IMPACT OF CONVENTIONAL AND BIOIDENTICAL HORMONE REPLACEMENT THERAPY ON

Cardiovascular & Breast Health: a review

ABSTRACT **Several large studies demonstrated increased cardiovascular and breast cancer risks with conventional hormone therapy. Bioidentical hormone replacement therapy is thought to be a safer alternative to conventional hormone therapy. The objective of this review was to compare the cardiovascular and breast cancer risks associated with conventional hormone therapy and bioidentical hormone replacement therapy. Pubmed/MEDLINE was used to search studies published in English between 1995 and 2010. Articles were narrowed to clinical and randomized controlled trials in human females and were selected based on relevancy to cardiovascular or breast cancer risks in either conventional hormone therapy or bioidentical hormone replacement therapy. Large randomized controlled trials documented increased coronary heart disease events with conjugated estrogens plus medroxyprogesterone acetate. Some trials suggest that conjugated estrogens monotherapy may provide coronary heart disease risk reduction if initiated soon after menopause. No studies have examined coronary heart disease events with bioidentical hormone replacement therapy; however, randomized controlled trials have demonstrated that estradiol beneficially improves lipoproteins, carbohydrate metabolism, and vascular reactivity, decreases carotid intima media thickness, and slows the progression of subclinical atherosclerosis. Progesterone does not interfere with these beneficial effects. Other randomized controlled trials have documented increased breast cancer risk with conjugated estrogens + medroxyprogesterone acetate; conjugated estrogen monotherapy has not been associated with an increased risk. Smaller randomized control trials and observational studies demonstrated that estradiol induces breast epithelial proliferation; however, crystalline progesterone decreases breast proliferation and decreases breast cancer risk compared to that of hormone therapy never users. Conjugated estrogens + medroxyprogesterone acetate is detrimental to cardiovascular and breast health. Conjugated estrogens monotherapy appears to be cardiovascular and breast neutral, particularly if initiated soon after menopause. Estradiol improves cardiovascular markers but may induce breast epithelial proliferation if administered without progesterone.**

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DISTINCTION BETWEEN CONVENTIONAL HORMONE THERAPY AND BIOIDENTICAL HORMONE REPLACEMENT THERAPY

Conventional hormone therapy (CHT) consists of hormones obtained from animal sources or derived from molecular modifications to endogenous hormones.[1,2] The most common CHT options are conjugated estrogens (CE) and medroxyprogesterone acetate (MPA).[1,3] These hormones are different from natural human hormones with respect to molecular structure, receptor affinity, metabolism, and physiological traits.[2,4] In contrast, bioidentical hormones (BH) are derived from various sources, such as plants or animals, and are chemically modified to be molecularly identical to endogenous hormones.[5] The most common bioidentical hormone replacement therapy (BHRT) options are estradiol (E2), estriol (E3), and progesterone (P4).[1,4,5] Unlike CHT, BHRT mimics normal physiology and metabolism of endogenous hormones.[6]

THE HISTORY OF HORMONE REPLACEMENT THERAPY

Natural menopause is defined as twelve months of amenorrhea due to the absence of ovarian follicles.[7] If not induced by surgical means, menopause typically occurs in women between the ages of 50 to 52 with a mean age of 51.4 years.[8] For the treatment of menopausal symptoms, hormone therapy (HT) traces its origins to an 1897 publication noting the beneficial effects of ovarian extracts in relieving hot flashes.[9] This publication highlighted the therapeutic uses of ovarian hormones. The next breakthrough in HT would not occur until decades later. In 1934, Ayerst Pharmaceuticals manufactured Emmenin as the first hormone replacement therapy (HRT) to contain CE for the use in ovariectomized women. Unlike the CEs in use today, these CEs were extracted from the urine of pregnant women.[4,10] In 1937, a few years after the marketing of Emmenin, crystalline progesterone (P4) was isolated and found to prevent ovulation in rabbits. This discovery began the hunt for marketable progestins, which would be used for preventing endometrial hyperplasia beginning in the 1970s.[11-15] In 1942, Ayerst Laboratories began marketing Premarin, which would eventually become the most popular form of estrogen replacement therapy (ERT) in the U.S.

Recent publications, most notably the Women's Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study (HERS),[6,16,17] have brought to light additional adverse effects associated with CHT; namely CE + MPA. The WHI was terminated early due to findings of increased risk for breast cancer, coronary heart disease, stroke, and venous thromboembolism.[7] CHT use significantly declined within one year of publication of these trials; use of combination therapy with CE + MPA declined 66%, and CE monotherapy declined 33%.[18]

Prior to the WHI and HERS findings, hormone therapy was believed to decrease cardiovascular disease and possibly increase the breast cancer risk in postmenopausal women.[19-21] Publications as early as 1953 touted BHRT as a "natural hormone replacement"; however BHRT was not popularized until the 1990s by Drs. Lee and Wright.[22-26] BHRT proponents claim safety that surpasses CHT with no increased risk beyond that of placebo. However, data are needed to support these claims.[1,22,23] Currently, the only FDA-approved BHs are E2, formulated as topical, vaginal, and oral preparations; and P4, manufactured as oral capsules and vaginal gel preparations.[27]

Prior to the publication of the WHI trials in 2002, it was estimated that fewer than 1 in 3 women chose CHT, while 30% choose complementary and alternative medicine (CAM) therapies, including BHRT.[28,29] Several studies have documented the efficacy of BHRT to alleviate vasomotor symptoms.[1,30,31] Other studies have reported positive health effects on the genitourinary tract,[32-42] skeletal health,[35] lipid profile,[36,37] and central nervous system[38-40] of postmenopausal women. Although perceived as a safer alternative to CHT, few large randomized controlled trials (RCTs) have evaluated the efficacy of BHRT, and the majority of the BHRT safety data has been derived from small controlled trials and observational studies. To date, the largest RCTs of BHRT are the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial and Estrogen in the Prevention of ATherosclerosis (EPAT) trial. The largest observational studies are the EStrogen and THromboEmbolism Risk (ESTHER) study and the French E3N Cohort Study.[36,41-43]

The remainder of this review critically examines the clinical evidence regarding cardiovascular and breast cancer risks associated with CHT and BHRT.

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HORMONE THERAPY AND CARDIOVASCULAR HEALTH

Conventional Hormone Therapy

A Pubmed/MEDLINE search was conducted with the following terms: ("MESH risk" or "MESH heart disease") and "conjugated estrogen" and "MESH hormone replacement therapy." The search was limited to clinical and RCTs published in English in core clinical journals between 1995 and 2010 that pertained to human females 65 years or older. The search returned 62 papers. The titles and abstracts were reviewed, and the list was narrowed by relevancy to five articles. Of the articles excluded, 54 did not pertain to coronary heart disease (CHD) prevention, one study was a nonoriginal publication, one was a continuation study, and one was excluded because it described the same population to a lesser degree than an included trial. The five remaining articles are discussed below.

The 1998 HERS and 2002 Heart and Estrogen/progestin Replacement Study Follow-up (HERS II) were the first RCTs to examine the impact of CHT on CHD.[17,44] With a similar objective, the WHI published the largest CHT trial in 2002 and largest CE monotherapy trial in 2004.[6,45] In 2007, the WHI 2002 and 2004 RCTs were combined and evaluated for CHD reduction, resulting in the largest CHT trial to date. The aforementioned trials were systemically evaluated to assess CHD outcomes associated with CHT.

HERS enrolled 2,763 women in 20 clinical centers from 1993 to 1998.[17] HERS patients had an average follow-up of 4.1 years. The objective of the study was to evaluate the effects of CHT on recurrent cardiac events in postmenopausal women with established CHD, defined as nonfatal myocardial infarctions (MI) or CHD death (death due to MI, death with cardiac symptoms, death judged to be CHD related). Women with an intact uterus and <80 years were eligible for enrollment. With a mean enrollment age of 66.7 years, women were randomized to receive oral CE (0.625 mg) + MPA (2.5 mg) or placebo. Overall, the number of CHD events was similar for CHT and placebo (331 vs 336 events/10,000 patient years; p=0.91). An increase in CHD events was noted during the first year of therapy (see the Table that accompanies this article); however, this difference did not persist during the remaining years. The rate of overall thrombotic events was higher in women on CHT (60 vs 21 events/10,000 patients years; p=0.002). Although results highlighted an initial increase in CHD rates with no overall protection, it was believed additional treatment time would yield CHD reduction due to CHT's perceived beneficial effect on atherosclerosis via effects on lipoproteins. The authors concluded CHT should not be used for cardioprotection in women with pre-existing CHD.

HERS II intended to capture the decrease in CHD believed to occur with continued CHT use.[44] Of the surviving HERS population, 93% consented to an additional 2.7 years of unblinded treatment and follow-up. Results showed CHD events did not decrease with continued use (418 vs 421 events/10,000 patient years; 95% CI, 0.77 to 1.29). The authors concluded that a decline in CHD events did not occur with continued use of CHT in women with pre-existing CHD.

The WHI designed a series of trials to investigate strategies of prevention and control for most of the common causes of morbidity and mortality in postmenopausal women. The WHI CE + MPA study was the first hormone-based RCT.[6] It was initiated in 1993 and was terminated early because risks exceeded benefits over an average 5.2 years of follow-up. Healthy postmenopausal women (n=16,608) with a mean age of 63.3 years were randomized to receive either oral CE (0.625 mg) + MPA (2.5 mg) or placebo. The WHI results reinforced the absence of cardioprotection with CHT. Results per 10,000 patient-years (95% CI) revealed 7 more CHD events (1.02 to 1.63), 18 more thrombotic events (1.58 to 2.82), and 25 more total cardiovascular diseases with CHT as compared to placebo. A subgroup analysis of women meeting the HERS criteria found a 28% nonsignificant increase in CHD events with 19 vs 16 events occurring during 4.8 years of follow-up (95% CI, 0.64 to 2.56). The trial was terminated early since continued therapy would unlikely yield favorable results. It was concluded that CHT does not confer cardioprotection. Interestingly, the authors remarked that topical estradiol and progesterone, closer in natural physiology and metabolism, would possibly produce different risk to benefit results.

As the previous trials demonstrated possible negative implications of CE + MPA on CHD outcomes, the progestin component was perceived to be possibly responsible for the negative cardiovascular outcomes.[6] Therefore, to focus on the function of unopposed CE on CHD prevention, hysterectomized women were simultaneously enrolled in a WHI CE monotherapy trial.[46] This trial was also terminated after an average of 6.8 years of follow-up. Again, healthy postmenopausal women (n=10,739) with a median age of 63.6 years were randomly assigned to receive either oral CE (0.625mg) or placebo. Results per 10,000 patients years revealed a nonsignificant overall decrease in CHD events with CE therapy (53 vs 56; p=0.63). To further investigate the potential decline, the authors

TABLE. Heart and Estrogen/progestin Replacement Study Events by Year.

1° CHD events	CHT (Events/ 10,000 pt Years)	Placebo (Events/ 10,000 pt Years)	95% CI
Year 1	425	280	1.01 to 2.29
Year 2	370	371	0.67 to 1.49
Year 3	288	331	0.55 to 1.37
Year 4 to 5	230	344	0.43 to 1.04
Overall	331	336	0.80 to 1.22

CHD = coronary heart disease; CHT = conventional hormone therapy

performed two subgroup analyses: one by age group and another by years since menopause (Figure 1 and Figure 2). The authors concluded that women between the ages of 50 to 59 may receive some degree of CHD reduction due to a nonsignificant reduction of 10 events/10,000 patient years in the absence of adequate power. They did not find a significant correlation between time since menopause and CHD risk. Subsequently, a combined analysis of the two WHI trials also observed nonsignificant correlations between CHT use and reduced CHD events in women between the ages of 50 to 59 years, and those <10 years since menopause. These data suggest that the later a woman initiates CHT after menopause, the higher the risk for CHD.

Despite observational trials demonstrating CHD risk reduction with CHT, RCTs have revealed otherwise.[6,17,19-20,37,46] HERS demonstrated that CHD is increased during the initial year of CE + MPA use and continued use does not provide cardioprotection. WHI concluded that CE + MPA increased CHD, increased thrombotic events, and should not be used for CHD risk reduction. The WHI trial of CE monotherapy suggested potential CHD risk reduction when CE monotherapy is initiated soon after menopause or between the ages of 50 to 59; however, these data are not definitive. Therefore, neither CHT with CE + MPA or CE monotherapy are recommended for CHD risk reduction.

FIGURE 1. Women's Health Initiative subgroup analysis of conventional hormone therapy on coronary heart disease events by age group.

***p=0.03 compared to 50 to 59**
‡p(trend)=0.16

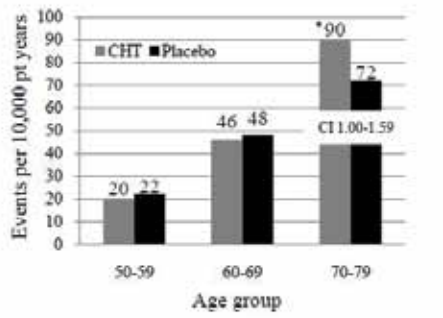
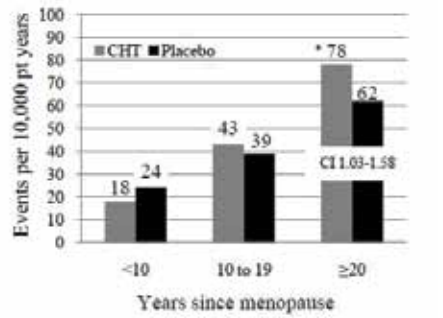


FIGURE 2. Women's Health Initiative subgroup analysis of conventional hormone therapy on coronary heart disease events by years since menopause.

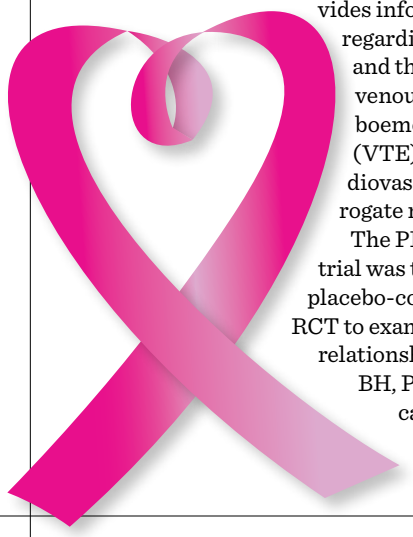
***p=0.03 compared to <10**
‡p(trend)=0.02



Bioidentical Hormone Replacement Therapy

A Pubmed/MEDLINE literature search was performed with the following terms: ("MESH risk" or "MESH heart disease") and (estradiol not conjugated estrogen) and "MESH hormone replacement therapy." No studies in the search results pertained to BHRT and CHD outcomes. An additional search was performed to expand search criteria to capture articles related to BHRT: ("MESH myocardial infarction" or "MESH thromboembolism" or "MESH arteriosclerosis" or "MESH endothelium") and [estrogens not ("MESH ethinyl estradiol" or "MESH conjugated estrogens")] and "MESH hormone replacement therapy." The search was limited to clinical trials published in English in core clinical journals between 1995 and 2010 that pertained to human females. The search returned 24 articles. Review of titles and abstracts excluded 19 articles because they did not discuss BHRT and cardiovascular health.

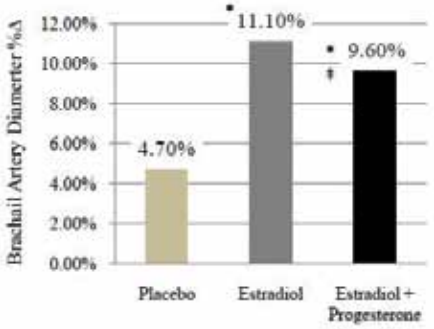
Unlike CHT, no RCTs exist evaluating BHRT and the outcome of CHD events. Rather, existing studies typically evaluate a BH as monotherapy, combined E2 + P4, or a BH plus a conventional hormone, CE, or a progestin. Furthermore, RCTs, which focus on cardiovascular surrogate markers, are smaller in size in comparison to their CHT counterparts. The first and largest RCT evaluating BH and cardiovascular markers was the publication of the PEPI Trial followed by the publication of the smaller EPAT and Postmenopausal HOrmone REplacement in Atherosclerosis (PHOREA) trials.[36,41,47,48] The ESTHER trial is a large case-controlled trial that provides information regarding BHRT and the risk of venous thromboemobolism (VTE), a cardiovascular surrogate marker.[41]



The PEPI trial was the first placebo-controlled RCT to examine the relationship of a BH, P4, and cardiovascular disease.[36] CHD surrogate markers were examined with a comparison of CE + P4 therapy to both placebo and combination CE + MPA. The PEPI trial enrolled 875 women across seven clinical sites from 1989 to 1991. The objective of the study was to examine the effects of the aforementioned HT on the following cardiovascular surrogate markers: lipid metabolism, blood pressure, carbohydrate metabolism, and coagulation/hemostasis. Healthy postmenopausal women with no contraindication to HT between the ages of 45 to 64 were eligible for enrollment. Women with a mean age of 56.1 years were randomized to receive CE (0.625 mg), CE (0.625 mg) + cyclic MPA (10 mg); CE (0.625 mg)+ continuous MPA (2.5 mg), CE (0.625 mg) + cyclic P4 (200 mg), or placebo. Analysis revealed that CE + P4, when compared to placebo, had a positive effect on lipoproteins, fibrinogen levels, and carbohydrate metabolism without adversely effecting blood pressure. When compared to placebo, the combination CE + P4 group experienced a significant decrease in both total cholesterol (TC) (-4.2 vs 7.8 mg/dL) and low-density lipoprotein (LDL) (-4.1 vs 14.8 mg/dL) (p<0.001, both comparisons). Furthermore, a comparison of placebo to CE + P4 demonstrated a significant increase in high-density lipoprotein (HDL) (-1.2 vs 4.1 mg/dL) and triglycerides (TG) (-3.2 vs 13.4 mg/dL) (p<0.001, both comparisons). Aside from lipid changes, fibrinogen levels were found to be lower with CE + P4 therapy when compared to placebo (0.01 vs 0.10 g/L; p≤0.02). With regards to carbohydrate metabolism, fasting glucose levels were lower with CE + P4 therapy when compared to placebo (-2.5 vs -0.5 mg/dL; p=0.03). Although, combination CE + P4 was associated with improved lipoproteins when compared to either cyclic or continuous CE + MPA, similar benefit was not observed with other CHD surrogate markers. Study results demonstrated that combination CE + P4 significantly increased HDL (4.1 mg/dL) when compared to CE + MPA (1.6 mg/dL) (p<0.004). The authors commented that the observed increase in HDL could potentially decrease CHD risk by 20% to 25% based on data extrapolated from observational trials. Given the aforementioned results, the authors noted that unlike MPA, P4 has not been shown to interfere with estrogen's cardioprotective characteristics.

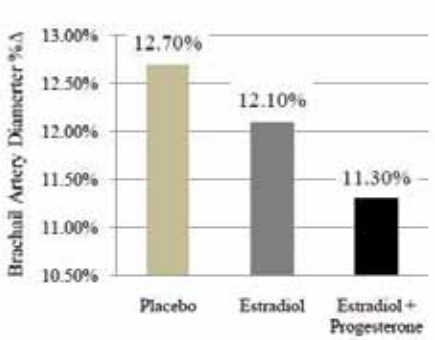
Following publication of the PEPI trial, Gerhard et al (1998)[47] conducted a 32-week single center, randomized, double-blind, placebo-controlled crossover trial. The objective of the trial was to evaluate the effects of E2 and P4 on vascular reactivity. Women between the ages of 48 to 75 with mild hypercholesterolemia were eligible for enrollment. Women with a mean age of 60 years were randomized to receive placebo or active treatment. Active treatment consisted of 8 weeks of 0.2 mg transdermal E2 followed by combination E2 and 2-week cycles of 200 mg vaginal P4 administered on weeks 9 to 10 and 13 to 14. Initial randomization to placebo resulted in 14 weeks of placebo, with a one-month washout period, and concluded with 14 weeks of treatment (vice versa if randomized to

FIGURE 3. Gerhard et al estradiol and crystalline progesterone effects on flow-mediated endothelium-dependent vasodilation.



*p<0.001 compared to placebo
‡p=nonsignificant compared to estradiol

FIGURE 4. Gerhard et al estradiol and crystalline progesterone effects on flow-mediated endothelium-independent vasodilation.



therapy first). The authors concluded that E2 was the only significant indicator of endothelium dependent vasodilation (p<0.0001). However, combination E2 + P4 also improved vascular reactivity compared to placebo (p<0.001). Furthermore, E2 + P4 decreased total cholesterol by 5.8% and LDL by 8.4% (p<0.001 for both comparisons) (Figure 3 and Figure 4). The authors concluded that P4 does not interfere with E2 vascular effects, and E2's effects on vascular reactivity are independent of its lipid lowering effects.

Publication of the EPAT and the PHOREA placebo-controlled RCTs were the first to examine the effects of E2 on atherosclerosis.[41,48] The primary difference between the two studies was that PHOREA included a progestin in the therapy and included women with preexisting increased carotid intima-media thickness (CIMT) in their trial. In the EPAT study, 222 women were randomized to receive either placebo or 1 mg oral E2, whereas the 321 women in the PHOREA trial were randomized to receive either 1 mg E2 and cyclic 0.024 mg gestodene (group 1), or 1 mg E2 and cyclic 0.024 mg gestodene every third cycle (group 2), or placebo (group 3).

Outcomes of the EPAT and PHOREA trials differed. EPAT participants in the E2 group experienced a decrease in CIMT progression (-0.0017 mm/year) whereas the placebo group experienced an increase in CIMT progression (0.0036 mm/year) (p=0.046). Conversely, all PHOREA participants experienced mean 0.03 mm increase in CIMT in all groups including placebo (p=0.2). In addition, the EPAT trial performed a subgroup analysis of women not on lipid lowering therapy. Subgroup results demonstrated that E2 decreased CIMT progression (-0.0013 mm/year) unlike the increase in CIMT observed in the placebo group (0.0134 mm/year) (p=0.002). Interestingly, CIMT progression rates did not significantly differ among placebo patients on lipid lowering therapy compared to the E2 group not on lipid lowering therapy (p>0.2).

Secondary outcomes of cardiovascular risk factors for the EPAT and PHOREA also differed. EPAT patients treated with E2 experienced an increase in HDL (7 mg/dL) and TG (7.9 mg/dL), and a decrease in LDL (26.6 mg/dL) and TC (19.4 mg/dL) when compared to placebo (p<0.05 for all outcomes). In comparison, PHOREA patients on E2 + low- and high-dose progestin experienced a decrease in LDL (16.3 mg/dL and 15.9 mg/dL, respectively) when compared to placebo (p<0.001, both groups). However, only a comparison of low-dose progestin to placebo was associated with a significant increase in HDL (3.3 mg/dL) (p=0.028). Subgroup analysis of the EPAT secondary outcomes of women not on lipid lowering therapy revealed E2, in comparison to placebo, increased HDL (7.89 vs 4.35 mg/dL; p<0.001) and TG (7.58 vs -6.8 mg/dL; p=0.02) and decreased LDL (-36.5 vs 26.26 mg/dL; p=0.02). In addition to lipoprotein improvements, EPAT participants noted an improvement in HbA1c compared to placebo (0.8 vs -0.04; p<0.007). Given the results, the authors concluded subclinical atherosclerosis progressed slower in menopausal women who received E2; yet combination with progestin blunted this effect. Authors from the PHOREA study also point out a lower dose progestin does not result in a more beneficial effect on CIMT. Unlike the PHOREA authors, EPAT investigators concluded E2 could possibly serve as an alternative to lipid lowering therapy to slow the progression of subclinical atherosclerosis.

The ESTHER trial, the most current and largest BHRT clinical trial, provides additional BHRT information to the literature regarding CHD surrogate markers with its focus on VTEs.[42] ESTHER enrolled 881 women with a mean age of 61.5 years in seven clinical centers from 1999 to 2005. The objective of the study was to evaluate the impact of the route of estrogen administration and progestogens on VTE risk among postmenopausal women. Cases were matched 3:1 for a total of 271 cases and 610 controls. Results identified that more cases than controls (17.4% vs 6.5%; 95% CI, 1.4 to 11.4) were treated with oral estrogens. The authors noted that E2 was the predominant estrogen and CE was only used in two cases and no controls. Unlike transdermal E2, oral ERT resulted in an increase in VTE events

in cases compared to controls (45 vs 39; odds ratio (OR) 3.6, 95% CI, 1.5 to 8.8). Similar to oral ERT, norpregnane-derivative progestins increase the risk of VTE compared to controls (40 vs 37; OR 3.8, 95% CI, 1.6 to 8.7). However, P4 and pregnane-derived progestins did not increase the VTE risk. Study outcomes lead the authors to conclude oral, but not transdermal, ERT increases thrombotic risk, and micronized P4 and pregnane derivatives may be safe with respect to VTE risk. Furthermore, data suggest that transdermal ERT in combination with P4 is associated with a safe VTE risk profile.

With the absence of BHRT RCTs with CHD events as the primary outcome, practitioners are left to rely on literature with main outcomes of cardiovascular surrogate markers. Women treated with E2 + P4 combination experience improved cardiovascular markers. E2 monotherapy beneficially improves lipoproteins, carbohydrate metabolism, and vascular reactivity, as well as decreases CIMT, and slows the progression of subclinical atherosclerosis. P4 does not interfere with these beneficial cardiovascular effects. Based on the favorable effects on cardiovascular risk factors, BHRT may prove to be cardioprotective.

HORMONE THERAPY AND BREAST HEALTH

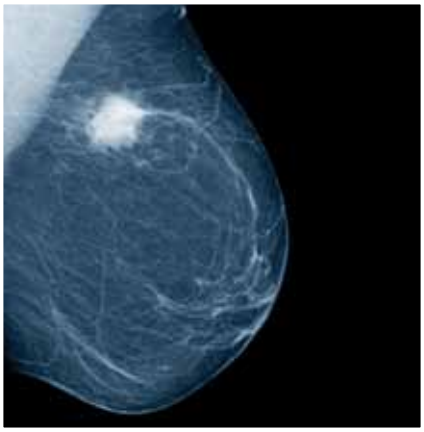
Conventional Hormone Therapy

To investigate the breast cancer risk associated with CHT, a Pubmed/MEDLINE literature search was performed with the following terms: "MESH hormone replacement therapy" and "MESH risk" and ("MESH breast disease" or "MESH neoplasms") and conjugated estrogen. The search was limited to RCTs published in English in core clinical journals between 1995 and 2010 that pertained to human females 45 years or older.

The search returned 14 articles. Review of titles and abstracts excluded 11 articles because they did not discuss CHT and the associated breast cancer risk.

In 2002, the WHI was the first and largest RCT to evaluate the association between CHT and breast cancer risk as the primary adverse outcome. The WHI temporarily deserted the 2002 research due to an increased adverse risk-benefit profile.[6] WHI shifted focus to the evaluation of CE therapy and breast cancer risk in 2006.[49] This pair of WHI trials will be utilized to assess the effects of CHT and CE therapy on breast cancer outcomes.

As stated in the previous sections, the WHI was the first research group to prospectively evaluate the risk associated with CHT. The WHI CE + MPA trial enrolled 16,608 postmenopausal women with a mean age of 63.3 years into their 2002 CHT trial.[6] Analysis of data after 5.2 years of follow-up revealed women treated with CHT experienced an overall nonsignificant increase in invasive breast cancer when compared to placebo (38 vs 30 cases/10,000 person years; 95% CI, 1 to 1.59). Subgroup analysis by never users, <5 years prior HT, 5 to 10 years prior HT, and ≥10 years prior HT use, revealed a nonsignificant increase in women with no prior HT and ≥10 years prior HT. However, women with <5 years prior HT use experienced a near 2-fold increase in breast cancer incidence compared to placebo (40 vs 20 cases/10,000 person years; 95% CI, 1.15 to 3.94). Moreover, women with 5 to 10 years prior HT use experienced a near 5-fold increase in breast cancer incidence per 10,000 person years compared to placebo (50 vs 11; 95% CI, 1.01 to 21.02). Evaluation of breast cancer by year revealed evidence of an increased breast cancer risk over time with CHT use (z=2.56; nominal z=1.96 for significance). Data lead the authors to conclude that the risk for breast cancer emerges several years after treatment with CHT.



Lateral mammogram of female breast with tumor.

Results were also found to be consistent with epidemiological data with increased progestin use.[50-54] Since the trial combined CE and MPA, the trial could not differentiate the effects of estrogen from progestin.

The 2006 WHI CE trial permitted the influences of CE and MPA on breast cancer to be differentiated.[49] The trial of 10,739 healthy women with a mean age of 63.6 years focused on the effects CE on breast cancer. Unlike the WHI CHT trial, women randomized to CE, when compared to placebo, experienced a nonsignificant reduction in invasive breast cancer (34 vs 42 cases/10,000 person years; 95% CI 0.62 to 1.04). Censoring of data six months after an episode of nonadherence (<80% compliance) revealed a significant reduction in breast cancer incidence (HR, 0.67; 95% CI, 0.47 to 0.97). Overall, women treated with CE experienced fewer breast cancers with localized disease (18 vs 25; 95% CI, 0.51 to 0.97) and ductal carcinomas (16 vs 23; 95% CI, 0.52 to 0.99) per 10,000 person-years. However, patients treated with CE experienced larger invasive breast cancers [(1.8 cm (SD, 1.2) vs 1.5 cm (SD, 0.9); p=0.03)]. Subgroup analysis by hormone use found women with no prior hormone use experienced a breast protective effect with fewer cases/10,000 person-years (27 vs 40; 95% CI, 0.46 to 0.92). Women without prior CE + MPA use also experienced a significant decrease in breast cancer incidence (27 vs 40; nominal p=0.03) as did those without history of benign breast disease (27 vs 35; 95% CI, 0.41 to 0.78) and those lacking a first-degree relative with breast cancer (23 vs 34; 95% CI, 0.5 to 0.92). Given such favorable results, the authors concluded that CE might possibly decrease the risk of early stages of breast cancer and ductal carcinomas. With regard to early trials observing an increase risk of breast cancer with CE therapy, it was noted these trials were largely uncontrolled for mammography screenings resulting in possible confounded outcomes. Additional comments highlighted that continued or subsequent use of ERT would not further reduce breast cancer risk in those with prior HT use since sensitive breast cancer cells would have previous exposure to exogenous estrogen.

Planned from the initial design, women from the WHI CHT trial were followed for an additional 2.4 years post discontinuation of CHT and results were published in 2008.[55] Of the surviving women (95%), a nonsignificant increase in breast cancer cases per 10,000 patient years was observed compared to placebo (42 vs 33; 95% CI, 0.91 to 1.78). No difference in breast cancer incidence during the post-intervention phase was observed when compared to the trial period (p=0.97). Moreover, an overall significant increase in breast cancer incidence was observed for the combined trial and post intervention phase (43 vs 34 cases/10,000 person-years; 95% CI, 1.06 to 1.51). Given the observed increases, it was concluded breast cancer risk persisted despite discontinuation of CHT. Yet in 2003, a reported 6.7% decline in breast cancer incidence occurred coinciding with both publication of the WHI CHT 2002 trial and decrease in prescriptions for HT. However, it was commented that data from the WHI CHT follow-up trial could not support or rebuke the claim.

Breast cancer was believed to be a plausible risk of HT, and the WHI RCTs quantified and differentiated the risk associated with combination CE + MPA and CE therapy. The WHI CHT trial demonstrated that CE + MPA increased the risk of breast cancer. Not only did the risk of breast cancer increase over time, but the risk persisted after discontinuation. Since it was perceived that the progestin component was responsible for the increased risk, it is not surprising the WHI CE trial demonstrated that CE therapy does not increase the risk of breast cancer. Moreover, CE therapy may potentially be breast protective in certain groups if initiated early. Given the available data, use of CE monotherapy, when initiated early in menopause, can possibly provide the safest option with regards to CHT and breast cancer risk.

Bioidentical Hormone Replacement Therapy

To investigate the breast cancer risk associated with CHT, a literature search was performed with the following terms: "MESH

hormone replacement therapy" and "MESH risk" and ("MESH breast disease" or "MESH neoplasms") and (estradiol not conjugated estrogen). The search produced one nonrelevant article discussing conjugated estrogens effects on breasts. An additional search was performed with the following word combinations: (menopause or middle age) and ["MESH breast neoplasms" or ("MESH breast" and "MESH cell division)] and [(estrogens not (conjugated estrogen or ethinyl estradiol)] and "MESH progesterone." The search was limited to RCTs or non-U.S. government-funded trials published in English between 1995 and 2010 that pertained to human females 45 years or older. The search returned 42 articles. Of the 42 articles, 31 studies did not address BH, two studies combined E2 with a progestin, three articles were review articles, one study was a continuation study with subgroup analysis, one had low-level evidence, and one study did not address breast cancer or breast proliferation. The remaining three articles are discussed below.

Published RCTs assessing BHRT and breast cancer correlation are limited. Dating back to 1995 and 1998, these trials consist of smaller populations, are shorter in duration, and only evaluate tissue response to hormone exposure.[56,57] In addition, a large French cohort, the E3N cohort, published their most recent findings in 2008 from retrospective evaluations on the breast cancer risk associated with varying forms of hormone therapy including BHRT.[43]

Chang and colleagues[56] conducted a 1995 RCT evaluating human breast epithelial cellular response to BHRT exposure. The trial randomized 34 women between the ages of 18 to 45 undergoing removal of benign lump to receive placebo, topical E2 (1.5 mg), topical P4 (25 mg), or topical E2 (1.5 mg) + P4 (25 mg). Hormones were applied to the breast from day one of menstrual cycle to the day of surgery. Surgery was scheduled to occur on day 11, 12, or 13 of menstrual cycle. Breast epithelial proliferation was measured by counting mitosis and the more sensitive proliferating cell nuclear antigen (PCNA) via immunostaining quantitative analyses. Outcomes with BHRT when compared to placebo showed P4 significantly decreased mitotic divisions (0.17 vs 0.51 divisions/1,000 cells) and the PCNA labeling index % (1.9% vs 7.85%) ($p<0.05$, both comparisons), whereas E2 increased the PCNA labeling index % (17.4% vs 7.8%; $p<0.05$). When E2 was compared to P4, both mitotic divisions (0.83 vs 0.17 divisions/1,000 cells) and PCNA labeling index % (17.4% vs 1.9%) were significantly increased ($p<0.05$, both comparisons). When combination therapy was analyzed, women treated with E2 + P4 experienced less proliferation via PCNA than women treated with E2 alone (6.5% vs 17.4%; $p<0.05$). Data from the present study strongly supports the hypothesis that physiological P4 secretions favorably influence the breast epithelial cells. The authors further concluded that P4 used more than 10 days per month at substitutive doses possesses a therapeutic effect at preventing breast epithelial hyperplasia.

In further support of Chang and colleagues' study, Foidart et al[57] conducted a nearly identical RCT. Differences between the studies include surgery on day 15 of the menstrual cycle and a slightly larger population (n=40). Results revealed similar overall outcomes to those of Chang and colleagues. Comparison of E2 to placebo demonstrated an increase in breast epithelial proliferation via mitotic index per 1,000 cells (0.6 vs 0.15; $p<0.05$) and PCNA labeling index (11.5% vs 0.1%; $p<0.001$). E2 comparison to P4 demonstrated similar outcomes with an increase in mitotic index per 1,000 cells (0.6 vs 0.19; $p<0.001$) and PCNA labeling index (11.5% vs 1.5%; $p<0.001$). Although P4 was found to increase the PCNA labeling when compared to placebo (1.5% vs 0.1%, $p<0.001$), it decreased E2 induced breast cellular proliferation when compared to E2 monotherapy. When compared to E2, combination E2 and P4 decreased the mitotic index per 1,000 cells (0.2 vs 0.6; $p<0.05$) and PCNA labeling index (1.3% vs 11.5%; $p<0.001$). Founded on results similar to Chang and colleagues', the authors concluded that estrogen may possibly result in continued epithelial proliferation that could be thwarted by progesterone.

Over a decade after publication of Foidart and colleague's RCT, the E3N cohort group published the largest and most recent BHRT study with regards to breast cancer outcomes.[43] The E3N study enrolled 80,837 women between the ages of 40 to 65 years in their prospective cohort study and observed how HRT affected breast cancer risk. Women participating in the study completed questionnaires regarding medical history, menopausal status, and a variety of lifestyle characteristics. The self-administered surveys were completed in 1990, 1992, 1993, 1995, 1997, 2000, and 2002. Examination of results revealed outcomes concordant and contradictory to trials reviewed here. In contrast to the WHI CE trial, estrogen therapy consisting of primarily topical E2, was found to have a 1.3 fold increased risk for invasive breast cancer when compared to HRT never users (36 cases, 10,000 person-years; 95% CI, 1.02 to 1.65). Interestingly, the authors found that weak estrogens such as estriol (E3) did not increase the risk of breast cancer with a reported hazard ratio of 0.90 (33 cases/10,000 person-years; 95% CI, 0.68 to 1.18). Conversely, results were congruent with WHI CHT since combination estrogen and progestin (MPA and norpregnane derivatives) increased the risk of invasive breast cancer by 1.7 fold (51 cases/10,000 person years; 95% CI, 1.5 to1.91). Furthermore, outcomes were also congruent with both Chang's and Foidart's RCTs conclusion of P4's breast protective effect. Estrogen therapy + P4 was not found to increase the risk of breast cancer when compared to hormone therapy never users with a hazard ratio of 1 (32 cases/10,000 persons years; 95% CI, 0.83 to 1.22). Given the results, the authors emphasized the expected variability of progestin's actions on breast tissue given

their highly variable chemical structure, metabolism, pharmacokinetics, and potencies. The authors concluded that estrogen in combination with P4 might confer a lower breast cancer risk than combination estrogen and progestin HRTs.

In the absence of large RCTs like the WHI breast cancer trials, smaller RCTs on tissue response and observational trials provide guidance on breast cancer outcomes with BHRT. Trials conducted by Chang and Foidart have demonstrated that E2 induces breast epithelial proliferation. Their results support observations of the E3N group, which found E2 alone significantly increased the risk of breast cancer. Interestingly, the E3N cohort also demonstrated that weak estrogens such as estriol do not increase the risk of breast cancer. Although the aforementioned trials contradict results of the WHI, the mentioned trials utilized predominantly topical E2 therapy in contrast to oral CE therapy in the WHI. In accordance with the WHI, trials analyzed in this section demonstrated that progestins such as MPA and norpregnane derivatives increase the breast cancer risk when combined with estrogen replacement therapy. However, these trials also indicate that the addition of P4 significantly decreases E2's breast proliferative actions and decreases the breast cancer risk compared to that of hormone therapy never users. Published BHRT literature indicates that the combination of E2 and P4 may provide the best-risk benefit with regard to breast cancer and postmenopausal hormone therapy.

CONCLUSION

CE + MPA is detrimental to cardiovascular and breast health. CE monotherapy appears to be cardiovascular and breast neutral, particularly if initiated soon after menopause. Estradiol improves cardiovascular markers but may induce breast epithelial proliferation if administered without progesterone.

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