Commentary

The Women's Health Initiative after 17 years: Has it done more harm than good?*

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This commentary is focused primarily on the relationship between menopausal hormone therapy (MHT) and breast cancer risk, the primary adverse outcome measure of the Women's Health Initiative (WHI) hormone trials.

The WHI hormone trials are to date the largest randomized, placebo-controlled studies that evaluated the risks and benefits of hormone therapy in postmenopausal women. There are two arms: the estrogen-progestin (conjugated equine estrogen/medroxyprogesterone acetate) arm for women with intact uterus and the estrogen-alone (conjugated equine estrogen) arm for women who had a hysterectomy[1]. Both arms, planned to continue for 8.5 years, were stopped prematurely, the CEE/MPA arm after a mean of 5.2 years of follow-up and the CEE-alone arm after a mean of 7.2 years follow-up[3].

The Women's Health Initiative press conference and press release

The initial results of the WHI CEE/MPA trial were announced dramatically in a press conference and press release[4] a week before they were published in the Journal of American Medical Association[2] in July 17, 2002. The study, according to the press release, was stopped primarily due to 'a 26% increase in breast cancer risk and lack of overall benefit'. The findings also show 'a 22% increase in total cardiovascular disease, with a 29% increase in heart attacks, a 41% increase in strokes, and a doubling of the rate of blood clots in the lungs.' It was declared that 'the results have broad applicability; the study found no differences in risk by prior health status, age, or ethnicity.' It concluded that 'the risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases.'

The media reacted with shock and terror and controversy[5]. The subsequent media attention and negative sensationalism led to worldwide fear and confusion among both health care providers and women.

The United States Federal Drug Administration revised its labeling for hormone therapies making them more stringent to reflect FDA's analysis of the WHI data.[6] The FDA limited the use of hormone therapies to treatment of moderate to severe vasomotor symptoms and to treatment of moderate to severe symptoms of vulvar and vaginal atrophy. It downgraded hormone therapy from first line to second-line therapy for prevention of postmenopausal osteoporosis. The FDA further advised that health care providers should 'use the lowest dose for the shortest duration for the individual woman.'

Postmenopausal hormone use declined immediately[7] and the precipitous decline to painfully low levels has been sustained up to the present time,[8] due in large part to the continuing barrage of adverse articles from the WHI. In the United States, only about 5% to 6% of eligible women are current users. A 2008 survey of Filipino women in Metro Manila showed a rate of MHT use of only 1%.[10]

17 Years after the WHI

During the next decade and a half, the initial and subsequent data from the WHI were subjected to extensive analysis and re-analyses.[11-13] During the same time, the results of meta-analyses[14,15] and other major clinical studies (Danish Osteoporosis Prevention Study[16], Early versus Late Postmenopausal Treatment with Estradiol study[17], and California Teachers Study[18]) were published. The WHI re-analyses and the results of meta-analyses and clinical studies generally contradict the conclusions of the WHI, fueling more confusion on the parts of healthcare providers and menopausal women.

Seventeen years after the initial publication from the WHI, where are we now? Has the WHI protected women from the risks of menopausal hormone therapy or has it done more harm than good?

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The WHI: is the increased risk of breast cancer real?

Even before the WHI, the increased risk of breast cancer is the main reason why women are reluctant to use MHT. In 2001, Bush, et al[19] analyzed 65 studies published over a 25-year period that examined the relation between breast cancer and hormone therapy (Figure 1). Of 45 studies on combined estrogen plus progestins regimens, 82% found no increased risk; 13% found a small increased risk (none greater than 2.0); and 5% found a significantly decreased risk. Of 20 studies on estrogen-only regimens, 80% found no increased risk, 10% found a significantly increased risk, and 10% found a significantly decreased risk. The authors concluded that the relatively large body of literature on the association between estrogen and breast cancer is inconsistent, and the distribution of risk estimates is what would be expected if there were no association. That is, most of the estimates of risk converge around 1.0, and the range of the estimates is limited. Therefore, the body of literature does not support an association between MHT use and breast cancer. Though a small increase in breast cancer risk with hormone therapy or an increased risk with long duration of use (15 years or more) cannot be ruled out, the likelihood of this must be small, given the large number of studies conducted to date.

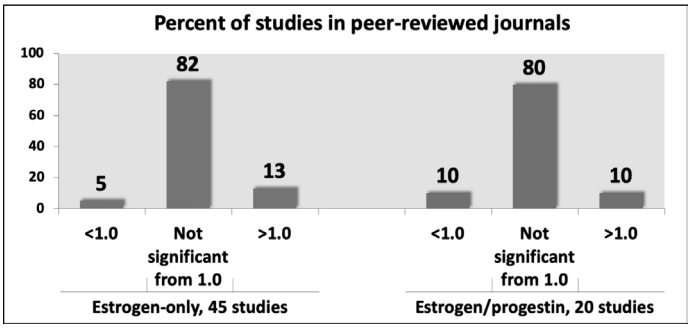

Figure 1. Review of epidemiological studies from 1975 to 2000 on the relation between hormone therapy and breast cancer risk.
Bush TL, et al. *Obstet Gynecol*. 2001 Sep; 98(3):498-508.

The breast cancer risks in the combined CEE/MPA arm[2] and in the CEE-alone arm[3] of the WHI are presented in Figure 2. The hazard ratios and two forms of confidence intervals, nominal and adjusted, are presented. A 95% confidence interval provides a range (an interval) with a specified probability that a given result, with continued replications, will be due to chance only 5% of the time. In the case of large-scale epidemiological studies, if the spread of the confidence interval includes the number 1.0, the result is usually considered not statistically significant. Generally speaking, the lower limit of the 95% CI should be at least 3.0 before the finding is considered a strong, reliable one.[20]

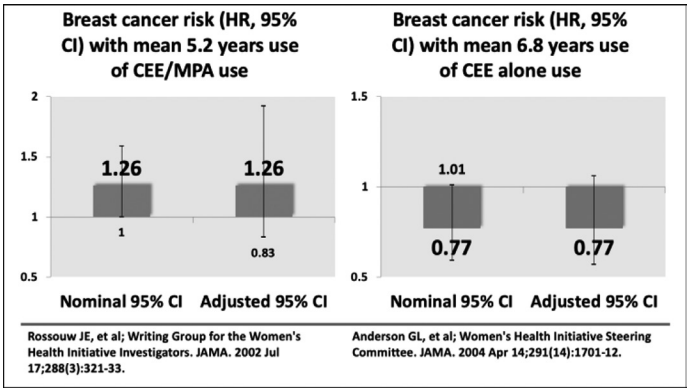

Figure 2. Breast cancer risk with hormone therapy in healthy postmenopausal women.
Rossouw JE, et al; Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002 Jul 17; 288(3):321-33. Anderson GL, et al; Women's Health Initiative Steering Committee.
JAMA. 2004 Apr 14; 291(14):1701-12.

It is clear that, in the CEE/MPA and the CEE-alone arms of the WHI, the nominal and adjusted risks for breast cancer are both not statistically significant. The most that can be concluded is that there is a statistically insignificant *trend* toward increased breast cancer risk with CEE/MPA use just as there is a statistically insignificant *trend* toward a decreased breast cancer risk with CEE-alone use.

Is the increased breast cancer in the WHI an artefact?

In 2003, the WHI reported[21] intent-to-treat analyses that revealed significantly elevated hazard ratio of 1.24 (CI, 1.01-1.54) for invasive breast cancer by treatment with CEE/MPA.

However, a subanalysis of these data by Kuhl[22] revealed that the breast cancer risk was only elevated by CEE/MPA in the 2225 women who reported hormone therapy prior to the WHI study, but not in those 6277 women who never used hormones before initiation of the WHI study (HR, 1.09). A graphic representation of the data over 6 years (Figure 3) show that the time-dependent increase in breast cancer risk under CEE/MPA in the women pretreated with hormones prior to the WHI study is on average similar to that in the women without prior hormone therapy. This represents the age-dependent increase in breast cancer incidence. However, the elevated cancer risk in the group of women pretreated with hormones and now treated with CEE/MPA is due to the unusual low number of breast cancer diagnoses in the women on placebo, which show no age-dependent rise. The elevated breast cancer risk calculated in this group is, in all probability, an 'artifact due to a pretreatment-associated selection bias'.[22]

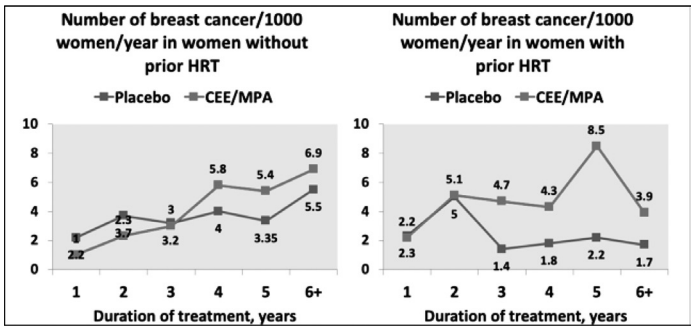

Figure 3. Sub-analysis of WHI based on 5.6 years follow-up.
Kuhl H. Climacteric. 2004 Sep; 7(3):319-22.

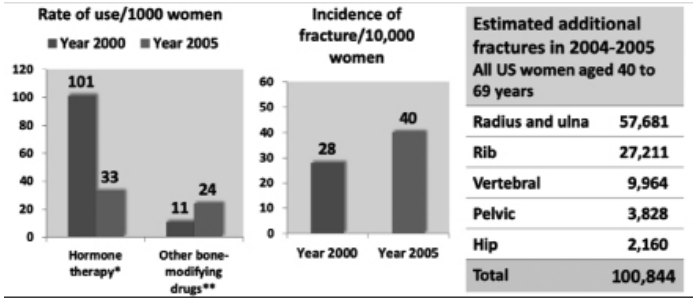

Figure 4. Incidence of fractures increased after publication of WHI results.
Islam S, et al. *Menopause*. 2009 Jan-Feb; 16(1):77-83.

The WHI: a victory or a loss for women and their health?

In 2013, the WHI investigators reported on a comprehensive, integrated overview of findings from the two hormone trials with extended postintervention follow-up.[23] The investigators claimed that the findings from the intervention and extended post-intervention follow-up of the 2 WHI hormone therapy trials 'do not support the use of MHT for chronic disease prevention, although it is appropriate for symptom management in some women.' In an accompanying editorial[24], the editor hailed the WHI as a 'model for publicly funded rigorous, thorough, and objective clinical trials that have broadly affected human health. It is a victory for women and their health.'

In reaction, a group of opinion leaders in menopausal medicine evaluated the claims of the integrated overview of the WHI findings[23] by applying epidemiological criteria of causation.[25] They stated that under 'worst case' and 'best case' assumptions, the changes in the incidence of the outcomes attributable to MHT were minor. With regard to breast cancer risk, the WHI study 'did not establish that CEE/MPA increases the risk of breast cancer.' Furthermore, the findings suggest that 'CEE-alone does not increase the risk, and may even reduce it'. They concluded that 'over-interpretation and misrepresentation of the WHI findings has damaged the health and well-being of menopausal women by convincing them and their health professionals that the risks of hormone therapy outweigh the benefits.'

The WHI: has it done more harm than good?

Increased fracture risks. To determine the trend in incidence of fractures among perimenopausal and postmenopausal women during the periods immediately before and after publication of the WHI, a large insurance claims database from 2000 to 2005 was analysed. The incidence of fractures (Figure 4) among perimenopausal and postmenopausal women increased significantly in the 3 years after publication of Women's Health Initiative results. This trend followed a decline in the use of hormone therapy, concurrent with an increase in the use of other bone-modifying agents. Projecting their results to all U.S. women in this age range, the authors estimated that an additional 57,681 radius and ulna, 27,211 rib, 9964 vertebral, 3828 pelvic, and 2160 hip fractures occurred in 2004–2005 compared with 2000–2001.

In a similar longitudinal study with a mean follow-up of 6.5 years[27], women in the Southern California Kaiser Permanente health management organization who discontinued MHT had significantly increased risk of hip fracture and lower bone mineral density compared with women who continued taking MHT. The protective association of MHT with hip fracture disappeared within 2 years of cessation of MHT and the risk of hip fracture incrementally increased with longer duration of cessation (P for trend <0.0001) (Figure 5).

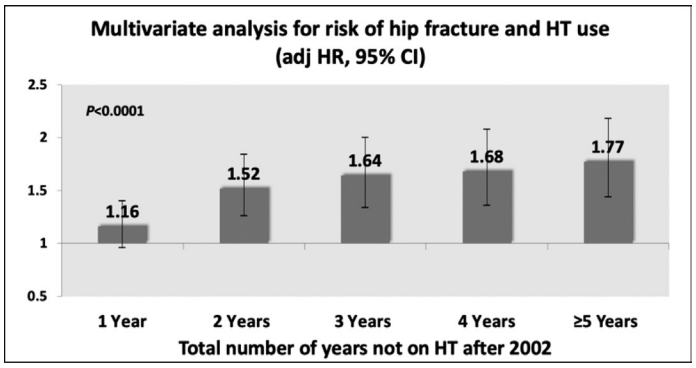

Figure 5. Hip fracture in postmenopausal women after cessation of hormone therapy.
Karim R, et al. *Menopause*. 2011 Nov; 18(11):1172-7.

Mortality toll of estrogen avoidance. Based on a recent analysis of United States census data, Sarrel, et al[28], claimed that many thousands of excess deaths resulted in US women who had undergone bilateral oophorectomy without adequate hormone replacement. Given the hysterectomy rate and decline in estrogen use in this group of women, the authors extrapolated

which deaths could have been attributed to estrogen not being used. It was estimated that estrogen-only therapy in women aged 50-59 years declined nearly 79% between 2001 and 2011. During that time, a minimum of 18,601 and a maximum of 91,610 excess deaths were attributed to estrogen avoidance. If the data are truly representative of the current situation, this may well have arisen due to concerns generated by the results of the WHI combined study. The authors concluded that 'unwarranted mistrust and fear of MHT have become deeply rooted and prevail among health practitioners, women, and the media……this is a major health education challenge.'

The WHI: cascade of effects. The most serious consequence of the fear of MHT generated and exaggerated by the misrepresentation of the WHI results is the current neglect of the study of the menopause. Recent reports lament the fact that physicians now lack the competencies and experience necessary to manage menopausal women.[29,30] Residency programs do not provide adequate education in menopause management and the new generation of medical graduates lacks training and core competencies in menopause management.[31]

By 2030, the number of postmenopausal women in the world is expected to be approximately 1.2 billion[32], who will take care of their health needs?

Menopause management: the need to get clinical care back on track

Manson and Kaunitz, in a 2016 editorial, stated that the 'reluctance to treat the [menopause] has derailed and fragmented the clinical care of midlife women, creating a large and unnecessary burden of suffering'.[31]

Sarrel, in a 2019 editorial, issued a call to increase the use of MHT to prevent disease in symptomatic postmenopausal women.[33] Otherwise, 'millions of women who could be safely treated hormonally are not and as a result have menopause symptoms affecting their quality of life, adverse effects on the cardiovascular system, bone, mood, sexual health, and cognition, and increased risk of dying before age 70.'

Utian, in a valedictory editorial that reflected on his life spent in a study and practice of menopause[34], labelled the WHI as the 'the greatest misdirection in science in the history of women's health.'

We need, therefore, to get the clinical care of the menopausal woman back on track. Clinicians must stay current regarding hormonal and nonhormonal treatments and help women make informed treatment choices. In addition, we must train and equip the next generation of health care providers with the knowledge and skills to address the current and future needs of menopausal women, the unfortunate victims of a misguided study. ■

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