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COMMENT

The WHI's Continued Misrepresentation of its Breast Cancer Claims: a Critique and Evidence

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The recently published paper by Chlebowski and Aragaki is one of many from the Women's Health Initiative (WHI) that continues to claim that conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) increase the risk of breast cancer [1]. In their first outcomes paper in 2002 [2], the WHI investigators reported a 26% increased risk of breast cancer among women randomized to CEE + MPA, a finding that contributed to worldwide alarm and caused menopausal hormone therapy (MHT) prescriptions to plummet [3]. Many physicians were misled, failing to notice that the reported increase in breast cancer "*almost reached* nominal statistical significance." Although "almost" means it did not, the investigators nonetheless concluded that "The WHI is the first randomized controlled trial to *confirm* that combined estrogen + progestin does increase the risk of incident breast cancer."[our emphasis.] [2]. Less than 2 years later their finding of no increased breast cancer with CEE alone, but rather a likely reduction in risk, was barely publicized. That key insight remains largely unknown among women and clinicians [4].

In the 2003 paper focused only on breast cancer in the CEE + MPA trial, the WHI claimed that they had now found a statistically significant increase in breast cancer risk for the use of CEE + MPA (Hazard Ratio (HR) 1.24, Confidence Interval (CI) 1.01—1.54). However, when the most basic and protocol-mandated adjustment was made, the 95% Confidence Interval was no longer statistically significant (CI, 0.97—1.59) [5].

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Over the ensuing 23 years, the WHI has steadily walked back almost all initial concerns about MHT. Today, WHI investigators acknowledge that MHT is the most effective treatment for managing menopausal vasomotor and genitourinary symptoms [6], and if begun less than 10 years from the onset of menopause, it is associated with a 32 to 48% reduction of coronary heart disease [7] and a 30% decrease in deaths from all causes [8]. As shown by the WHI, MHT is also the best preventive therapy for bone fracture in a general population of women not preselected for increased risk of osteoporosis [9]. In 2020, the WHI reported that CEE alone was associated with a 24% lower breast cancer incidence during the intervention period, and a 40% lower breast cancer mortality [10].

However, the WHI has yet to acknowledge one central error: They did not, in fact, demonstrate that CEE + MPA increases the risk of breast cancer. Consider the evidence:

1. Per the WHI protocol for the Hormone Therapy trials [11], breast cancer, unlike heart disease, was a secondary outcome that required statistical adjustment for breast cancer risk factors. When, in 2006, the data were adjusted accordingly, the reported "increased" risk observed among women randomized to CEE + MPA fell from HR 1.24 (CI, 1.02–1.50) to HR 1.20 (CI, 0.94–1.53) and was no longer statistically significant. Nevertheless, the authors of that article wrote that this adjustment "did not substantially alter this estimate" [12].
2. The WHI's own data clearly show that women naïve to MHT at the time of initiating CEE + MPA, constituting the overwhelming majority of women receiving hormones in the trial (and in clinical practice), did *not* have a statistically significant increased risk of breast cancer relative to placebo. The apparent increase in the incidence of breast cancer among all women randomized to CEE + MPA was, in fact, not due to taking hormones, but to an unexpectedly *low* rate of breast cancer in the placebo group. This lower rate was likely

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driven by women who had been taking MHT before entering the study, and who were randomized to the placebo arm. When the analysis was restricted to women with *no prior* hormone use, the risk of breast cancer in the CEE + MPA group did not differ from the placebo group. This information was presented in their 2006 paper [12], but was misinterpreted by the authors. This misinterpretation was explained in subsequent publications not authored by the WHI investigators [13–15]. The WHI investigators themselves have yet to explain why they misrepresented the conclusions generated by their own data [16].

3. Even if the increased risk of breast cancer were statistically valid, which it was not, it would amount to approximately 1 additional case of nonfatal breast cancer per 1,000 women per year in the CEE + MPA group, and the WHI has never reported an increased risk of breast cancer mortality. Although the WHI has never presented convincing evidence supporting its claim that MPA added to CEE increases the risk of breast cancer development, as a result of concern about increased epithelial proliferation in the postmenopausal breast that has been reported for MPA [17], it has been largely replaced by more physiologic progestogen options, which provide equivalent endometrial protection.
4. In the current as well as previous manuscripts, Chlebowski and Aragaki continue to claim that by discouraging the use of MHT starting in 2002, they reduced the breast cancer rate in the U.S. as soon as 2003 [18–20]. There are several major issues with this assertion. First, the decline in breast cancer incidence in the U.S. was evident as early as 1999, three years before the release of the WHI's initial results [21]. The decline was reported among white but not black women, and there was no decline in breast cancer rates in many countries that also experienced dramatic declines in MHT prescriptions [22]. A sudden drop in breast cancer within a year after the first published WHI report, allegedly caused by the big drop in MHT use, is biologically improbable given how many years it takes for breast cancer to become clinically detectable. It also ignores the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) 1975–2003 warning: "While most of the rates in this publication have been age-adjusted to the 2000 US standard population, some previous SEER publications have used the 1970 US standard million population. *Therefore, rates given in this publication cannot be compared to rates given in those publications"* ("https://seer.cancer.gov/archive/csr/19752003/results_figure/sect01intro21pgs.pdf). This observation is confirmed by the fact that publish U.S. Cancer Statistics show a steady rise in the annual number and rate of new breast cancers from 2003 to 2021 (except for a Covid-19 disruption in 2020) (https://gis.cdc.gov/Cancer/USCS/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcancer%2Fdataviz%2Findex.htm#/Trends/).

The WHI has no problem claiming credit for their inaccurate reporting of a fall in breast cancer incidence noted within 6 months of the release of their 2002 paper, while at the same time claiming that the reported rise in breast cancer incidence, which they erroneously attribute to the 5.6 years of CEE + MPA administration, persists for over 20 years [10].

In virtually all of their publications acknowledging MHT's many benefits, the WHI investigators continue to insert warnings about breast cancer based on inappropriate analyses that lack protocol-mandated adjustment, and they did so again in their recent paper for this journal [1]. Other faulty interpretations of its own data by the WHI have promoted additional misdirected concerns. In a 2009 paper, WHI investigators claimed that MHT increased lung cancer deaths (without increasing the risk of developing lung cancer) [23], a claim they never repeated and that was convincingly rebutted in the literature [24, 25]. In this latest publication, they assert that CEE, but not CEE + MPA, causes ovarian cancer, deriving this result using retrospective substratification on their already collected data [1]. In 2003, they had claimed that CEE + MPA, but this time not CEE alone, caused ovarian cancer [26]. When confronted on this point by Wulf Utian in 2004 [27], the WHI investigators recanted their claim of causation, acknowledging that their data did not reach the statistical significance required to support their conclusion [28].

The WHI's intransigence on the breast cancer risk of MHT is puzzling because its investigators themselves have concluded that for most symptomatic women, the benefits of MHT outweigh the risks: It prolongs lives and saves lives [29]. These findings would be immensely reassuring to the countless young postmenopausal women who are typical candidates for MHT—if only more of them were given this information and physicians were appropriately educated about the data regarding breast cancer risk.

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Declarations

Conflict of Interest The authors declare no competing interests.

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