment are emphasized. The Cochrane database has identified a dose-response relationship wherein the lowest effective dose of MHT is given for the shortest possible duration to manage symptoms [118]. In contrast, estrogen-only MHT has a different risk profile. For women who have undergone a hysterectomy, estrogen-only therapy does not seem to significantly elevate breast cancer risk and may even have a protective effect over extended periods of use [115,119]. Third, the type of MHT regimen is critical in breast cancer risk management. Combined MHT, which includes both estrogen and progestin, is associated with a higher risk of breast cancer than estrogen-only MHT. This elevated risk is particularly pronounced with continuous combined regimens where both hormones are taken daily [114]. For women with a history of breast cancer, systemic MHT is generally contraindicated due to the potential for recurrence, particularly with estrogen-progestin regimens. In such cases, non-hormonal therapies or localized treatments, such as vaginal estrogen for genitourinary symptoms, are often recommended [120–122]. Given the complexity of individual risk factors and varying responses to therapy, MHT should be personalized. For women at high risk of breast cancer, either due to family history or genetic predisposition, non-hormonal alternatives are often recommended. The risk of breast cancer should also be considered in young women. While the relationship between MHT and breast cancer is now well-established, significant knowledge gaps remain, particularly regarding the long-term effects of newer MHT formulations, such as transdermal patches or bioidentical hormones. Future studies should focus on the comparative risks of different delivery methods, as transdermal estrogen may have a more favorable risk profile than oral preparations due to its lower impact on liver metabolism and clotting factors. Another area requiring more research is the impact of lifestyle factors

on MHT-related breast cancer risk. While existing studies have adjusted for obesity, smoking, and alcohol consumption, more granular data are needed to understand how these factors interact with MHT to modulate breast cancer risk. In conclusion, MHT remains a valuable tool for managing menopausal symptoms, but it must be prescribed judiciously, particularly in women at elevated risk of breast cancer. Current evidence supports the use of the lowest effective dose for the shortest duration necessary, emphasizing personalized therapy based on individual risk factors. Future research will help further refine these recommendations and potentially expand the options available to young as well as post-menopausal women who need symptom relief while minimizing breast cancer risk.

5. Personalized Approaches to MHT: Estrogen-Only *vs.* Estrogen-Progesterone Therapy and Considerations for High-Risk Populations

Estrogen-only therapy: recent analyses suggest that estrogen-only therapy may be associated with a reduced risk of breast cancer, particularly when initiated early in the menopausal transition. A meta-analysis of randomized controlled trials, including the WHI study, found that women who took estrogen alone had a 35%–37% lower risk of developing breast cancer compared to those who did not receive hormone therapy [123]. Estrogen-only therapy has also been shown to improve cardiovascular outcomes, particularly in women without a uterus. However, it does carry an increased risk of stroke and VTE [124].

Estrogen-progesterone therapy: for women with an intact uterus, estrogen-progesterone therapy is necessary to protect the endometrium from hyperplasia. However, progesterone, particularly synthetic forms like medroxyprogesterone acetate, has been associated with an increased risk of breast cancer [123]. In contrast, micronized progesterone, a more natural form, has not been linked to increased thrombotic risk or higher breast cancer incidence. This combination therapy may provide fewer cardiovascular benefits than estrogen alone, as progesterone has been shown to negatively impact lipid profiles and may increase thrombotic risk [124].

Women at high risk of blood clots: this population includes those with a history of deep vein thrombosis, pulmonary embolism, or inherited blood clotting disorders (e.g., Factor V Leiden mutation). For this group, transdermal estrogen is preferred due to a lower risk of VTE compared to oral forms, as it bypasses the liver's first-pass metabolism [124].

Women with cardiovascular risk factors: this group comprises individuals with conditions such as hypertension, hyperlipidemia, or a family history of CVD. MHT may have cardiovascular benefits if started early in menopause (before age 60 years or within 10 years of onset). Estrogen-alone therapy, when appropriate, could lead to better cardiovascular outcomes, but decisions should be individualized based on comprehensive risk assessments [124].

Obese women or those with metabolic syndrome: studies showed that obese female students faced menorrhagia and estradiol may deal with body weight regulation [25,125]. Women with obesity, insulin resistance, or metabolic syndrome often have a higher risk of complications from MHT. For them, low-dose or transdermal estrogen might be safer options, as these can mitigate the metabolic impact [124].

Women with a history of breast cancer or high breast cancer risk: systemic MHT is generally contraindicated in women with a personal history of breast cancer due to an increased risk of recurrence. However, localized vaginal estrogen may be considered for severe genitourinary symptoms, as it has a minimal systemic effect [123].

Women with persistent, severe menopausal symptoms: for women whose quality of life is significantly affected by menopausal symptoms and who do not respond well to non-hormonal treatments, MHT may be considered after carefully weighing the risks and benefits and closely monitoring their health outcomes.

Overall, these findings emphasize the need for individualized treatment based on a patient's health history, age, and specific risks. Estrogen-only therapy may be more beneficial for those without a uterus and with lower cardiovascular risks, while estrogen-progesterone therapy remains necessary for those with an intact uterus despite its additional risks. Special consideration is needed for women in high-risk groups, such as those with a history of blood clots, CVD, obesity, or breast cancer. For these populations, transdermal estrogen or low-dose options are often recommended, as they may be safer alternatives with fewer metabolic impacts and thrombotic risks. Personalized care is essential, accounting for individual health factors to optimize the benefits of MHT while minimizing potential risks.

6. Conclusions

In conclusion, MHT has significant benefits, alleviating menopausal symptoms, improving quality of life, and potentially reducing cardiovascular risks when initiated early in menopause. Timing plays a critical role, as early initiation may help reduce the progression of atherosclerosis, whereas late introduction can pose greater risks. Estrogen-only therapy, typically used in women without a uterus, has been associated with greater cardiovascular benefits and a reduced risk of breast cancer but carries risks of stroke and VTE. In contrast, estrogen-progesterone therapy, required for women with an intact uterus to prevent endometrial hyperplasia, offers symptom relief but is linked to a higher risk of breast cancer and may have diminished cardiovascular benefits. These benefits and risks must be carefully balanced, particularly in older women or those with pre-existing conditions. The relationship between MHT

and breast cancer involves multiple mechanisms, including genomic, non-genomic, and genotoxic pathways, as well as the expansion of BCSC. Given the complexity of each patient's health profile, the personalization of MHT is paramount. Recommendations include using the lowest effective dose for the shortest duration while tailoring therapy to patient-specific risk factors, such as age, time since menopause onset, obesity, smoking, and alcohol use. By adopting a personalized approach, clinicians can optimize MHT's therapeutic potential while minimizing adverse effects, ensuring that each patient receives the most appropriate and effective care.

Abbreviations

↑, increase; ↓, decrease; CVDs, cardiovascular diseases; CHD, coronary heart disease; MI, myocardial infarction; MHT, menopausal hormone therapy; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IL-6, interleukin-6; TNFα, tumor necrosis factor-α; CRP, C-reactive protein; HIFIα, hypoxia-inducible factor-I α; ECM, extracellular matrix; FFAS, free fatty acids; WHI, the Women's Health Initiative; VANs, vagal afferent neurons; NTS, nucleus of the solitary tract; PVH, paraventricular hypothalamus; LH, lateral hypothalamus; VMH, ventromedial hypothalamus; ARC, arcuate nucleus; AMPK, adenosine monophosphate-activated protein kinase; BAT, brown adipose tissue; WAT, white adipose tissue; CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; COX-2, cyclooxygenase-2; CAMs, cell adhesion molecules; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; VSMC, vascular smooth muscle cell; ER(s), estrogen receptor(s); SP-1, specificity protein 1; AP-1, activator protein 1; eNOS, endothelial nitric oxide synthase; CBS, cystathionine β-synthase; DNA, deoxyribonucleic acid; MAPK, mitogen-activated protein kinase; GPCR, G-protein-coupled receptor; CREB, cAMP response element-binding protein; OXPHOS, oxidative phosphorylation; TCA, tricarboxylic acid; ERR, estrogen-related receptor alpha; MMP, matrix metalloproteinase; VTE, venous thromboembolism; MPA, medroxyprogesterone acetate; GPER, G protein-coupled estrogen receptor; ERE, estrogen response element; E_1, estrone; E_2, estradiol; E_3, estriol; 16 α-OH E_1, 16α-hydroxyestrone; 17β-HSD1 and 17β-HSD2, 17β-hydroxysteroid dehydrogenase type 1 and type 2; CYP3A4, CYP1A1/2, and CYP1B1 are cytochrome P450 enzymes; COMT, catechol-O-methyltransferase; 2-OH E_2 and 4-OH E_2, 2-hydroxyestradiol and 4-hydroxyestradiol; E_2-2,3-Q and E_2-3,4-Q, estradiol-2,3-quinone and estradiol-3,4-quinone; ROS, reactive oxygen species; BCSC, breast cancer stem cell; SOX2, sex determining region Y-box 2; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; AKT, protein kinase B; GSK3β, glycogen synthase kinase-3 beta; Tbx3, T-box transcription factor 3; ALDH1, aldehyde dehydrogenase 1; TAZ, Tafazzin; HR, hazard ratio; CEE, conjugated equine estrogens; RR, relative risk; cAMP, cyclic adenosine monophosphate; ERRγ, estrogen-related receptor gamma; DNA, deoxyribonucleic acid; OCT4, octamer-binding transcription factor 4; Gli-1, glioma-associated oncogene homolog 1; Bmi-1, B lymphoma Mo-MLV insertion region 1 homolog.

Author Contributions

TTTT and THN designed the research study. THN was responsible for manuscript writing. The table was conducted by ATMD while the graphic figures were created by TMP, the data from studies were compiled by QTML. ATMD and QTML contributed to preparing draft and editorial revisions. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated suffciently in the work and agreed to be accountable for all aspects of the work.

Declaration of AI and AI-assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGpt-3.5 and QuillBot to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication. The authors independently reviewed and edited the content to ensure its accuracy and quality, taking full responsibility for the final content of the publication.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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