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Personal Perspective

'Tis but a scratch: a critical review of the Women's Health Initiative evidence associating menopausal hormone therapy with the risk of breast cancer

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Abstract

Use of menopausal hormone therapy (HT) fell precipitously after 2002, largely as a result of the Women's Health Initiative's report claiming that the combination of conjugated equine estrogen (CEE) and medroxyprogesterone acetate increased breast cancer risk and did not improve quality of life. More recently, Women's Health Initiative (WHI) publications acknowledge HT as the most effective treatment for managing menopausal vasomotor symptoms and report that CEE alone reduces the risk of breast cancer by 23% while reducing breast cancer death by 40%. Their sole remaining concern is a small increase in breast cancer incidence with CEE and medroxyprogesterone acetate (1 per 1,000 women per year) but with no increased risk of breast cancer mortality. This article closely examines evidence that calls even this claim of breast cancer risk into serious question, including the WHI's reporting of nonsignificant results as if they were meaningful, a misinterpretation of its own data, and the misleading assertion that the WHI's findings have reduced the incidence of breast cancer in the United States. A generation of women has been deprived of HT largely as a result of this widely publicized misinterpretation of the data. This article attempts to rectify this misunderstanding, with the goal of helping patients and physicians make informed joint decisions about the use of HT.

Key Words: Breast cancer – Hormone therapy – Menopausal hormone therapy – Menopause – Women's Health Initiative.

HISTORICAL PERSPECTIVE

For more than 21 years, criticisms of the Women's Health Initiative (WHI)'s findings, initially reported in a press conference on July 8, 2002,[1] and released in print July 17, 2002,[2] have mounted. Although the WHI investigators have walked back almost all of the initial negative claims that generated international alarm, Chlebowski and Aragaki,[3] in an article published earlier this year in *Menopause*, continue to insist that combination hormone therapy (HT), composed of conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA), increases breast cancer risk.

This misleading conclusion contradicts WHI data that showed no increased breast cancer risk with CEE+MPA treatment among women who had not taken HT before entering the WHI trial[4,5] or among women with a family history of breast cancer, or for CEE+MPA with statistical adjustments per protocol for this secondary outcome.[4,6] It minimizes the WHI findings that CEE alone is associated with a decreased risk of breast cancer,[7] a decreased risk of death from breast cancer, and a decreased risk of death from all causes.[8] Indeed, senior investigators for the WHI acknowledge that HT is the most effective treatment for managing menopausal vasomotor symptoms.[9-11] They acknowledge many benefits of HT, particularly among women who initiate HT within 10 years of their last menstrual period,[12] consistent with the vast majority of the published literature.[13-20]

Nevertheless, Chlebowski and Aragaki[3] continue to maintain that CEE+MPA increases the risk of breast cancer, albeit with no increased risk of death from breast cancer. Because even this sole remaining claim has been challenged,[21] their article in *Menopause* was intended as a response to criticism.[3] They begin by citing, in support of their view, the Collaborative Group on Hormonal Factors in Breast Cancer[22] and the Million Women Study,[23] ignoring widely published critical comments questioning those studies' validity while also dismissing the glaring, contrasting findings between these studies and the WHI.[24]

Consider these issues with the collaborative reanalysis:

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1. No increase in breast cancer was observed among women who had taken HT in the past, no matter how long they had taken it. In contrast, the WHI reports a persistently elevated risk of breast cancer among past users,[10] even after 20 years of follow-up.
2. The reported increase was 6 per 10,000 women years, hardly a strong or compelling finding.
3. More than 80% of the women were on estrogen alone and yet were reported to have an increased risk of breast cancer—precisely the opposite of the finding reported by the WHI of a decreased risk for women on estrogen alone.[7] Nonetheless, Chlebowski and Aragaki[3] claim this point as support for an increased risk while ignoring their own data showing that estrogen alone reduces risk.

Also, consider these challenges to the Million Women Study:

1. Although called a study, it consisted of only two questionnaires, separated by approximately 3 years and sent to a million women, of whom only 44% responded to both surveys.
2. Total incidence of breast cancer was 1% among estrogen-only users and 1.4% among estrogen-progestogen users.
3. Of that 1% to 1.4%, the increased risk was identified in only current, but not past, users even if past use had exceeded 15 years. While acknowledging the differing results of estrogen alone administration between this study and the WHI, Chlebowski and Aragaki[3] note that "These divergent results for estrogen therapy and breast cancer have been difficult to reconcile" but do not attempt to resolve this conundrum.
4. The authors of the Million Women Study did not discuss the possibility that, in a significant number of their cases, breast cancer may have been present before these women joined the study since participants were invited because they had had a mammogram, a fundamental selection bias.[25,26] In support of that interpretation, the average time from joining the study to diagnosis of breast cancer was only 1.2 years; the median time from diagnosis to death from breast cancer was only 1.7 years. Given that breast cancer requires 9 to 16 years to become clinically identifiable,[27,28] it is more likely that the breast cancers were not directly related to HT use but were already present at the time the women were enrolled.

Thus, although these two profoundly flawed and contradictory studies continue to be cited as if they confirm the WHI's position, they do not.

Of greater concern is the WHI's (1) failure to acknowledge its reporting of nonsignificant results as if they were meaningful, (2) misinterpretation of its own data, and (3) misleading assertion that its findings have reduced the incidence of breast cancer in the United States.

THE WHI'S REPORTING OF NONSIGNIFICANT RESULTS AS IF THEY WERE MEANINGFUL

Two issues in the WHI's statistical analyses highlight the lack of significance between CEE-MPA and breast cancer.

First, the WHI continues to publish "nominal" rates as the primary statistic. This potentially confusing label means a "simple, unadjusted" analysis that does not take into consideration factors that can create a false-positive result for a given outcome. The initial 2002 claims of breast cancer risks were based on this method. The result was a nominal, unadjusted hazard ratio (HR) of 1.26 for breast cancer among participants randomized to CEE+MPA, which "almost reached nominal statistical significance" (95% CI, 1.00-1.59). Per-protocol adjustment for multiple outcomes and multiple looks at the data[29] included in the same article found a 95% CI of 0.83 to 1.92. The WHI's 2003 article, which also focused on the association between CEE+MPA and breast cancer, reported an HR of 1.24 and claimed statistical significance with the nominal 95% CI of 1.01 to 1.50. However, with minimal adjustment for sequential monitoring (per protocol for this secondary outcome), it was not statistically significant (95% CI, 0.97-1.59).[30]

Second, the WHI protocol mandated multivariate adjusted analyses for secondary outcomes.[29] Breast cancer in the HT trials was in this category. An analysis with adjustment for breast cancer risk factors including age, ethnicity, body mass index, physical activity, smoking, alcohol use, parity, age at first birth, oral contraceptive use, family history of breast cancer, and mammography use was published in 2006, by Anderson et al.[4] With that per-protocol adjustment, the association between CEE+MPA and breast cancer was not statistically significant (HR, 1.20; 95% CI, 0.94-1.53).[4,31] These results indicate that the difference between CEE+MPA and placebo was due to an imbalance of baseline risk factors. Indeed, in all instances where the WHI has reported adjustment for sequential monitoring, multiple outcomes, or risk factors, the results for an association between CEE+MPA and breast cancer have not been statistically significant.

The WHI has claimed that randomization for the primary outcome of coronary heart disease should account for breast cancer risk factors. However, it is well known that randomization for a primary outcome cannot balance the myriad risk factors that could account for differences between active treatment and placebo for secondary endpoints no matter how large the trial, and the WHI is no exception. For this reason, adjustment for covariates is used in randomized clinical trials to avoid false-positive findings for secondary outcomes.

THE WHI'S MISINTERPRETATION OF ITS OWN DATA

Chlebowski and Aragaki[3] consistently ignore these important statistical issues. However, as early as 2004, Kuhl[32] observed that their position on CEE+MPA's risk was a misinterpretation of the data: the trend toward a difference was not caused by a higher rate of breast cancer in the HT group but by a low rate in the placebo group. Anderson et al,[4] in their 2006 article, acknowledged this point and dismissed it. They examined the incidence of breast cancer in four subgroups defined by prior/no prior use of HT and assignment to CEE+MPA or placebo. (Fig. 1.) The risk of breast cancer was the same in three of those four groups: women with no prior HT use randomized to placebo, women with no prior HT use randomized to CEE+MPA, and women with prior HT use randomized to CEE+MPA.

The only group with a different incidence rate was women with prior HT use randomized to placebo. This subgroup had a very low incidence of breast cancer, lower than that in the

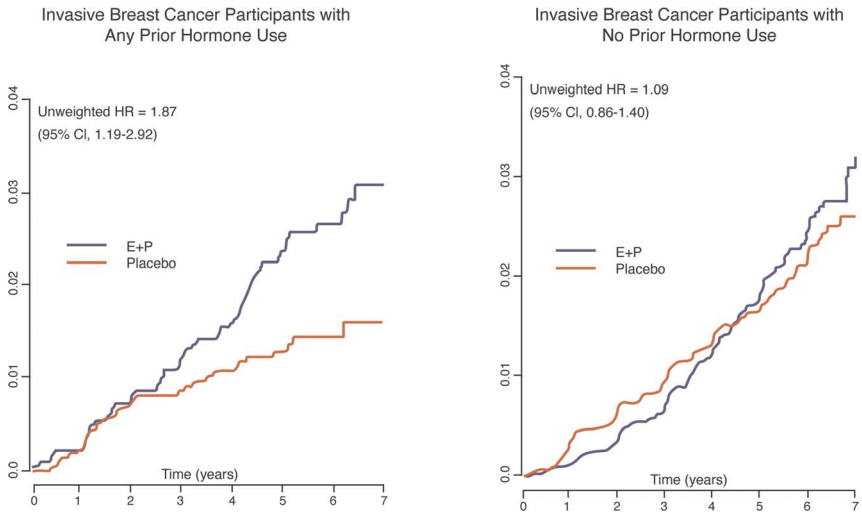

FIG. 1. Risk of invasive breast cancer with and without prior hormone use.

general population. To illustrate how unusual this was, the comparable control arm of women assigned to continue their usual diet in the WHI Diet Modification Trial had an 80% higher breast cancer incidence than did the placebo arm in the CEE-MPA trial.[33] Furthermore, when women who used HT before joining the CEE+MPA trial were eliminated from the analyses, mirroring the experience for most women starting HT during perimenopause, the remarkably low incidence of breast cancer observed in the placebo group returned to its expected incidence and the increased HR disappeared (Fig. 1.)

The key point is that any explanation for the low incidence rate in the placebo group is irrelevant. Whether due to prior HT use, unequal covariates, or anything else does not change the fact that the remarkably low incidence rate in the placebo group elevates the HR, which the WHI misleadingly interprets as an increase in breast cancer risk.

Moreover, if CEE+MPA really did increase breast cancer risk, the incidence of breast cancer should be greater among adherent women (those confirmed to be taking 80% of their assigned pills) compared with all women randomized to that same arm. However, it is not. The incidence of breast cancer among those exposed to HT before joining the study and who were adherent to CEE+MPA therapy during the study was identical to the incidence in the overall cohort of those randomized to CEE+MPA (compare the blue lines in Figures 1 and 2.)

THE WHI'S MISLEADING ASSERTION THAT ITS FINDINGS REDUCED THE INCIDENCE OF BREAST CANCER

Chlebowski and Aragaki[3] defend their claim of CEE+MPA's harm by citing a report of decreased incidence of breast cancer observed shortly after the trial was halted in 2002. They immediately attributed this "decline" to the nationwide decreased use of HT.[34,35] First, this is implausible because of the previously noted long lag time between initiation of a breast cancer and growth to a clinically detectable size. In addition, their own data showed a continuous increase in breast cancer rates among the study's women who stopped taking CEE+MPA.[36] Moreover, according to Centers for Disease Control

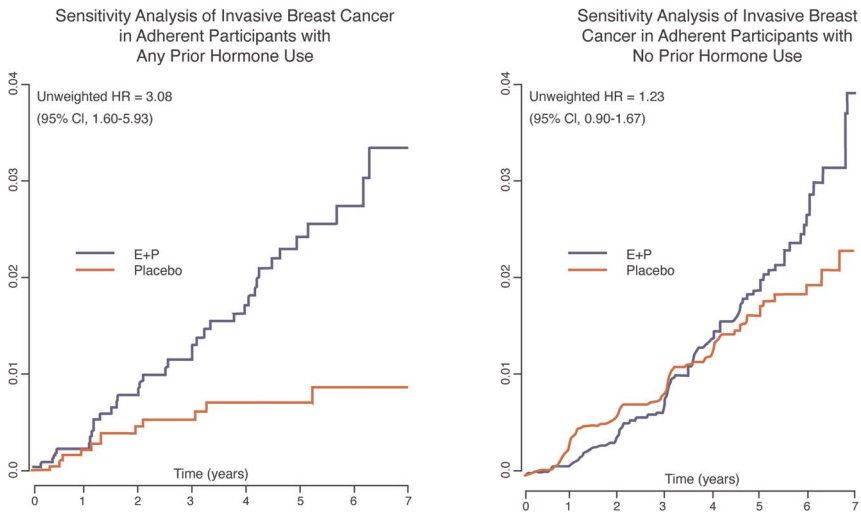

FIG. 2. Sensitivity analysis of the risk of invasive breast cancer among adherent patients with and without prior hormone use.

statistics, the decline in breast cancer incidence was evident as early as 1999 in the United States, 3 years before release of the WHI's initial results.[37] The decline was reported among White but not Black women, and there was no decline in breast cancer rates in many western countries that also experienced dramatic declines in HT prescriptions, such as Austria, Belgium, Denmark, England, Finland, Germany, Ireland, Israel, the Netherlands, Norway, Scotland, Sweden, and Switzerland.[38,39]

Nonetheless, the WHI, with Chlebowski as a prominent spokesperson, has continuously claimed credit for saving millions of lives by alerting women to the purported dangers of HT and thereby causing hormone prescriptions to plummet.[40,41] Actually, breast cancer incidence rates in the United States have increased by roughly 0.5% annually since the premature termination of the WHI's CEE+MPA trial in 2002,[42] even though HT use has remained low. In a 2023 Food and Drug Administration report, although 82% of US women older than 45 years reported at least one menopausal symptom, only 10.5% had used any form of menopausal HT.[43]

Chlebowski and Aragaki[3] now maintain that estrogen is not the culprit behind breast cancer, adding MPA is what raises the risk. We are aware that estrogen alone, or together with MPA, has been reported to stimulate breast epithelial cell proliferation[44] and, by increasing breast density overall, can lead to frequent mammography, resulting in early detection of existing breast cancers. That evidence, however, is not proof that MPA is responsible for increasing the risk of breast cancer, especially because other studies have reported that MPA is as effective as tamoxifen in treating breast cancer.[45,46] Furthermore, as already noted, given the doubling time for breast cancer creating up to a 16-year lag from initiation to clinical detection,[27,28] the assertion of a causal relationship between CEE+MPA and breast cancer emerging 3 years into the WHI is not biologically plausible.

Considering the reports by senior WHI investigators confirming the benefits of estrogen and rescinding the dangers they originally announced,[6] we were dismayed by this inaccurate statement in a *New York Times* Letter to the Editor by Garnet Anderson, a biostatistician, on behalf of the WHI Steering Committee. The worldwide decrease in the use of menopausal HT, she wrote, "undoubtedly has saved millions of lives and billions of US healthcare dollars."[47] This enthusiastic assertion is even less valid today than it was in 2014, when this same writer joined other WHI investigators in celebrating a postulated $35.2 billion net economic return from the WHI trials.[48] Unfortunately, data have shown that the fear generated by the WHI has actually increased mortality, especially among hysterectomized women denied estrogen treatment and older women dying of heart disease and hip fracture,[49] and has also increased healthcare spending.[50,51]

CONCLUSIONS: SETTING THE RECORD STRAIGHT

After decades of sounding the alarm about menopausal HT, the WHI now acknowledges that it is the most effective treatment for managing menopausal vasomotor symptoms. CEE alone reduces the risk of breast cancer by 23% and reduces the risk of breast cancer death by 40%. The sole remaining issue is whether CEE+MPA increases the risk of breast cancer and, if so, whether it is to a degree that makes its risk overwhelm its many benefits. Today, primarily as a result of the WHI reports, MPA has been largely replaced by other progestogens and bazedoxifene.[52,53]

In sum, findings generated by the WHI to date warrant the following conclusions:

1. CEE alone significantly reduces breast cancer risk and breast cancer mortality.
2. CEE+MPA, when initiated in HT naïve women, does not increase breast cancer risk and does not increase breast cancer mortality, even for women with a family history of breast cancer.
3. Even if the WHI estimate of an increased risk of breast cancer is accepted based on the elevated HR, a result driven solely by a low incidence of breast cancer in the placebo group, CEE+MPA would be responsible for less than 1 additional nonfatal breast cancer diagnosis for every 1,000 women treated.
4. No estimate of an association between CEE+MPA and breast cancer remains statistically significant with per-protocol adjustment.[4,6,36]

If the WHI had transparently reported their breast cancer findings in 2002, emphasizing, among other things, lack of statistical significance in breast cancer risk in the per-protocol adjusted statistic; had quickly followed up by publishing a per-protocol analysis adjusting for baseline breast cancer risk factors; and reminded the public that their findings did not apply to women initiating HT in perimenopause or early postmenopause, there would have been minimal controversy, no confusion, and women's health would not have suffered so dramatically over the ensuing decades.

In *Monty Python and the Holy Grail*, the Black Knight loses an arm to King Arthur's sword, and his other three extremities are then amputated in the same swordfight. Nevertheless, the Black Knight never admits defeat: "Tis but a scratch," he says. Critical analyses of the WHI's claim about breast cancer can no longer be seen as scratches. It is increasingly difficult to defend the WHI's initial conclusion that CEE-MPA increases the risk of breast cancer. Efforts like the article of Chlebowski and Aragaki[3] intended to minimize and deflect substantive criticism do nothing but apply an ineffective band-aid to a bleeding wound. Worse, they prolong both the worry, so deeply felt by women and physicians, and the resulting underutilization of HT produced by the WHI's press conference July 8, 2002, at the expense of women's health. As a new generation of women ponders the benefits and risks of HT, with breast cancer fear as driving factor in women's health choices, it is time to be honest about these findings from the WHI.

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