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The Effect of Menopausal Hormone Therapies on Breast Cancer: Avoiding the Risk

Valerie A. Flores¹ and Hugh S. Taylor²

¹Women and Infants Hospital/Warren Alpert Medical School of Brown University

²Yale School of Medicine

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Introduction

Menopausal Hormone therapy (MHT) is an effective treatment for menopausal symptoms, and based on observational studies demonstrating numerous beneficial effects, was popularized as a first line approach to menopause management. MHT was found to be very effective in treating vasomotor symptoms, and preventing osteoporosis. ¹ It was also thought to reduce the risk of coronary heart disease. ¹ These findings provided support for broadening the use of MHT in an effort to help prevent age-related deficits associated with loss of sex steroid hormones. Thus MHT was heralded for use in the prevention of disease in postmenopausal women. ² While breast cancer has always been a risk associated with MHT, the effects of treatment on other life threatening diseases, namely cardiovascular disease, were thought to outweigh the risk of breast cancer. However, randomized controlled trials (RCTs) demonstrated that MHT did not afford the positive benefits that had previously been predicted from observational studies. ¹ On the contrary, in some instances, it was found to increase the risks for breast cancer, heart disease, and pulmonary embolism. ¹ The Women's Health Initiative (WHI) Trial, in its landmark study findings in 2002, reversed many of the perceptions of positive health benefits of MHT that were seen in observational studies. ^{1,2} Briefly, the WHI hormone trials were RCT's of postmenopausal women aged 50–79 (average age of 63) designed to determine whether or not MHT (estrogen only, and estrogen plus progestin combination) prevented cardiovascular disease. A global index was designed to assess the risks and benefits of MHT with respect to coronary heart disease (CHD), breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death by other causes. The WHI trials looked at combination of conjugated equine estrogen

Corresponding Author: Hugh S. Taylor, MD, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06520, 203-785-4001, hugh.taylor@yale.edu.

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(CEE) and medroxyprogesterone acetate (MPA) (together referred to as EPT) use in postmenopausal women with an intact uterus, and CE (ET) use in those with prior hysterectomy. In the WHI EPT arm, women were randomized to receive 0.625 mg/d of CEE plus 2.5mg MPA or placebo, whereas CEE alone was compared with placebo in the ET trial.¹

While the WHI trials failed to demonstrate reduction in risk of CHD with use of MHT, as regards risk for breast cancer, these trials yielded paradoxical and intriguing data. Long-term use of EPT was associated with an increased risk of breast cancer (HR 1.25; 95% CI 1.07–1.46; $p = .004$)³; the risk, however, was reversed in women who had had hysterectomy and were randomized to E alone (HR 0.82; 95% CI 0.65–1.04).⁴

In this review we will specifically focus on the risk of breast cancer associated with MHT. Without the potential to extend life through reduction of cardiovascular disease, a risk/benefit analysis on the use of MHT is rendered substantially less favorable. The risk of breast cancer has become the largest concern to women considering the use of MHT to avoid hot flashes. Breast cancer is the second leading cause of cancer death in women and the most commonly diagnosed cancer. The risk of a woman in the United States developing breast cancer over her lifetime is approximately one in eight. Most women have experienced breast cancer in their lives, either personally or through an afflicted relative or friend. It is thus important to address this prevalent concern and put patient perceived risks in perspective.

Menopausal Hormone Therapy in Clinical Trials

While there are many factors that influence a woman's risk of breast cancer, the role of MHT deserves special consideration. While the absolute risk of breast cancer associated with use of MHT is quite small, a lack of appreciation of the distinction between absolute and relative risks has influenced both the public and prescribers.

In observational studies, inconsistent effects of estrogen (E) alone or E combined with a progestogen (P) were seen in postmenopausal women. In the largest observational study to date—the Million Women Study—it was found that E plus P treatment increased postmenopausal women's risk of breast cancer; treatment with E alone, as commonly undertaken in women who have had hysterectomies, increased this risk slightly, however far less than seen with combination therapy.⁵ Current users of MHT were more likely than never users to develop breast cancer (adjusted RR 1.66; 95% CI 1.58–1.75, $p < 0.0001$) and to die from it (RR 1.22; 95% CI 1.00–1.48, $p = 0.05$). Past users of MHT were, however, not at an increased risk of disease.⁵ The incidence of breast cancer was significantly increased with E (RR 1.30; 95% CI 1.21–1.40, $p < 0.0001$) as well as with combination of E plus P (RR 2.00; 95% CI 1.88–2.12, $p < 0.0001$).⁵ In this study, the results did not significantly vary by the type of progestogen used or the route of administration. Time since menopause appeared to influence MHT related breast cancer risk. Women starting MHT (whether E alone or in combination with P) less than five years since menopause had a small increased risk of breast cancer (RR 1.43; 95% CI 1.36–1.49 in the E alone group, and 2.04; 95% CI 1.97–2.12 in the EPT group), compared to women initiating MHT greater than five years since

menopause (RR 1.05; 95% CI 0.89–1.23 in the E alone group, and 1.53; 95% CI 1.38–1.69). The risk of breast cancer declined to levels seen in never-users of MHT following cessation of treatment (RR 1.00; 95% CI 0.97–1.03).⁶

Similar to the Million Women Study, The Nurses' Health Study was a large observational study conducted in the United States that linked long term MHT use to breast cancer.⁷ The risk of breast cancer was significantly increased among users of E alone (RR 1.32; 95% CI, 1.14 to 1.54) or of combination MHT (E plus P) (RR 1.41; 95% CI, 1.15 to 1.74), as compared with postmenopausal women who had never used MHT.⁷

The E3N French cohort, another observational study, found that risk of breast cancer was greatest in women using an estrogen in combination with synthetic progestogens, but not with use of natural progesterone.⁸ Unlike the WHI ET arm, but similar to the Million Woman Study, the E3N French cohort study found an increased risk of breast cancer in E alone users (the majority being estradiol rather than CE), although this risk was still lower compared to the substantially elevated risk seen with estrogen plus progestagen (i.e. not including progesterone) treatment (RR 1.29; 95% CI 1.02–1.65 and 1.69; 95% CI 1.50–1.91 respectively).⁸

Similarly, in the California Teachers Study, a prospective observational study, use of combination MHT with E+P was associated with a greater increase in breast cancer risk (RR 1.65; 95% CI 1.48–1.84) when compared to E use alone (RR 1.17; 95% CI 1.04–1.31), and when compared to those classified as never-hormone users (RR 1). The type of estrogen and progestogen used among women were not specified.⁹

The Heart and Estrogen/Progestin Replacement Study (HERS) was a randomized control study that assessed CEE plus MPA's effects on cardiovascular disease prevention.¹⁰ In their follow-up observational study, HERS II, the effects of EPT on non-cardiovascular disease outcomes were also assessed. This follow-up study found no statistically significant increased risk of breast cancer, although the study was underpowered to evaluate this endpoint.¹¹

While observational studies assist in understanding relationships, definitive conclusion as to cause and effect cannot be drawn from these studies. Thus, randomized controlled trials like the WHI Trials offer the best available insight into the role MHT plays in breast cancer risk.

Discrepancies in breast cancer outcomes, especially with ET use, between the WHI and observational trials may be due to selection bias, confounding or the type of hormones used. The use of CEE, a mixture of multiple estrogens— some with Selective Estrogen Modulator (SERM) like properties, in the WHI may have had distinct advantages to the breast. Lastly, as use of the combination of E and P results in a greater risk of breast cancer than E alone, further research has been aimed toward understanding the role progestogens play in this risk. Data from RCT's are deemed more reliable compared to that accrued from observational studies given a potential for bias introduced by measurable and non-measurable confounders inherent to any observational study design. Results of the large WHI hormone trials thus offer high quality evidence of the effect of MHT on breast cancer risk.

Mammary Gland Biology and Breast Cancer

During normal mammary gland development, both estradiol and progesterone are responsible for enhancing cellular division and promoting lobular-alveolar breast development.¹² The mammary epithelium expresses both estrogen and progesterone receptors, and progesterone is needed for proper breast development and differentiation.¹³ Similarly in the adult, during the luteal phase of the menstrual cycle and during pregnancy, progesterone facilitates breast cell proliferation, migration, and invasion.¹⁴ In normal breast cells, proliferation occurs via paracrine interactions—as dividing epithelial cells do not contain estrogen and progesterone receptors—relying on growth factors secreted by adjacent stromal cells, which do contain sex hormone receptors.¹⁴ In the progression from normal breast development to carcinoma, it is postulated that there is a transition from paracrine to autocrine signaling, as neoplastic cells express estrogen and progesterone receptors.¹⁴

Previous studies have demonstrated that estrogen plus progestogen results in increased breast proliferation compared to what is seen with estrogen treatment alone.¹⁵ This suggests that the progestogen component itself may contribute to the carcinogenic effect of sex steroids.¹⁶ Progestogens exert their intracellular effect by modulating the transcription of various target genes. As such, it is hypothesized that progestogens alter the normal signaling pathways facilitating normal proliferation; however with increased proliferation and DNA replication comes an increased potential for new mutations and subsequent malignant transformation.¹⁶ The exact pathway by which progestogens affect breast cancer cell proliferation/progression to breast cancer has not been fully characterized, however studies on human breast cancer cells, as well as animal models have contributed to a better understanding of progestogen's effects in the mammary glands.

Breast Cancer Cells: studies in vitro

As both the WHI hormone trials, as well as most observational studies have clearly demonstrated an increased risk of breast cancer with combined EPT, understanding the mechanism by which this may occur is critical. Studies utilizing breast cancer cell culture systems have demonstrated that the effects of progestogens *in vitro* are influenced by progestogen type, dose and length of exposure, as well as cell culture conditions. Research using human breast cells has demonstrated that progestogens differentially affect breast cell proliferative activity.¹⁷ A study by Courtin *et al* analyzed the effects of estradiol (E2) alone, E2+progesterone (P4), and E2+MPA on cellular proliferation and apoptosis in breast cancer cells, as well as normal human breast cells.¹⁸ Treatment with E2 alone in all cell types resulted in increased cell proliferation. In normal human breast cells, the addition of P4 blocked estradiol's proliferative effect, and also resulted in an increased number of apoptotic cells. When normal cells were treated with E2+MPA however, there was little effect on cellular proliferation, and the number of apoptotic cells was decreased. In MCF-7 and T47-D breast cancer cell lines, MPA did not induce cellular proliferation and neither MPA nor P4 affected apoptosis in these cells.¹⁸ Microarray studies revealed induction of different sets of genes in hormonally treated cells, compared to control cells. E2+MPA modified genes in a distinctly different pattern from E2+P4. Sweeney *et al* found that MPA combined

with E2 stimulated proliferation in long-term estrogen deprived MCF-7 (MCF-7:5C) cells, while E2 alone resulted in cell death.¹⁹

The progesterone receptor exists as two isoforms (PR-A and PR-B) and is present in the female reproductive tract, mammary glands, brain, and in some immune cells.²⁰ In addition, some progestogens can bind to other steroid receptors, including the glucocorticoid receptor (GR), as well as the androgen receptor (AR).²⁰ Progestogens exert their effect via interactions of steroid receptors with growth factors, oncogenes, and estrogen metabolizing enzymes.²² Changes in the ratio of PR-A to PR-B are thought to be involved in the development of breast cancer.²⁰ Progestogens' aberrant effects in breast cancer pathogenesis may also be mediated by binding to steroid receptors other than PR, such as GR and/or AR. Sweeney *et al* identified a potential role for GR in breast cancer pathogenesis by studying MPAs effect on breast cancer cells as compared to that of dexamethasone (Dex) and norethindrone acetate (NETA).¹⁹ Like Dex, MPA blocked E2-induced apoptosis, allowing for continued proliferation of these cells. In addition, like Dex, MPA blocked E2-induced genes related to apoptosis. While this is not the first study to demonstrate MPA's function as a glucocorticoid^{21,22}, it differs from others in implying that the increased proliferation of human breast cancer cells is mediated through MPA binding to the GR.

A role for the AR as a mediator of progestogens' carcinogenic effect was assessed in a study using an *ex vivo* culture system.²³ Breast explant tissue from postmenopausal women was cultured and exposed to MPA at concentrations similar to seen in women taking an MPA containing formulation of EPT. While the normal physiologic role of AR signaling results in inhibition of breast cell proliferation,²⁴ this study found that in postmenopausal women MPA blocked the normal signaling effect of AR, preventing AR from inhibiting epithelial cell growth.²³

Further support for progestogens' role in breast cancer comes from studies analyzing progestogen effects on estrogen metabolizing enzymes in breast cancer cells. Using T47-D and MCF-7 cells, Xu *et al* demonstrated that E2+MPA increased the expression of estrogen activating enzymes—aromatase, 17 beta hydroxysteroid dehydrogenase type 1 (17BHSD1), and sulfatase, but did not increase expression of the estrogen inactivating enzymes, 17 beta hydroxysteroid dehydrogenase type 2 and sulfotransferase.²⁵ The increase in cellular expression of estrogen activating enzymes with E2+MPA was greater than that seen when cells were treated with E2 alone. Interestingly, the increase in estrogen activating enzymes was not associated with an increase in cell proliferation, although there was an increase in estrogen levels. It is known however that locally increased estrogen levels are seen in the breast cancer cell environment, and this high-estrogen environment facilitates cancer cell growth.²⁵ Thus, it is postulated that MPA may exert its carcinogenic effect via induction of a local hyperestrogenic state, rather than directly through cell proliferation.

Progestogen Regimens

The regimen of progestogen administration has also been suggested to influence breast cancer risk.²⁶ Analysis of the effects of combined continuous, versus a combined sequential

regimen of E2+MPA *in vitro* demonstrated that estrogen-activating enzymes were stimulated by the continuous regimen, but not the sequential regimen.²⁵ Lyytinen *et al* found that sequential progestin use resulted in a trend toward a smaller increase in relative risk of breast cancer compared with continuous progestin use.²⁷ Within the EPT arm of the WHI, more women in the treatment group reported breast pain. While the association between breast pain and breast cancer is uncertain, more women who were ultimately diagnosed with breast cancer reported breast pain during EPT use.²⁸ and breast discomfort appears to be a marker of breast gland stimulation. An ancillary study of the Kronos Early Estrogen Prevention Study (KEEPs)—a RCT designed to assess route of estrogen administration on cardiovascular effects (with cyclic progesterone administered daily for 12 days)—found that breast pain did not differ between MHT and placebo groups. While MPA was given continuously in the EPT WHI trial, progesterone was given cyclically in KEEPs, suggesting differential effects of progesterone regimen on breast cancer risk. However, one must exercise caution in extrapolating information solely from this ancillary study, as sample sizes were small; future studies will facilitate the understanding of the role progestogen type, and the timing of progestogen administration, play in influencing breast cancer risk.

Breast Cancer in Animal Models

Studies in animal models have further contributed to our understanding of role of progestogens in breast cancer. The characteristic response of breast cells to progesterone is ductal side branching and alveolar budding.¹⁴ Studies in ovariectomized mice have demonstrated that estrogen plus progestogen therapy results in significantly increased breast cell proliferation when compared to estrogen treatment alone.^{29–31} It is well known that mammary gland proliferation increases during the luteal phase, when progesterone levels are higher than the estrogen levels. In progesterone receptor knock out (PRKO) mice, estrogen plus progestogen treatment did not result in the lobular-alveolar changes characteristic of EPT, suggesting that PR signaling plays an important role in breast gland tumorigenesis.^{32–35}

A randomized trial in adult ovariectomized female macaques was used to study the effects of progestogens on risk markers for breast cancer.³⁶ This primate model is ideal for studying hormonal effects on breast tissue, as they have over a 90% average genetic coding sequence identity to humans.^{37,38} In addition, the steroid receptor response to sex hormone administration, and the development of neoplastic breast tissue in this model is similar to what occurs in humans.³⁶ The postmenopausal animals received one of four treatment regimens, with doses reflecting commonly prescribed doses in MHT for postmenopausal women—placebo, E2 daily, E2+P4 daily, or E2+MPA daily. After two months of treatment macaques treated with E2+MPA demonstrated a significant increase in proliferation of breast lobular and ductal cells, compared to placebo; this proliferative activity was not seen with E2+P4 treatment.³⁶ There was also increased expression of proliferation markers Ki67 and cyclin B1 in the E2+MPA treated monkeys, but not in the E2+P4 treatment group. In a follow-up study using this same animal model, Wood *et al* also demonstrated differences in gene expression profiles for a given progestogen treatment.¹⁵ Breast biopsies were collected after two months of treatment, and analyzed for differences in gene expression. It was found that breast tissue exposed to E2+MPA demonstrated increased expression of genes in the

ErbB proliferative pathway—epidermal growth factor (EGF) and transforming growth factor alpha (TGFA). Genes of the Jak/Stat signal transduction pathway, including c-MYC gene expression were also differentially expressed, with a 2.5 fold change in the E2+MPA treatment when compared to control ($P < 0.01$). cMYC induces signals for cell proliferation, and is known to be involved in tumorigenesis.¹⁵ There were no significant effects on genes related to apoptosis (TGF beta pathway), or genes related to estrogen receptor activity (Trefoil 1, stanniocalcin, cyclin D) seen in any group of treated animals. Thus, rather than directly enhancing ER's mediated response to increase breast cell proliferation, MPA may instead act via modulation of growth factor pathways. E2+MPA enhanced E2's effect on ErbB pathway related genes, providing further support for MPA's role in promoting breast cell proliferation through growth factor signaling mechanisms.¹⁵

The EGF receptor is present in normal epithelial cells, and is overexpressed in over half of breast cancers.³⁹ It is postulated that EGFR contributes to tumorigenesis not only by increasing cellular proliferation, but also by increasing angiogenesis and promoting cell survival. *In vitro* studies on breast cancer cells have also demonstrated that PR may result in EGFR activation, suggesting that progestogens exert their carcinogenic effect via PR-mediated regulation of downstream growth factor pathways.^{40,41}

Using a human-mouse model system, Liang *et al* analyzed the effects of progestogens on xenograft tumors.⁴² BT-474 breast cancer cells—which expressed PR and mutant p53—grown on a Matrigel substrate were used to create the tumors. These cells were then injected into nude mice, which had been pre-treated with estradiol prior to cancer cell transfer. The study found that in the presence of estradiol alone, xenograft tumors initially underwent growth, followed by tumor regression. However, with administration of either progesterone or MPA, tumor re-growth ensued. The mechanism by which this occurs was felt to be related to VEGF expression, mediated by PR. Support for the role of PR was further confirmed by addition of the PR antagonist mifepristone, which inhibited the proliferative capacity of tumor cells. VEGF has previously been implicated in tumor growth.^{30,43} VEGF is pro-angiogenic, and promotes endothelial cell survival and proliferation.^{44,45} An increased expression of VEGF in tumors following administration of progestogens suggests a progestogen dependent regulatory mechanism. In MCF-7 cells that do not express mutant p53, there is no induction of VEGF expression and no associated growth of tumors in response to progestogens, which supports the hypothesis that acquisition of mutations predispose to breast cancer, with progestogens potentially acting on cells with existing mutations.⁴⁶ Interestingly, and in support of the ET arm of the WHI, although estrogen was needed initially to facilitate tumor growth, it did not enhance tumor growth over time but instead resulted in tumor regression—again suggesting that it is the progestogen component itself that is responsible for inducing breast tumorigenesis *in vivo*.⁴⁶

While these studies provide insight into the mechanisms involved in breast cancer acquisition, it is important to note that several differences exist in mammary development in murine models compared to humans, thus results from such studies must be interpreted with caution. As mentioned previously, given the marked similarities between Macaque and human gene coding sequences, this primate serves as a more reliable model for studying the effects of MHT on breast cancer acquisition/risk.

Breast Cancer and WHI - Post Intervention Clinical Data

Following the initial results of the WHI Hormone Trials, the statistically significantly increased risk of invasive breast cancer with EPT use was affirmed on long-term follow up after the intervention was stopped.⁴⁷ Both intervention and post-intervention follow up in the EPT arm of the WHI demonstrated an increased risk of breast cancer and breast cancer mortality.³ The intervention phase of the EPT ended in 2002, after a median of 5.6 years, due to increased breast cancer risk and an unfavorable risk/benefit ratio.¹ Extended follow-up continued through 2010, with a median post-intervention follow up of 8.2 years. The statistically significant increased risk of breast cancer incidence seen in the intervention phase remained significantly elevated during the post-intervention phase (HR 1.27, 95% CI 0.91 to 1.78).¹ –In a sensitivity analysis adjusting for adherence, a significant difference in the hazard ratios (HR) slopes for the two study phases was found. There was a trend toward mitigation of breast cancer risk in EPT users in the post-intervention phase (HR 1.26; 95% CI 0.73–2.20) compared with a hazard ratio of 1.62 (95% CI 1.10–2.39) in the intervention phase.⁴⁸ In a sensitivity analysis adjusting for continued EPT use during the post-intervention phase however, ongoing EPT use had a higher association with breast cancer than was seen with EPT use in the intervention phase of the clinical trial ($p < 0.001$). Breast cancer mortality was greater in the EPT group compared to the placebo group ($p = 0.049$).³ The breast tumors diagnosed in the post-intervention phase were also larger than those seen in the placebo group ($p = 0.03$), however there was no difference in receptors status based on EPT use.^{3,48}

Chlebowski *et al*, analyzed EPT's effect on the ability of mammography and breast biopsy to detect breast cancer in the WHI EPT. There were significantly more abnormal mammograms in the EPT group compared to the placebo group. Interestingly, the number of breast cancers diagnosed by biopsy in the hormone group was less than that in the placebo group, despite the fact that breast cancers were not only increased in the EPT group, but also more cancers were diagnosed at higher stage and were more likely to be lymph node positive.⁴⁹ Women who began EPT within five years of menopause were at greater risk of breast cancer compared to women who were >5 years since menopause; however the risk did not reach statistical significance and did not substantiate the gap hypothesis, which states there is a time frame at which administration of HRT would be most protective/beneficial, whereas administration past this optimum time frame may result in more harmful effects.⁵⁰ Sub group analyses demonstrated no significant relationship in EPT and breast cancer incidence with respect to age, BMI, and the Gail breast cancer risk assessment tool score.⁴⁹ Postmenopausal women aged 50–59 years in the hormone group were also found to have a shorter time to first biopsy and overall more biopsies after 5 years of EPT compared to placebo. Following discontinuation of study medications, abnormal mammograms persisted for women in the EPT group for one year, however post intervention data demonstrated that thereafter there were not statistically significant differences.³

The intervention and post-intervention WHI data highlight several important points. First, the increased risk in breast cancer is significant, and although it decreases over time, the risk persists even after discontinuation of hormone therapy.⁵¹ In addition, although the absolute risk of death following breast cancer diagnosis in the EPT users was 2 per 10,000 women,

caution and extensive counseling for women is important when considering long term EPT use for relief of menopausal symptoms.⁵¹

An unanswered question regarding breast cancer and EPT is – if cessation of EPT results in fewer breast cancer cases, *where do the cancers go?* More than five years are needed for a new breast cancer to be clinically detected. The time frame of the WHI is too brief to account for a new breast cancer arising de novo, and subsequently resolving within a year of MHT termination. A more plausible explanation is that EPT acts on a pre-existing, sub-clinical breast cancer, spurring the initial growth of precancerous cells, which then slow or regresses following hormone therapy cessation.^{26,48} This explanation is further supported by the WHI data demonstrating that there were no more in situ lesions in the EPT users compared to the placebo group, nor were there more new in situ lesions found upon discontinuation of EPT.⁴⁹ New cancers were not forming in response to EPT therapy.

The breast cancer data from the ET arm of the WHI trials are distinct from the EPT arm. Not only was use of estrogen alone not associated with an increased risk in breast cancer, but in contrast to the EPT data, ET data even suggested an element of risk reduction with use of E alone (RR 0.80; 95% CI 0.62–1.04).⁵² Age specific comparisons also demonstrated fewer invasive breast cancers in the ET group compared to placebo in all age groups.⁵² The intervention phase of the ET trial ended in 2004, after a median of 7.2 years of follow-up. The post-intervention phase began shortly after the intervention phase was stopped, and continued through 2010. The decreased risk of breast cancer in the CEE group reached statistical significance in the post-intervention phase.⁵³ In the post-intervention phase of the WHI, women with prior hysterectomy followed up for 11.8 years, users of CEE for a median of 5.9 years had a significantly decreased risk of developing breast cancer (HR 0.77; 95% CI, 0.62–0.95).⁵³ Tumor receptor status, size, and nodal status were not statistically different between ET users and placebo. Unlike the EPT post-intervention phase, there was a significantly lower mortality risk from breast cancer in the ET group compared to placebo (HR 0.37, 95% CI 0.13–0.91).⁵³ Despite both trials having an increased number of mammograms in participants randomized to receive hormone therapy, those in the ET group did not have a significant increase in mammographic abnormalities compared to placebo (5.4% vs 5.1%, $p=0.53$) and the diagnostic utility of mammograms was not significantly compromised.⁵⁴ The specificity and negative predictive value of mammograms between the ET group and placebo group were comparable, except during the first two years of estrogen use, where the diagnostic performance of mammography was inferior to that seen in the placebo group. Estrogen use for two years did increase breast density compared to placebo to some degree, but did not affect interpretation of mammograms.⁵⁴ As such, there was no delay in breast cancer diagnosis in the CEE group. While more biopsies were needed in the ET group in order to find tumors, when compared to the placebo group, a diagnosis of breast cancer was made in 8.9% and 15.8% of biopsies in the ET and placebo groups respectively ($p=0.04$).⁵⁴

In sum, use of ET for over five years was safe, decreased breast cancer, and was associated with lower breast cancer mortality; these findings are in stark contrast to EPT use, which had an associated increased risk of breast cancer, delay in diagnosis, and increased breast cancer mortality.^{3,53} As previously discussed, the progestin component itself is highly

implicated, as cessation of EPT was associated with a decline in breast cancer, and the breast cancer rates for the placebo groups in both arms of the WHI were the same.^{47,53}

The choice of CEE in the ET arm of the WHI may explain the favorable effects seen on the breast. CEE contains a mixture of multiple estrogens, and each estrogen-type not only preferentially binds the two estrogen receptors, but may also exert differential actions depending on the target tissue.^{55,56} While E2 is the well characterized estrogen, less is known about the many estrogenic components of CEE.⁵⁶ Unlike E2, these other estrogens differ in their B-ring saturation and in their chemical moieties at the 17-position.⁵⁵ In a study assessing the activity of an estrogenic compound with similarities to several estrogens in CEE (NCI 122— 17 beta-methyl-17alpha-dihydroequilenin), it was found that NCI 122, as well as two other equine estrogens, were estrogen agonists that binds both ER alpha and beta, but are less potent estrogens than E2.⁵⁵ Despite their lower potency, NCI 122 and equine estrogens are able to exert transcriptional changes distinct from E2, which are postulated to account for the positive effects seen in several tissue types.^{57–60} Bhavnani *et al* analyzed the effects of 11 equine estrogens (in CEE preparations) on the transcriptional activity of ER alpha and beta, and found that many of the equine estrogens preferentially bind ER beta.⁶¹ ER beta activation can inhibit ER alpha activity on cell proliferation.^{62,63} This inhibition induced by equine estrogens may in part explain the decreased risk of breast cancer observed in the WHI ET study. Further support for beneficial SERM (selective estrogen receptor modulatory)-like properties of CEE comes from work by Sang *et al*, where the effects of CEE and E2 on breast cancer cells were compared.⁶⁴ CEE and E2 were noted to have distinct effects on gene expression. Research by Berrodin *et al* also demonstrated that several estrogenic compounds in CEE act as partial estrogen agonists;⁶⁵ thus, like SERMs, the differences in binding and downstream cell signaling may afford CEE with specific tissue manifestations that are unlike estradiol's purely stimulatory effects.⁶⁴ Additional research identifying which equine estrogens exert more SERM-like properties is needed, as they can not only be preferentially used in menopausal hormone therapy (MHT), but perhaps may even be of benefit in the treatment of breast cancer.

Tissue Selective Estrogen Receptor Complex and Breast Cancer

While MHT is the most effective pharmacologic treatment for vasomotor symptoms, the risks that MHT imposes on cancers, including breast and endometrial cancer risk, cannot be ignored. Efficacious treatment options for addressing menopausal symptoms that do not inherently increase cancer risk are needed, and research and development efforts to identify such alternative options are ongoing. Recently, a SERM and CEE have been paired to form a Tissue Selective Estrogen Complex (TSEC). TSECs pair a SERM with an estrogen, ideally blending the effects of the SERM and estrogen in a way that is more favorable than treating with one form of therapy alone.^{66–68} The first TSEC to be approved by the FDA pairs Bazedoxifene (BZA), a SERM, with CEE. In the phase 3 Selective Estrogen Menopause and Response to Therapy (SMART) trials, enrolling postmenopausal women at risk for osteoporosis with a uterus, BZA/ CEE improved hot flashes and prevented bone loss.^{66,69} There were no associated adverse effects on the breast, uterus, or ovary. Importantly, given BZA's anti-estrogen effects on the uterus, combined treatment with BZA and CEE does not require the addition of a progestin, thus likely reducing the probability of breast cancer risk

that has been associated with EPT treatment.^{68–70} Furthermore BZA neither stimulates breast cells, nor increases mammographic breast density.^{68,71,72} Data from the SMART trials was reassuring with incidence of breast cancer being comparable in BZA/CEE and placebo groups, although these trials were underpowered to fully evaluate this end point.⁷² Additional insight comes from an *in vitro* study assessing the effect of BZA/CEE on MCF-7 breast cancer cells.⁶⁴ BZA was found to block the effects of CEE on breast cancer cell proliferation, and blocked anti-apoptotic effects of CEE. Furthermore, like tamoxifen and raloxifene, BZA used alone did not induce estrogen agonist effects on breast cancer cells.⁶⁴ Furthermore, in tamoxifen resistant breast tumor xenografts, BZA was able to inhibit cancer cell growth.⁷³ BZA appears to have an effect of breast tissue that is similar or superior to other commonly used SERMs.

For menopausal women with a uterus, a TSEC offers theoretical advantage over traditional combined MHT as the risk of breast cancer is theoretically absent.

Alternatives to Traditional MHT and Breast Cancer Risk

As their name implies, Selective estrogen receptor modulators (SERMs) are compounds that are capable of exerting both agonist and antagonist effects on estrogen receptors, depending on their target tissue.^{67,74} When bound to estrogen receptors in the breast, SERMs act as estrogen antagonists, inhibiting estrogen's stimulatory action on breast tissue.⁷⁴ Tamoxifen and raloxifene were initially classified as anti-estrogens, given their effects on breast tissue, however were subsequently re-named SERMs once they were found to exert estrogen-like effects in bone and the endometrium.^{75,76} Tamoxifen is used as an adjuvant treatment for breast cancer. It also reduces invasive breast cancer risk in women with ductal carcinoma in situ, and women at high-risk of breast cancer.⁷⁷ Raloxifene also reduces breast cancer incidence and ductal carcinoma in situ.^{78,79} Raloxifene is approved for treating and preventing osteoporosis as well as preventing breast cancer in postmenopausal women.⁸⁰ Tamoxifen and raloxifene, unlike estrogen, do not improve vasomotor symptoms, but instead can even cause worsening of vasomotor symptoms.^{81–83} Although early SERMs were not developed for the purpose of treating menopausal symptoms, newer SERMs, such as ospemifene, have been developed with the intent of treating specific menopausal symptoms. While oral ospemifene is fairly effective for the treatment of the genitourinary syndrome of menopause, it can however exacerbate hot flashes.^{68,84} There are currently no clinical data on the effects of ospemifene on breast cancer risk.

Conclusion

Treatment with the combination of E and P results in a greater risk of breast cancer than placebo. In contrast, not only does treatment with E alone not increase the risk of breast cancer, but E alone use by women who have had a hysterectomy may even result in a decreased risk of breast cancer. The two prevailing theories to explain the increased risk with combination MHT focus on estrogen and progesterone acting in concert to increase breast cancer risk, versus progesterone alone having carcinogenic properties. Given the rapid development of clinically apparent tumors and the lack of new in situ lesions seen with MHT use, it is logical to surmise the carcinogenic effect of progesterone to a mechanism

that involves hormone actions on pre-existing, small lesions.^{86,87} Variations in the various progestogens differing in their affinity for PR, GR, and AR, variability of progestogen component of different MHT regimens, and variability in the duration of progestogen use across MHT regimens may all modulate EPT's deleterious effects on breast tissue. Continued research utilizing breast cancer cell culture systems and animal models will hopefully allow for an improved understanding of the interplay between estrogen and progestogens that predispose to adverse effects on breast tissue. The FDA approved TSEC (BZA/CE) holds promise as a treatment option that will eliminate the increased risk of breast cancer by avoiding administration of a progestogen along with estrogen in symptomatic menopausal women with intact uteri. Caution over this hypothesized benefit is warranted until it is substantiated by data on the incidence of breast cancer in TSEC users.

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Key Points

- Menopause is often accompanied by significant symptoms that affect quality of life, yet concerns over breast cancer risk associated with menopausal hormone therapies is the principle reason women may choose to avoid treatment.
- Data from prospective randomized trials (principally the Women's Health Initiative, WHI) confirm an increased risk of breast cancer associated with long term use of combined estrogen (E) and progestin (P) hormone therapy.
- In contrast to the effects of combined E+P on the breast tissue, the risk of breast cancer was decreased after use of estrogens in the WHI E alone trial.
- Progestogens, and not estrogens, seem to convey the risk of breast cancer; however, estrogens cannot be used alone in a woman with a uterus, given the known risk of endometrial hyperplasia and even endometrial cancer with long term exposure to E alone.
- The recent addition of bazedoxifene combined with conjugated estrogens (BZA/CE) provides a progestin free regimen that can be used in a woman with a uterus.