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REVIEW

The evidence base for HRT: what can we believe?

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ABSTRACT

Prior to the unexpected early termination of the Women's Health Initiative (WHI) trial of continuous conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA), the prevailing view was that hormone replacement therapy (HRT) was a low-risk intervention with immediate value for symptom relief in recently menopausal women, and that it probably conferred long-term protection against the major chronic diseases that affect women after menopause. Rather than replicating prior studies, the WHI was designed to test whether the beneficial associations consistently seen in women starting HRT near menopause would be found in women well beyond menopause. Views of the benefits and risks of HRT changed dramatically in 2002 with the unexpected early termination of the CEE + MPA trial and the alarming initial WHI report. HRT use plummeted world-wide, driven by fear of breast cancer and skepticism about cardiovascular benefits. Stunningly, the contrasting findings of the WHI trial of CEE alone reported 2 years later – suggesting prevention of coronary heart disease in women who began HRT at age <60 years, and a reduction in breast cancer overall – were largely ignored. Key lessons from the WHI are that the effects of HRT on most organ systems vary by age and time since last physiologic exposure to hormones and that there are differences between regimens. In the years since the first WHI report, we have learned much about the characteristics of women who are likely to benefit from HRT. The range of HRT regimens has also increased. Not all women have indications for HRT, but for those who do and who initiate within 10 years of menopause, benefits are both short-term (vasomotor, dyspareunia), and long-term (bone health, coronary risk reduction). Critically, the 'facts' that most women and clinicians consider in making the decision to use, or not use, HRT are frequently wrong or incorrectly applied.

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Designed in the early 1990s, the Women's Health Initiative (WHI) hormone replacement therapy (HRT) trial was built upon findings in a variety of observational studies that consistently suggested HRT could prevent major age-related diseases, especially cardiovascular disease. Those prior studies largely reflected initiation of HRT in newly menopausal women and long-term use, primarily of high-dose unopposed oral estrogen (typically conjugated equine estrogens 1.25 mg daily) as used in the 1960s and 1970s. Combined HRT came into wide use in the 1980s following the rise in rates of endometrial carcinoma in the mid-1970s associated with the early unopposed regimens. Observational studies published in the 1980s that reported outcomes associated with earlier regimens suggested that HRT might reduce the risk of coronary heart disease (CHD) events – the leading cause of death in women living in developed nations – by approximately 50%[1–4]. As the WHI was being planned, observational studies of combined HRT with mid-level doses of estrogen, e.g. conjugated equine estrogens (CEE) at 0.625 mg/day plus medroxyprogesterone acetate (MPA) 10 mg for 10–12 days per cycle, also suggested CHD protection but at the somewhat reduced level of approximately 30%[5,6].

Also as the WHI was being designed, additional support for the idea that HRT could prevent CHD was becoming available from the first major clinical trial to address the question, the Postmenopausal Estrogens Progestins Interventions (PEPI) trial[7]. PEPI enrolled women aged 45–64 who were at least 1, but not more than 10, years postmenopausal. Participants with and without a uterus were randomized to one of five regimens: (1) placebo; (2) CEE 0.625 mg/day alone; (3) CEE 0.625 mg/day with MPA 10 mg/day for 12 days per 30-day cycle; (4) CEE 0.625 mg/day with MPA 2.5 mg/day continuously; or (5) CEE 0.625 mg/day with micronized progesterone 200 mg/day for 12 days per cycle. PEPI evaluated changes in biological intermediates for cardiovascular disease (lipids, insulin and glucose, clotting factors, blood pressure), as well as bone mineral density, quality of life, and endometrial safety. The emerging results from PEPI were consistent with potential cardiovascular benefits, and the WHI design incorporated two of the four active HRT regimens studied in PEPI[8].

The WHI study design was a deliberate departure from what had come before in a very important way. In contrast to the prior observational studies that generally looked at HRT started near menopause, and in contrast to PEPI which enrolled women between 1 and 10 years postmenopausal, *the WHI focused on women well beyond menopause*. The idea was that there seemed to be clear and consistent evidence

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for HRT benefits in reducing CHD in women who started within 10 years of menopause, yet CHD generally strikes women in the decades beyond that. In CHD prevention studies, the greatest benefit is often seen in the people at highest risk. There was similar strong reason to test fracture prevention, and emerging evidence in support of colorectal cancer prevention. With those points in mind, the WHI set out to test whether (contemporary in 1993) HRT prevents CHD, fractures, and bowel cancer, in women well beyond menopause who are at greater risk of those diseases than the younger women represented in the prior studies. Enrollment was restricted within age groups so that no more than 10% of women would be 50–54 years old, and no more than 20% would be between 55 and 59 years old. Fully 70% of WHI women were to be 60–79 years old[8]. Actual recruitment came quite close to these goals so that the average age of WHI HRT women was 63 years, with an average of 12 years since menopause[9].

As the WHI was beginning, some scientists questioned the merits of the substantial anticipated investment. Concerns were raised about all three overlapping clinical trials (Diet Modification (DM) – 48 000 women, Calcium/Vitamin D Supplementation – 36 000 women, and HRT – 27 500 women). In response, the US Congress asked its scientific advisory consultancy, the Institute of Medicine (IOM), to evaluate the study design[10]. The HRT arm was questioned in light of the evidence for HRT benefit already available. The IOM report noted these key points in advising that the HRT trial proceed:

- HRT with both estrogen and progestin (PERT) has been in common use for a shorter period of time than HRT with estrogen alone (ERT) in the United States, and evidence about the long-term effects of PERT is less certain.
- Based on studies of effects of PERT on lipoprotein levels, the beneficial effect of combined therapy may be less than that of ERT alone, although that would be dependent to some extent on the particular progestin used. Whether to use ERT or PERT is an important question among many postmenopausal women and the clinicians who advise them.
- The effects of initiating HRT at various ages after the menopause have not been well studied. The proposed trial would offer the opportunity to study risks and benefits associated with initiating HRT at older ages (see reference 10, p. 53).

The WHI HRT trial was well designed to assess the questions it set out to answer, i.e. the effects of regimens being used in 1993 on the incidence of major chronic diseases in older menopausal women. It was not designed to test the effects of HRT in recently menopausal women and did not have statistical power to do that. A major failing of the study has been the generalization of the results in older menopausal women to younger menopausal women.

Highly unusual circumstances prevailed when the WHI CEE + MPA trial was stopped prematurely in July 2002. The investigators most capable of correcting the critical misinterpretations of the data were actively excluded from the writing and dissemination activities. The initial results paper was written by a small group from the coordinating center and program office and submitted to the journal without informing or consulting the clinical site principal investigators. After the paper was accepted, a handful of clinical investigators holding administrative roles in the study were asked to review and comment. They were given a short timeline and relatively limited influence since the paper was already accepted. Disclosure to the other WHI investigators was strictly forbidden. On June 27th, the entire investigator group consisting of the principal investigators for the 40 clinical sites, the coordinating center team, and the NIH program staff gathered for the semi-annual meeting in Chicago. After minor preliminaries, the investigator group was stunned by the announcement that the Data Safety and Monitoring Committee (DSMB) had recommended stopping the CEE + MPA trial and that the Director had accepted their recommendation. Minutes later the group was shocked by the distribution of a typeset copy of the primary results paper soon to be published in *JAMA*. This was the first time that the vast majority of principal investigators had seen the paper. The meeting was paused so that we could read it. Some of us were aghast. Concerns were raised about the propriety of producing a paper on behalf of the entire study group in this manner. More importantly, concerns were raised about the tone, the analyses conducted and reported, and the interpretation of the results in the paper. After some discussion, it was agreed that the concerned investigators could quickly provide edits addressing the tone and interpretation. The submission deadline was said to be imminent, so those edits would be taken directly to the *JAMA* Editorial Office (located nearby in Chicago) and incorporated in the final version. Edits were produced in the brief time remaining before lunch and taken to *JAMA*. The courier returned shortly with the message that the journal issue had already been printed. It was in warehouses ready to be distributed for mailing. The suggested edits were moot.

The DSMB advised stopping the CEE + MPA trial after just over 5 years of average follow-up for a breast cancer rate crossing a time-weighted monitoring boundary, not a statistically significant finding of harm; a persistent early increase in cardiovascular events, much of it not CHD, but venous thromboembolic disease (VTE); and a composite 'Global Index' of all major outcomes that did not support benefit[9]. This early stopping, particularly for breast cancer, was wholly unanticipated. The WHI Protocol states (underlined emphasis added): *"Sample size calculations indicate that for the HRT component, 27 500 women, and for the DM component 48 000 women, treated for an average of 9 years would provide adequate power for the primary outcomes of interest ... Post-trial mortality and breast and endometrial cancer incidence surveillance for a further five years is envisaged, so that total follow-up will be for an average of 14 years. The longer follow-up will protect against the possibility of missing adverse effects, such as breast cancer in relation to HRT, which may not have had sufficient time to manifest clinically during the nine year average follow-up period."*[11].

The DSMB plan for the HRT trial anticipated the need for at least 3 years of follow-up to achieve the full effect for CHD, as the estrogen-associated protection caught up with the age-related disease rates, and for at least 10 years of follow-up to detect a difference in breast cancer rates[12,13]. The breast cancer surveillance interval was based on age-related disease rates, cancer cell doubling times related to potential initiation, and estimates from prior observational studies. Rather than attempting to interpret the findings in the CEE + MPA trial in light of this prior knowledge, the primary results paper insinuated that the trial demonstrated a causal relationship between HRT and breast cancer (not even limiting it to continuous CEE 0.625 mg + MPA 2.5 mg daily) and not making clear that the relationship was not statistically significant[9].

Building upon that unfortunate decision, the NIH press release announcing the stopping of the study began with the headline "NHLBI Stops Trial of Estrogen Plus Progestin Due to Increased Breast Cancer Risk, Lack of Overall Benefit"[14]. The draft press release was distributed to the investigator group after lunch on June 27th, following on the news that the journal was already printed and the paper could not be edited. There was heated discussion about the wording of the press release. But, in the end, the wording favored by the program office prevailed. That headline, pandering to women's greatest fear – the fear of breast cancer – ensured that word of the study would spread like wildfire. And it ensured that the conversation would be driven much more by emotion and politics than by science.

The analyses reported in the primary results paper largely abandoned the analysis plan stipulated in the Protocol which stated "... *we will estimate intervention versus control group relative risks as a function of time from randomization using relative risk (Cox) regression methods stratified as just described, with suitably defined time-dependent covariates*"[15]. In fact, the paper focused primarily on the nominal, unadjusted, results. Contrary to the usual procedure in clinical trials and the protocol statement above, no covariate adjusted analyses were reported. The only adjusted analyses reported were results accounting for multiple looks at the data over time[9]. This unorthodox manner of conducting analyses has been perpetuated in the main reports of the WHI from that time forward.

The only significant findings in the 'adjusted' results were for a reduction in total fracture and an increase in VTE. The nominal results were significant for benefits in colorectal cancer, hip fracture and total fracture, and significant for adverse outcomes in CHD, stroke and VTE. Even the nominal results were not statistically significant for breast cancer; although the hazard ratio (HR) was 1.26, the 95% confidence interval (CI) (1.0–1.59) included 1.0. The 'adjusted' 95% confidence interval for breast cancer was 0.83–1.92. Nonetheless, incredibly, the paper included the statistically unsupported statement 'The WHI is the first randomized controlled trial to confirm that combined estrogen plus progestin does increase the risk of incident breast cancer and to quantify the degree of risk'[9].

Recall that the primary study outcome was CHD. Yet the first words in the Comment section on cardiovascular disease were "Even though the trial was stopped early for harm from breast cancer ..."[9]. The unmistakable and deliberate focus of the small group of self-appointed authors was to trumpet a finding of harm from breast cancer – the science and statistics notwithstanding. This was deeply embedded in the paper and emblazoned in the press release[14].

Another factor further insured that the discussion of the CEE + MPA results would be well established on emotional and political grounds before scientific consideration could take hold. A highly publicized press conference, centered around the inflammatory press release, was held on July 9th. But the year 2002 was before the simultaneous online publication of manuscripts, and on that date the hardcopy journal was wending its way through the postal service. The vast majority of scientists and clinicians who were capable of reading the paper critically were blind-sided by the presentation of these results in the press days before they received the journal in the mail.

Looking at the trends in major outcomes in the CEE + MPA trial over time, there was an increase in CHD within the first year, with a decreasing trend over time, and an increase in breast cancer beginning at about 3 years, which, considering doubling times, was too early to reflect initiation[9]. These were important clues to the real contributions and meaning of the WHI, yet neither of these observations were addressed in the primary paper. The breast cancer trends were heavily influenced by events that were likely due to growth of existing lesions promoted by MPA (a proliferative effect). The CHD trends were attributable to age-related differences in the pathophysiology of atheromatous plaque that were largely unrecognized prior to the WHI. Indeed, this observation regarding vascular pathophysiology is one of the WHI's most important contributions to clinical science.

Another critical problem with the CEE + MPA paper was the failure to clearly acknowledge that the WHI was not designed to assess outcomes, particularly the stipulated primary outcome of CHD, in younger menopausal women who were the vast majority of 'real world' patients using HRT. It did not acknowledge that only 30% of participants were <60 years old, with just 12% aged 50–54. Instead, it inappropriately generalized the findings in a predominantly older population that was not representative of typical users to the population of typical users. The press release further cemented this inappropriate generalization with the following quote from the WHI Acting Study Director "... the adverse effects of estrogen plus progestin applied to all women, irrespective of age, ethnicity, or prior disease status"[14]. This quote includes another inappropriate generalization embedded in the initial outcomes paper, the use of the term 'estrogen plus progestin' in describing the regimen tested in the WHI, rather than the more scientifically correct terminology naming the specific drugs used, CEE + MPA. This quickly led to generalizing the WHI findings, with all the caveats and distortions noted above, to all forms of HRT. Data that existed at the beginning of the WHI in 1993, and that had grown considerably by 2002, demonstrated clearly that that class assumption was inappropriate.

To the extent that hints could be gleaned from the small number of younger menopausal women in the study, the

subsequent paper on CHD with CEE + MPA reported hazard ratios for women <10 years postmenopausal, and for women aged 50–59 with vasomotor symptoms. While not statistically significant, both were less than 1, suggesting no harm, and consistent with the possible benefit shown in the prior studies that formed the foundation of the WHI design[16].

With the initial discussion of the WHI taking place in the press, the focus on HRs was also problematic. The general public, and most members of the press, are not schooled in statistics. The values of 1.26 for breast cancer and 1.29 for CHD were generally misinterpreted to mean that a woman taking HRT had a 26% chance of developing breast cancer and a 29% chance of having a heart attack. Those were staggeringly frightful numbers. Buried deep in the paper were much more user-friendly, far less inflammatory, numbers – the event rates per 10 000 woman-years[9]. These were seven more CHD events and eight more breast cancers in 10 000 woman-years, roughly 1 in 1200, not particularly worrying, but lost in the sea of fear sparked by HRs and headlines about breast cancer. Even that comforting message became distorted. The newsletter sent by the coordinating center to all 162 000 women participating in any part of the WHI soon after the CEE + MPA results were published had a figure illustrating the event rates per 10 000. But, instead of using a scale of 10 000 to provide proper perspective, a scale of 60 was selected, highly distorting the reality and suggesting meaningful harms[17].

Another key and reassuring fact regarding the breast cancer outcomes emerged relatively soon after the initial publications. It has been largely ignored in reporting and interpreting the study. This is the observation that the apparent increase in the breast cancer rate in the CEE + MPA group was due to an unexplained lower rate in the women randomized to placebo who had previously used HRT, NOT an increased rate in women randomized to CEE + MPA. Among women with no prior use of HRT before entering the WHI, there was no difference in breast cancer rates over time between the women assigned to placebo or CEE + MPA[18]. This HRT-naïve subgroup likely represents the best population for assessing HRT effects. The breast cancer trend in women with prior use of HRT who were assigned to active CEE + MPA was similar to that in the active and placebo HRT-naïve groups. In contrast, the breast cancer rate in women assigned to placebo who had previously used HRT was much lower than the rates in all three other groups. That unexpected and unexplained low rate, different from the rate in the other placebo group, was the basis for the apparent increased hazard.

To help put the CEE + MPA trial breast cancer rates in context, the WHI DM trial, with prevention of breast cancer as the primary outcome, provides an ideal external comparison[19]. The DM trial was publicized as showing that the low-fat diet reduced breast cancer in adherent women. So, since the CEE + MPA trial was publicized as showing an increase in breast cancer, we would expect to see high incidence rates with CEE + MPA and low rates with DM. But, in fact, the annualized breast cancer rate associated with CEE + MPA in women with prior HRT (0.46%) was essentially equal to the breast cancer rate in control women in the DM trial (0.45%) who were randomized to maintain their typical US diet. And, the rate in the women randomized to CEE + MPA who had no prior use of HRT (0.40%) was slightly LOWER than the rate (0.42%) in women who were reported to have modest protection from the low-fat diet. The outlier group was the women with prior HRT randomized to placebo in the CEE + MPA trial; the stunningly low annualized rate in that group was 0.25%[18,19].

Also, buried and downplayed in the paper stratifying on prior HRT use is an appropriately adjusted Cox model for breast cancer in the CEE + MPA trial. Specifically, the model was adjusted for age, race/ethnicity, body mass index, physical activity, smoking, alcohol use, parity, oral contraceptives use, family history of breast cancer, family history of fractures, mammography and presence of moderate to severe vasomotor symptoms. The resulting non-significant HR was 1.20 with a 95% CI of 0.94–1.53. In the text, this key finding follows the marginally significant unadjusted result (HR 1.24; 95% CI 1.02–1.50), but is said to "not substantially alter this [unadjusted] risk estimate"[18].

The CEE-alone trial testing CEE 0.625 mg daily versus placebo in women with prior hysterectomy was also stopped early. The decision was driven by an increase in stroke. However, the number of strokes in women 50–59 years old at enrollment was identical in the active and placebo groups, so that association was found only in women ≥60 years old[20].

There were striking contrasts between the results with CEE-alone and the results with CEE + MPA. There was a trend toward reduced breast cancer that was on the cusp of statistical significance with a HR of 0.77 and 95% CI of 0.59–1.01. There was also a trend toward reduced CHD (HR 0.91; 95% CI 0.75–1.12)[20]. Subsequent papers showed that CEE-alone was associated with statistically significant reduced rates in three key outcomes: breast cancer in adherent women[21]; CHD in women aged 50–59 when revascularization was included[22]; and a lower degree of coronary artery calcium in women aged 50–59[23].

The WHI Protocol states: "*In the HRT* [trial], *analyses comparing active hormone therapy to placebo, stratified by hysterectomy status, will be conducted to examine the effects of prescribing the hormone preparation most appropriate with regard to a woman's uterine status. This approach also serves to increase power …*"[24]. In other words, a combined analysis of the CEE + MPA and CEE-alone arms was stipulated in protocol. This key analytic approach – with the statistical power to address a multitude of still unanswered questions – has rarely been invoked. When it was, for cardiovascular disease, the report dismissed adjustments for age, years since menopause, race/ethnicity, education, physical activity, prior hormone use, body mass index, left ventricular hypertrophy, current smoking, hypertension, diabetes, and high serum cholesterol. The failure to adjust for these well-known risk factors was justified with the claim that "there were no striking differences in HRs … in unadjusted models and models adjusted for" these factors[25]. A look at any published non-WHI survival analysis focused on cardiovascular outcomes shows the absurdity of that statement. Outcomes in the extended post-trial follow-up period have been published. The findings are minimally changed from the original results.

The Cox models reported continue to cite nominal (unadjusted) results and do not account for major covariates despite the protocol intent to do so cited earlier[26].

Other clinical trials reported in recent years provide additional insight regarding HRT. The Danish Osteoporosis Prevention Trial (DOPS) randomized 1006 recently menopausal women aged 45–58 years 1 : 1 to active treatment or placebo. Active treatments were triphasic estradiol with norethisterone acetate (intact uterus) or 2 mg of estradiol (prior hysterectomy). Begun near the time of the WHI and planned as a 20-year trial, it too was terminated in 2002 as a direct consequence of the early termination of the WHI CEE + MPA trial. With 10 years of average follow-up, DOPS found statistically significant reductions for two key composite outcomes: breast cancer and mortality (HR 0.54; 95% CI 0.32–0.91) and myocardial infarction, heart failure or mortality (HR 0.48; 95% CI 0.26–0.87)[27].

The Early versus Late Intervention with Estrogen (ELITE) trial[28] enrolled women in two distinct age ranges to test the 'timing hypothesis' that emerged from the WHI and the earlier Heart and Estrogen Replacement Study (HERS)[29]. Briefly, the timing hypothesis holds that HRT initiated early in menopause reduces the risk of atherosclerotic vascular disease while HRT initiated a decade or so after menopause does not. ELITE randomized 643 women <6 years or >10 years postmenopausal to oral estradiol 1 mg daily or placebo. Women with an intact uterus also received 45 mg of vaginal progesterone gel for 10 days per cycle or placebo. The primary outcome was change in carotid intima medial thickness (CIMT) as a surrogate for coronary atheroma. After 5 years, women <6 years postmenopausal randomized to estradiol had significantly less progression in CIMT than women in that age group randomized to placebo. Among women >10 years postmenopausal, estradiol made no difference in CIMT progression[28]. DOPS and ELITE add further support to the WHI results supporting and validating the traditional clinical use of HRT in women aged 50–59 or within 10 years of menopause.

The major impact of breast cancer and CHD notwithstanding, osteoporosis is an extremely important consideration in postmenopausal women's health. In fact, the only statistically significant benefit in the adjusted results of the CEE + MPA trial was a reduction of 24% in total fracture[9]. Results from the WHI, PEPI and other studies have demonstrated clear increases in bone mineral density (BMD) with CEE + MPA and CEE alone[7,30]. Indeed, HRT remains indicated for prevention of osteoporosis in most countries. Sadly, the dramatic exodus from HRT caused by the WHI has been shown to be associated with a marked decline in BMD. A study using medical records from a large US health maintenance organization found that the post-WHI stopping of HRT was associated with a decline in BMD and, critically, that it was further associated with a step-wise increase in hip fractures that progressed quickly from a non-significant HR of 1.16 in the first year without HRT to 1.77 (95% CI 1.44–2.18) 5 years after stopping HRT[31].

The major harms of stopping HRT are not limited to fracture. A study using the national registries in Finland with nearly 2 million woman-years of follow-up found a HR for cardiac death of 2.3 (95% CI 2.12–2.50) in the first year for women who stopped HRT compared to women who continued using it. The risk was lower but still substantial after 1 year (HR 1.26; 95% CI 1.21–1.31). In contrast to the WHI concerns regarding stroke risk with HRT, risk estimates of magnitude similar to those for cardiac death were found for stroke among women who stopped HRT (HR 2.52; 95% CI 2.28–2.77) in the first year, and HR 1.25 (95% CI 1.19–1.31) after the first year[32].

The WHI trials were soundly designed to address the questions the program was intended to answer, with planned procedures duly noted in the protocol. That good science became distorted and ultimately caused substantial and ongoing harm to women for whom appropriate and beneficial treatment was either stopped or never started. Key faults have included: failure to properly identify the study goals and population characteristics in presenting and interpreting the results; inappropriately generalizing the findings to a key sub-group – newly menopausal women – that was not adequately represented; inappropriately generalizing the findings from specific medications to an entire class; failure to put the findings in the context of existing knowledge (taking the position that the prior studies were simply wrong); favoring publicity, fear and sensationalism over science; and departing from protocol – focusing on unadjusted results, while avoiding planned analyses with proper adjustments and better statistical power.

Where does that leave us in 2016? It is time to get past the misinformation and hysteria generated by the highly irregular circumstances of the WHI and stop denying potential benefits (control of vasomotor symptoms, prevention of fractures, prevention of CHD) to women who have indications and may be helped. HRT is appropriate for symptomatic women within 10 years of menopause who have no major contraindication. Good evidence from over 50 years of observational studies and clinical trials suggests that the benefits outweigh the risks for most women when started early. The International Menopause Society has recently published updated recommendations for HRT in a new format that highlights key messages and clinical pearls[33]. It is a well documented and authoritative guide for contemporary clinical practice.

Conflict of interest The author was the Principal Investigator for the WHI Vanguard Clinical Center at the University of California, San Diego for the entire primary study period from 1993 through 2005, Chairman of the WHI Principal Investigators Committee from 1994 to 1995, a member of the WHI National Steering Committee from 1994 to 2005, and Chairman of the WHI Observational Study Scientific Advisory Committee from 1996 to 2005. The opinions expressed herein are exclusively those of the author. They should not be construed as representing the views of other Women's Health Initiative Investigators or the WHI Program Office.

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