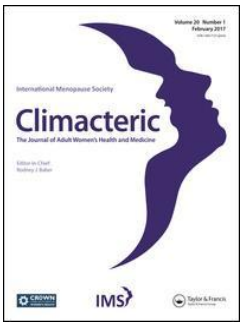

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REVIEW

Menopausal hormone therapy and breast cancer: what is the evidence from randomized trials?

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ABSTRACT

The relationship between menopausal hormone therapy (HT) and breast cancer is complex and further complicated by misinformation, perception, and overgeneralization of data. These issues are addressed in this mini-review through the lens of the Women's Health Initiative (WHI) that has colored the view of HT and breast cancer. In the WHI, unopposed conjugated equine estrogen (CEE) reduced breast cancer risk and mortality. In the WHI CEE plus continuously combined medroxyprogesterone acetate (MPA) trial, although the hazard ratio (HR) was elevated it was statistically non-significant for an association between CEE + MPA and breast cancer. In fact, the increased HR was not due to an increased breast cancer incidence rate in women randomized to CEE + MPA therapy but rather due to a decreased and unexpectedly low breast cancer rate in the subgroup of women with prior HT use randomized to placebo. For women who were HT naïve when randomized to the WHI, the breast cancer incidence rate was not affected by CEE + MPA therapy relative to placebo for up to 11 years of follow-up. The current state of science indicates that HT may or may not cause breast cancer but the totality of data neither establish nor refute this possibility. Further, any association that may exist between HT and breast cancer appears to be rare and no greater than other medications commonly used in clinical medicine.

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Hormone therapy; estrogen; breast cancer; Women's Health Initiative

Introduction

The relationship between menopausal hormone therapy (HT) and breast cancer risk is a complex and conflicting issue created in part by the data as well as by confusion surrounding interpretation of the findings themselves. This situation has been generated by observational studies as well as randomized trials where the association of breast cancer risk with HT has ranged from reduced risk, to neutral effects, to presumed increased risk. The Women's Health Initiative (WHI) trial has also contributed to the totality of literature with confusing findings that are conflicting in nature. Although it received little attention, daily conjugated equine estrogen (CEE) therapy was shown in the WHI CEE trial to significantly reduce the breast cancer risk relative to placebo. On the other hand, daily continuous combined CEE plus medroxyprogesterone acetate (MPA) therapy from the WHI CEE + MPA trial received excessive attention as proof that HT causes breast cancer. Attributed to potential differences that may exist in breast cancer risk between CEE-alone therapy and combined CEE + MPA therapy, close examination of the WHI CEE + MPA trial actually reveals a different story that this regimen had a null effect on breast cancer risk. Although different formulations and types of estrogen and progestogen, doses, timing of initiation, duration of therapy, and individual characteristics all likely play a role in the effect of HT on breast tissue, any conclusions that HT causes breast cancer have eluded definitive proof for over five decades, including the WHI. In the initial report from 2002, CEE + MPA therapy was heralded as causing breast cancer in the WHI CEE + MPA trial[1]. However, close examination of the initial and subsequent data and analyses from the WHI CEE + MPA trial over the last decade supports a different conclusion[2,3]. In light of multiple trial issues including deviation from the a-priori per-protocol defined statistical analyses, confounding variables, detection bias for breast cancer, lack of biological plausibility, and differences between HT naïve and prior HT use subgroups, the WHI CEE + MPA trial does not establish nor completely refute the association of CEE + MPA therapy with breast cancer risk. However, the data clearly show that CEE + MPA therapy had a null effect on breast cancer risk particularly in the subgroup of women representing the typical population of women treated with HT who are HT naïve before receiving menopausal HT.

Estrogen-alone therapy

Women's Health Initiative

Compared with women who received placebo, women in the WHI CEE trial showed a 21% (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.61–1.02) non-significant reduction

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in breast cancer risk after a median 7.2 years of randomized treatment, with 7 fewer invasive breast cancer cases/10 000 women/year of CEE therapy[4]. Among women who were actually taking their study pills and were at least 80% compliant with CEE therapy, breast cancer risk was statistically significantly reduced by 32% (HR, 0.67; 95% CI, 0.47–0.97) relative to placebo[5]. In addition, across all women regardless of compliance status, ductal carcinoma was statistically significantly reduced by 29% (HR, 0.71; 95% CI, 0.52–0.99) by CEE therapy relative to placebo after a mean 7.1 years of randomized treatment[5]. After a mean 10.7 years of follow-up (including a mean 7.1 years of intervention), the breast cancer risk assessed across all women regardless of compliance status was statistically significantly reduced by 23% (HR, 0.77; 95% CI, 0.62–0.95) in women originally randomized to CEE therapy relative to placebo[6]. A non-significant reduction in breast cancer of 20% (HR, 0.80; 95% CI, 0.58–1.11) was evident after a median 13.2 years of follow-up (including a median 7.2 years of intervention) in those women originally randomized to CEE therapy relative to those randomized to placebo[4]. After 18 years of cumulative follow-up of the WHI CEE cohort, breast cancer mortality was statistically significantly reduced by 45% (HR, 0.55; 95% CI, 0.33–0.92). This may well be the most significant and most overlooked finding of the WHI CEE trial[7].

Estrogen–progestogen therapy

Women's Health Initiative

The WHI CEE + MPA trial cohort was comprised of women who were on average 63.3 years old and 12 years since menopause, with an average body mass index (BMI) of 28.5 kg/m^2 (overweight) in which 34.1% had a BMI > 30 kg/m^2 (obese)[1]. As such, a major critical issue with the WHI CEE + MPA trial has always been the overgeneralization of data generated from overweight–obese women more than a decade since menopause to the typical population of women near the time of menopause when initiating HT. The WHI HT trials were not intended to evaluate the common clinical use of HT initiated near menopause and not statistically powered to do so; only 10% of the WHI cohort was 50–54 years of age when started on randomized HT[2].

Nonetheless, across the WHI CEE + MPA trial cohort there was an apparent 8 additional breast cancer cases/10 000 women/year of daily continuous combined CEE + MPA therapy relative to placebo after a median 5.6 years of randomized treatment[4]; an increased but rare absolute risk that is comparable to or less than other commonly used medications such as lipid-lowering medication[8] and anti-hypertensive medications[9]. The overall HR for breast cancer increased approximately 2.5–3 years after randomization and persisted throughout the median 5.6 years of randomized treatment with an apparent HR of 1.24[10]. However, what is poignantly important concerning this HR is understanding what ultimately constitutes this summary statistic as well as what confounds the underlying data, with each revelation indicating statistical non-significance and/or casting doubt of the validity on the findings.

Critical considerations for understanding the WHI CEE + MPA trial data

Application of a-priori per-protocol statistics

Although CEE + MPA therapy on the apparent risk of breast cancer was originally publicized as statistically significant, this was in fact a misrepresentation of the HR based on the nominal unadjusted statistic reported in 2002 as 'almost reached nominal statistical significance'[1] (page 327). Firstly, the nominal statistic (nominal 95% CI, 1.00–1.59) was not statistically significant since the CI included 1; and secondly, the nominal statistic was a-priori per-protocol reserved for the WHI CEE + MPA trial primary outcome of coronary heart disease[2,7,11]. 'Nominal 95% confidence intervals describe the variability in estimates [the HR] that arise from a simple trial for a single outcome' that is not adjusted for covariates or even for multiple 'looks' at the data over time as occurred for the breast cancer outcome in the WHI CEE + MPA trial[1] (page 325). 'Although nominal confidence intervals are traditional, they do not account for multiple statistical testing across time and across outcomes' as occurred for breast cancer in the WHI CEE + MPA trial[1] (page 325). As such, breast cancer was a-priori per-protocol defined as a secondary outcome mandating per protocol that this secondary outcome should be analyzed by a multiadjusted statistic[2,7,11,12]. 'The adjusted 95% confidence intervals use group sequential methods to correct for multiple analyses over time'[1] (page 325). When applying the per-protocol multiadjusted statistic to the a-priori defined secondary outcome of breast cancer, the HR of 1.24 was clearly statistically non-significant (multiadjusted 95% CI, 0.83–1.53)[1,10]. Although the appropriate use of the multiadjusted analysis was acknowledged in the 2002 WHI CEE + MPA trial manuscript[1] (page 327), the per-protocol analysis plan for the breast cancer outcome was actually abandoned and most of the WHI CEE + MPA trial manuscripts focus on the nominal unadjusted analyses. Although this unorthodox manner of conducting analyses was reported in the original 2002 WHI CEE + MPA trial results[1] and perpetuated in almost every subsequent manuscript concerning CEE + MPA therapy and breast cancer, whenever the multiadjusted statistic was reported it was statistically non-significant for the effect of CEE + MPA therapy relative to placebo on the outcome of breast cancer in the original and subsequent manuscripts[1,10].

Adjustment for confounders at baseline

Even if one accepts the unorthodox non-protocol borderline nominal statistic as valid, adjustment for confounders due to differing distribution of breast cancer risk factors across treatment groups at baseline (adjusted for age, race/ethnicity, BMI, physical activity, smoking, alcohol use, parity, oral contraceptive use, family history of breast cancer and fractures, mammography use, and vasomotor symptoms) resulted in the nominal statistic becoming clearly statistically non-significant (HR, 1.20; 95% CI, 0.94–1.53)[13]. Although randomization may have been adequate for the primary end point of coronary heart disease in the WHI CEE + MPA trial, clearly residual confounding remained for breast cancer risk

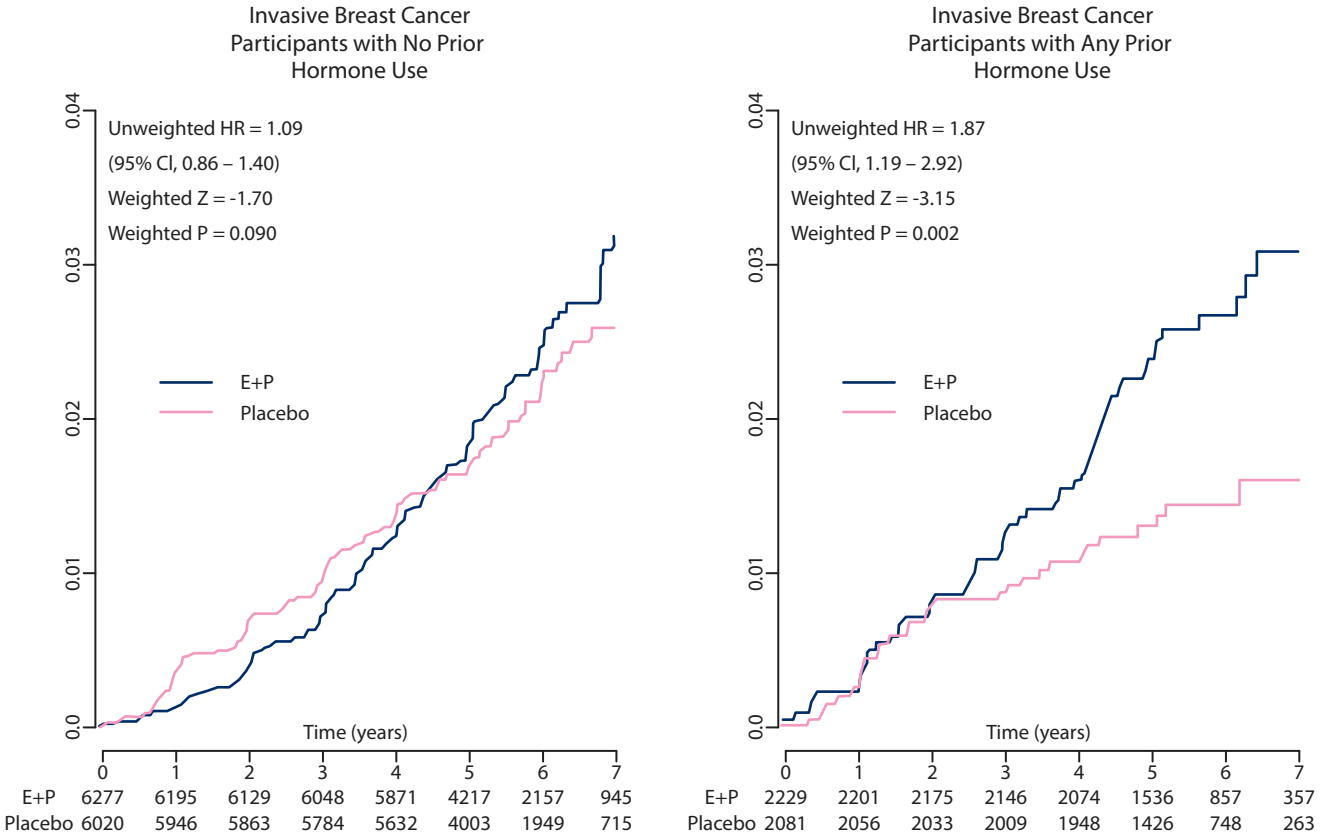

Figure 1. Breast cancer incidence in the Women's Health Initiative trial of conjugated equine estrogen plus medroxyprogesterone acetate (E + P) versus placebo, stratified by prior use of hormone therapy, showing similar trends for all subgroups except for women with prior hormone therapy use randomized to placebo where breast cancer incidence unexpectedly sharply diverges without explanation. It is the divergence in the trend line for women with prior hormone therapy use randomized to placebo that accounts for the elevated hazard ratio for breast cancer falsely giving the impression that breast cancer incidence was increased in the trial due to conjugated equine estrogen plus medroxyprogesterone acetate, where in fact the elevated hazard ratio was due to a decreased breast cancer incidence in the placebo-treated group. CI: confidence interval; HR: hazard ratio.

factors across the treatment groups as the adjustment for these confounders indicated.

Prior exposure to hormone therapy

In addition to the troublesome abandonment of protocol and statistical issues of the WHI CEE + MPA trial reviewed were revelations from the analysis of two distinct subgroups of women randomized to the WHI CEE + MPA trial; those women with no HT use prior to randomization (HT naïve) and those women who used HT prior to randomization. Although this subgroup analysis has been published no less than three times, including within the original WHI CEE + MPA trial publication in 2002, there has been little attention given to how this subgroup analysis impacts the interpretation of the overall HR for apparent breast cancer risk in the WHI CEE + MPA trial[1,13,14]. After adjusting for confounders, the HRs reported from the HT naïve and prior HT use subgroups were statistically different ($p = 0.027$) after a mean 5.6 years of randomized treatment[13]. Among the HT naïve subgroup of women (75% of the cohort), breast cancer incidence was not affected by CEE + MPA therapy (HR, 1.02; 95% CI, 0.77–1.36) relative to placebo after a mean 5.6 years of randomized treatment[13]. On the other hand, an increased HR for breast cancer was limited to 25% of the cohort with prior HT use who were randomized to CEE + MPA therapy (HR, 1.96; 95% CI, 1.17–3.27) relative to placebo after a mean 5.6 years of randomized treatment[13]. After a total mean follow-up of 11 years (including a mean 5.6 years of intervention) of the HT naïve women, breast cancer incidence was not affected by CEE + MPA therapy (HR, 1.16; 95% CI, 0.98–1.37) relative to placebo[14]. The increased HR for breast cancer was limited to the women with prior HT use who were randomized to CEE + MPA therapy (HR, 1.85; 95% CI, 1.25–2.80) relative to placebo[14]. The HRs for breast cancer in women with and without prior HT use was significantly different ($p = 0.03$) after a total mean follow-up of 11 years. Although the findings from the HT naïve and prior HT use subgroups were reported in the first WHI CEE + MPA trial manuscript in 2002[1] (page 328) after a mean 5.2 years of randomized treatment, this subgroup analysis and its implications for the apparently elevated HR for breast cancer were not addressed in the manuscript, press releases, or by the media, and women and health-care providers have remained largely unaware of these results and their implications.

Implications of the outlier low breast cancer incidence rate in women randomized to placebo

As shown in Figure 1, of the four trend lines the only one with a different slope represents the subgroup of women

with prior HT use who were randomized to placebo, falsely giving the impression that the elevated HR was due to an increased incidence of breast cancer due to CEE + MPA. The trend line representing the other placebo subgroup of HT naïve women and the trend lines representing the subgroups of HT naïve women and women with prior HT use who were randomized to CEE + MPA therapy are virtually identical[13]. It is the divergence in the trend line for women with prior HT use randomized to placebo that accounts for the elevated HR for breast cancer falsely giving the impression that breast cancer incidence was increased in the trial due to CEE + MPA. The cause of the extraordinary low incidence of breast cancer events in the subgroup of placebo women with prior HT use is unknown but this strikingly low rate has been externally validated as an outlier with WHI observational data. This finding of an outlier low breast cancer incidence rate in placebo recipients has been largely ignored in reporting and interpreting the HR for the breast cancer outcome in the WHI CEE + MPA trial. In the WHI observational study, the annualized breast cancer rate for HT non-users who had no prior HT use (0.35%) was the same as the annualized breast cancer rate for the HT naïve subgroup of women randomized to placebo in the WHI trial (0.36%) (Table 1)[15]. The annualized breast cancer rate for HT non-users with prior HT use in the observational study was 0.38%, similar to the aforementioned subgroups of women[15]. These data externally validate that the annualized breast cancer rate (0.25%) in the subgroup of women randomized to placebo who had prior HT use was clearly an outlier[2,13]. As an outlier, the low annualized breast cancer rate in the women randomized to placebo in the WHI trial with prior HT use drove the HR in this subgroup of women to statistical significance and increased the overall trial HR for breast cancer when the two subgroups of HT naïve and prior HT use were analyzed as one group[13]. This fact is also externally validated by comparing the breast cancer incidence rates from the WHI CEE + MPA trial with those from the WHI dietary modification (DM) trial[16].

Unlike the WHI HT trials where breast cancer was a-priori defined as a secondary outcome, breast cancer was the primary outcome for the WHI DM trial[7,11,16]. The WHI DM trial was publicized as showing that a low-fat diet reduced breast cancer while the WHI CEE + MPA trial showed an increase in breast cancer with CEE + MPA therapy. If true, then the breast cancer incidence rate with DM would be expected to be low and the breast cancer incidence rate expected to be high with CEE + MPA therapy. However, the breast cancer incidence rates are equal across both trials; 0.42% for the low-fat diet and 0.43% for CEE + MPA therapy (Table 2). Moreover, the breast cancer incidence rate in HT naïve women randomized to CEE + MPA therapy was slightly lower (0.40%) than the breast cancer rate in women who were reported to have modest protection from the low-fat diet (0.42%) in the WHI DM trial (Table 2). Further, the annualized breast cancer incidence rate associated with CEE + MPA therapy in women with prior HT use (0.46%) was essentially equal to the breast cancer incidence rate in the women (0.45%) who were randomized to maintain their usual diet in the WHI DM trial (Table 2).

The breast cancer incidence rates in the WHI DM trial and the WHI observational study externally validate that the key finding of the WHI CEE + MPA trial of an apparent increased HR for breast cancer risk was not due to an increased breast cancer incidence rate in women randomized to CEE + MPA therapy but rather was due to the decreased outlier low breast cancer incidence rate (0.25%) in the subgroup of women with prior HT use and randomized to placebo[2,13]. The decreased breast cancer incidence rate (0.25%) in the subgroup of women with prior HT use and randomized to placebo in the WHI CEE + MPA trial is an outlier rate that drove the HR in this subgroup of women to statistical significance and elevated the overall HR for breast cancer in the WHI CEE + MPA trial with the combined analysis of this subgroup of women with the HT naïve subgroup of women[2,13].

Table 1. Comparison of breast cancer incident rates between the Women's Health Initiative observational study and trial of conjugated equine estrogen plus medroxyprogesterone acetate (CEE + MPA) versus placebo.

Subgroup	CEE + MPA clinical trial placebo group (annualized % events)	Observational study hormone therapy non-users (annualized % events)
No prior hormone therapy use	0.36	0.35
Prior hormone therapy use	0.25	0.38

Exposure status and detection bias

Although the elevated HR for the breast cancer outcome of the WHI CEE + MPA trial was not due to an increased breast cancer incidence rate in women randomized to CEE + MPA therapy, the validity of any breast cancer diagnosis associated with CEE + MPA therapy is further cast in doubt by the fact that detection bias for breast cancer in the WHI CEE + MPA trial cannot be excluded[12,17]. Detection bias for breast cancer compounds the protocol and statistical issues reviewed that contributed to the overinterpretation of the breast outcome data. Detection bias is a well-known confounder in observational studies where women and their health-care providers are aware that they are using HT. Over

Table 2. Comparison of breast cancer incident rates between the Women's Health Initiative dietary modification (DM) trial of low-fat intake versus usual diet and trial of conjugated equine estrogen plus medroxyprogesterone acetate (CEE + MPA) versus placebo.

	CEE + MPA clinical trial	Dietary modification trial	
Subgroup	CEE + MPA group (annualized % events)	Low-fat diet group (annualized % events)	Usual diet group (annualized % events)
CEE + MPA overall	0.43		
DM overall		0.42	0.45
No prior hormone therapy use	0.40		
Prior hormone therapy use	0.46		

time, the WHI CEE + MPA trial took on characteristics of an observational study as participants became aware of their treatment assignment from unblinding. In the WHI CEE + MPA trial, minimally 44.4% of the women on active CEE + MPA therapy relative to 6.8% of the placebo recipients were unblinded to their treatment assignment mainly due to vaginal bleeding (in contrast, only 6% of women randomized to CEE therapy and 6% of placebo participants in the WHI CEE trial were unblinded to treatment)[1,17]. In addition, dense mammographic findings among CEE + MPA therapy recipients along with increasing publicity and focus on a possible association of breast cancer with HT would have also led to more intense surveillance among CEE + MPA therapy recipients than those receiving placebo, resulting in a greater differential detection of otherwise undiagnosed preexisting occult breast cancer. Importantly, there was a heightened awareness of WHI CEE + MPA trial participants to the potential breast cancer risk resulting from breast cancer warning letters sent to participants by the WHI investigators over the course of randomized treatment.

In any follow-up study, including most prominently the WHI CEE + MPA trial, participants who are aware that they are receiving active HT and who are also explicitly and repeatedly warned that their HT may increase their risk of developing breast cancer make it highly unlikely that outcomes such as breast cancer that are susceptible to detection bias can be interpreted. In terms of awareness of treatment status, detection bias for breast cancer intersecting with the large pool of undiagnosed preexisting occult breast cancer in women over the age of 50 years[18] is strongly plausible, especially since a HR of 1.20–1.26 with only 7–9 additional breast cancer diagnoses/10 000 women/year of CEE + MPA therapy cannot discriminate between causation and detection bias as alternative explanations for the breast cancer results[17]. In other words, on the null hypothesis, detection bias could have accounted for the rare absolute difference in breast cancer between CEE + MPA therapy and placebo if, on average, <1 additional breast cancer case/1000 women/year of CEE + MPA therapy was diagnosed that would otherwise have gone undetected.

Breast cancer doubling time

As noted previously, the HR for breast cancer increased approximately 2.5–3 years after intervention in the WHI CEE + MPA trial. However, based on the doubling time for the multiplication of malignant breast cells, it takes at least 10 years for breast cancer cells to become clinically evident[19]. As such, an increased risk for de-novo development of breast cancer during the mean 5.6 years of randomized treatment in the WHI CEE + MPA trial is biologically implausible[17,19]. On the other hand, with the lack of biological credibility, a much more likely explanation for the increased HR for breast cancer 2.5–3 years after randomization is shown in Figure 1 where the trend lines for the incidences of breast cancer in the subgroup of women with prior HT use randomized to CEE + MPA therapy and placebo diverge. As clearly shown in Figure 1, the divergence in the trend lines at approximately 2.5 years in the subgroup of women with prior HT use is due to the sudden and unexplained reduction in the incidence of breast cancer in the placebo group, whereas the trend line for those women with prior HT use randomized to CEE + MPA therapy continues along a similar slope as those women in the subgroup of HT naïve women randomized to CEE + MPA therapy and placebo[13].

Additional randomized trial and observational research data

Smaller randomized trials have shown similar reductions in breast cancer with estrogen-alone therapy to the WHI CEE trial with long-term estradiol therapy up to 10 years and total follow-up for 16 years[20,21]. Likewise, smaller randomized trials have shown similar non-significant effects on breast cancer with combination estrogen plus progestogen therapy to the WHI CEE + MPA trial with long-term combination HT up to 10 years and total follow-up for 16 years[20,22,23].

Most observational studies indicate no increased risk for breast cancer in women using estrogen-alone therapy. Observational breast cancer risk data associated with the use of combination HT are mixed, with most studies showing non-significant associations. Observational studies on a long duration of estrogen-alone therapy and combination HT are mixed, with a few studies showing elevated breast cancer risk after 5–10 years of use while other studies show no breast cancer risk with long-term use. Most observational data relating HT with breast cancer risk gravitate around the null, with risk ratios (odds ratio and relative risk; measures of association between exposure and outcome) rarely exceeding 1.5 and virtually all associations reported as <2.0[24,25].

In observational research, relative risks (cohort studies) of 2–3 or less and odds ratios (case–control studies) of 3–4 or less are considered not credible because of the high likelihood of biases and residual confounding; especially relevant where it concerns HT and breast cancer risk where detection bias, which increases over time, falsely increases observed risk since HT users are more carefully monitored for breast cancer[24–26]. To our knowledge, there are no published epidemiologic guidelines that consider risk ratios of 2 or less as credible in observational studies since they are difficult to interpret as a result of detection and other biases. Therefore, smaller risk ratios have little clinical or public health importance, especially if outcomes such as breast cancer are rare (<1 additional breast cancer diagnosis/1000 women/year of HT). Risk ratios of 2–3 or less cannot exclude detection or other biases as likely alternative explanations for the association between HT and breast cancer, especially since the majority of observed breast cancer effects of combination HT are expected on undiagnosed preexisting occult breast cancer present in the population of otherwise healthy postmenopausal women (16% of women dying from unrelated causes are found to have undiagnosed, small, occult breast cancer on autopsy)[27].

In terms of reduced breast cancer mortality as in the WHI CEE trial, findings from the Finnish Nationwide Comparative Study are relevant and representative of the totality of the literature. With 3.3 million cumulative exposure years in 489,105 women using HT, breast cancer mortality was

statistically significantly reduced in all HT users with exposure for >0–5 years (0.56; 95% CI, 0.52–0.60), for >5–10 years (0.46; 95% CI, 0.41–0.51), and for >10 years (0.62; 95% CI, 0.56–0.68). A significantly larger risk reduction was observed in the 50–59 years age group (0.33; 95% CI, 0.29–0.37) compared with the 60–69 years age group (0.64; 95% CI, 0.59–0.70) and the 70–79 years age group (0.78; 95% CI, 0.69–0.87). The mortality reductions in estrogen-alone therapy was larger in all age groups compared with the combined HT users with exposure for >0–5 years (0.49; 95% CI, 0.44–0.54 vs. 0.55; 95% CI, 0.51–0.60), for >5–10 years (0.46; 95% CI, 0.39–0.53 vs. 0.50; 95% CI, 0.44–0.56), and for >10 years (0.54; 95% CI, 0.48–0.62 vs. 0.68; 95% CI, 0.60–0.76)[28].

Conclusion

Close review of the original WHI CEE + MPA trial results from 2002[1] as well as subsequent publications from 2006[14] and 2010[15] clearly reveals that the HR for breast cancer masks an incredibly important fact for women and their health-care providers. The increased HR for breast cancer reported from the WHI CEE + MPA trial was not due to an increased incidence rate of breast cancer in the women randomized to CEE + MPA therapy. Instead, the increased HR for breast cancer was due to a decreased incidence rate of breast cancer in the women randomized to placebo who used HT prior to randomization to the WHI CEE + MPA trial[2]. Although the cause of this outlier low incidence rate of breast cancer in the placebo group of women who had prior HT use is unknown, it is stunning that this unappreciated fact has escaped a more conspicuous and transparent discussion of the important impact that this finding has on interpretation of the breast cancer results from the WHI CEE + MPA trial. With the currently available data more fully elucidated and reviewed, it is clear that breast outcome data from the WHI CEE + MPA trial has been misinterpreted and overgeneralized since the HR masks the actual incidence rates of breast cancer in the CEE + MPA therapy and placebo groups. Externally validated with breast cancer incidence rates from the WHI observational study and the WHI DM trial, the subgroup findings clearly provide a more likely interpretation of the WHI CEE + MPA trial breast cancer results. That is, the WHI CEE + MPA trial strongly refutes the possibility that CEE + MPA therapy increased the risk of breast cancer in this trial.

Randomization and size of a clinical trial, as exemplified by the WHI CEE + MPA trial, does not ensure application of a-priori per-protocol defined rules or clinical trial standards, or necessarily prevent risk factor confounders, detection bias, or biological implausibility that affect interpretation of the therapy under investigation. Individually or together, these factors can cause misleading results and/or lead to misinterpretation of the outcome data when not unbiasedly considered and devoid of any alternative explanation of the results. Skirting alternative explanations for the breast cancer findings from the WHI CEE + MPA trial with all of these factors obviously at play in the trial suggests a singular focus resulting in a biased interpretation of the results to fit a narrative rather than to advance science with demonstrable harm to women and women's health[29–31].

In the WHI CEE + MPA trial, application of the a-priori per-protocol multiadjusted statistic to the breast cancer data rendered statistically non-significant the unorthodox borderline significant nominal unadjusted statistic, as did adjustment for baseline confounders. Importantly, the rare number of additional breast cancers detected in the CEE + MPA therapy group cannot discriminate between causation and detection bias. Even a small detection bias resulting in the diagnosis of <1 additional breast cancer case/1000 women/year of CEE + MPA therapy that otherwise would have been undetected could have easily accounted for the rare number of additional breast cancers in the CEE + MPA therapy group. Biological implausibility for the de-novo development of breast cancer over the mean 5.6 years of randomized treatment makes the outlier low incidence rate of breast cancer in the women randomized to placebo with prior HT use the most likely explanation for the increased overall HR for breast cancer, especially since the incidence rates of HT naïve women randomized to placebo and the women with and without prior HT use and randomized to CEE + MPA therapy did not differ. Additionally, the biological implausibility for de-novo development of breast cancer over 5.6 years makes detection bias of tumor growth from the large pool of undiagnosed preexisting occult breast cancer in women over the age of 50 years a more likely explanation for the rare number of additional breast cancers diagnosed in the CEE + MPA therapy group.

After five decades of study, no conclusive evidence, including the WHI CEE + MPA trial, proves that HT causes breast cancer and, in fact, the overwhelming preponderance of data, including the WHI CEE + MPA trial, show that estrogen + progestogen therapy has a null effect on breast cancer. Additionally, estrogen alone, as randomized trials including the WHI CEE trial show, possibly prevents development of and mortality due to breast cancer. The WHI CEE + MPA trial clearly shows that HT naïve women who initiate CEE + MPA therapy have no increased risk for breast cancer; the typical population of women who initiate HT for menopause are HT naive. It should also be noted that the 8 additional breast cancers/10 000 women/year of CEE + MPA therapy reported across the entire WHI CEE + MPA trial cohort and the 4 additional breast cancers/10,000 women/year of CEE + MPA therapy in the subgroup of HT naïve women are rare and similar to or lower than the breast cancer risk associated with a host of other factors including obesity, low physical activity, <2 daily glasses of wine, being a flight attendant, and commonly used medications[8,9,24,25].

It can be argued that considerable damage to women and women's health has occurred through misinterpretation and overgeneralization of the breast cancer data from the WHI CEE + MPA trial since women are now reluctant to use and health-care providers to prescribe HT, either estrogen alone or in combination with a progestogen[29–31]. Unfortunately, this is true even for women who are clearly suffering from menopausal symptoms. On the background of misinterpretation and overgeneralization of the WHI

CEE + MPA breast cancer results and resultant negative press, women who are candidates for estrogen-alone therapy are often overlooked in postmenopausal HT discussions. In the Finnish study, >40% of the women received estrogen-alone therapy while in the United States, where the hysterectomy rate is much greater, the percentage of women who are candidates for estrogen-alone therapy approaches that of estrogen plus progestogen candidates. Separating the data for estrogen-alone therapy from combination estrogen plus progestogen therapy helps to recognize the distinct role that estrogen-alone therapy plays in reducing breast cancer risk and breast cancer mortality as supported by the totality of data, including the WHI CEE trial.

For women and health-care providers alike, fear of breast cancer with perceived risk of HT can be confidently replaced with current knowledge of risk determined from the totality of the literature. As such, it is more than reasonable to conclude that the current state of the science indicates that HT may or may not cause breast cancer, but the totality of data neither establish nor refute this possibility; and women should be so counseled. However, it is very clear that any potential breast cancer risk (especially for the typical population of women near the time of menopause who are HT naïve when initiating HT) is rare and no greater than other factors as reviewed. As such, HT can be used with the reassurance that, in addition to the rarity of potential risk when initiated near the time of menopause, 50 years of study has failed to conclusively prove cause-and-effect between HT and breast cancer, with the preponderance of evidence supporting benefits over risks with amelioration of downstream morbidity and mortality.

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