Menopausal Hormone Therapy and Breast Cancer

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Abstract: Associations of estrogen-alone and estrogen plus progestin with breast cancer incidence and related mortality are reviewed from observational studies (The Collaborative Group on Hormonal Factors in Breast Cancer and The Million Women Study, 2019) and the Women's Health Initiative's (2020) two randomized trials evaluating conjugated equine estrogen alone, for women with prior hysterectomy or with medroxyprogesterone acetate. Findings are generally concordant for estrogen plus progestin use with both observational and randomized studies reporting higher breast cancer incidence. Findings are discordant for estrogen-alone use where, in the WHI randomized trial, a lower incidence and lower breast cancer mortality was seen. In contrast, in the observational studies, estrogen-alone use was associated with higher breast cancer incidence and higher breast cancer mortality. Although these discordant findings are difficult to fully reconcile, we conclude with a discussion of public health implications of the available evidence on menopausal hormone therapy and breast cancer.

Key Words: Breast cancer, menopausal hormone therapy, randomized trials, Women's Health Initiative

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The relationship between menopausal hormone therapy (HT) and breast cancer, including potentially discordant effects of estrogen-plus-progestin and estrogen-alone therapy, has been controversial. In this review, we summarize the observational and clinical trial research on HT and breast cancer, offering perspectives to help resolve the discrepancies. We present in detail the breast cancer findings from the 2 HT trials in the Women's Health Initiative (WHI), including results during the intervention phase and cumulative long-term follow-up. We conclude with a discussion of public health implications of the available evidence on HT and breast cancer.

BREAST CANCER AND MENOPAUSAL HT: OBSERVATIONAL STUDIES

Menopausal hormone therapy has been used for management of menopausal symptoms for over 80 years, following the US Federal Drug Administration (FDA) marketing approval for diethylstilbestrol in 1941 and FDA marketing approval for conjugated equine estrogens (CEEs) in 1942.[1] The relationships between endogenous and exogenous estrogens and breast cancer have been under evaluation for over 120 years following Dr. Beatson's report that some breast cancers regressed following oophorectomy.[2]

A comprehensive review of clinical findings over past decades that support the concept that reproductive hormones influence breast cancer is beyond the scope of this report. In Table 1, selected reports of exogenous hormone use and breast cancer illustrate the pace of discovery leading to prevalent concepts in 2002, the year of the initial WHI report.[12] While exogenous estrogens have been used as breast cancer therapy, this issue will not be addressed further as pharmacologic dosage levels were used. For breast cancer therapy, the prescribed label for estradiol was 30 mg/d[13] compared with currently recommended dosages of 0.5 to 1.0 mg/d for vasomotor symptom management.[14]

An association of conjugated estrogens use with higher breast cancer risk was initially reported in 1976 in HT users compared with women in a general population,[4] and the finding received support from subsequent reports.[5–7] The emergence of evidence relating estrogen-alone use to higher endometrial cancer risk, with progestin addition mitigating that risk, led to studies evaluating combination estrogen plus progestin for women with an intact uterus.[15] Studies associating combined estrogen-plus-progestin use with higher breast cancer incidence subsequently followed.[6,7]

The preponderance of observational studies through 2002, with some exceptions,[16] describes favorable characteristics of breast cancers associated with menopausal HT use, compared with nonusers, with smaller, well-differentiated tumors[17,18] and more hormone receptor–positive cancers.[19,20] Significant increases in invasive lobular cancers with combined HT have also been described.[21–23]

A substantial body of new evidence emerged from 2 sources. The Collaborative Group on Hormonal Factors in Breast Cancer performed a meta-analysis of 51 case-control studies with 52,705 women with breast cancer and 108,411 controls (non-cases). In their analyses, both estrogen-alone and combined estrogen plus progestogens were associated with significantly higher breast cancer risk, which increased with longer duration of use.[8] In The Million Women Study, a cohort of 1.3 million women were recruited from 66 UK breast cancer mammography screening centers and followed. Beral[9] found that both estrogen-alone and estrogen plus progestin were associated with higher breast cancer incidence, with a trend for higher breast cancer mortality among estrogen-plus-progestin users.

These 2 reports from The Million Women Study and the Collaborative Group on Hormonal Factors in Breast Cancer consolidated understanding of the relationship between menopausal HT use and breast cancer prevalent at the time of the initial WHI reports of the randomized trial evaluating CEE and medroxyprogesterone acetate (MPA) use in 2002[12] with details of the breast cancer findings in 2003.[24]

The general concepts regarding menopausal HT and breast cancer in 2002 were (1) combined estrogen-plus-progestin use increases breast cancer risk; (2) estrogen alone increases breast cancer risk but may require longer duration exposure than combined estrogen plus progestin for adverse effects; (3) HT-associated breast cancers are mainly hormone receptor–positive and have favorable prognosis, with some reports suggesting particular influence on invasive lobular cancers; and (4) HT-associated breast cancers are diagnosed at the earlier stage.

The Collaborative Group report and The Million Women Study were updated in 2019 with findings supporting their analyses of more than 20 years previously. In the Collaborative Group report, now with 108,647 postmenopausal women who developed

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TABLE 1. Estrogen and Breast Cancer: Findings From Selected Studies

Year	First Author (Reference)	Study Design	Finding
1896	Beatson[2]	Case report	Oophorectomy associated with breast cancer regressions
1968	Feinleib[3]	Cohort analysis	Oophorectomy associated with lower breast cancer risk
2005	Stefanick[1]		FDA-approved diethylstilbestrol for menopausal symptoms
2005	Stefanick[1]		FDA-approved CEEs for menopausal symptoms
1976	Hoover[4]	Incidence rate in cohort vs. rate in general population	Estrogen alone associated with higher breast cancer risk
1980	Ross[5]	Case-control analysis	Estrogen associated with higher breast cancer risk
1989	Bergkvist[6]	Cohort analysis	Estrogen alone and estrogen plus progestin both associated with higher breast cancer risk
1995	Colditz[7]	Cohort analysis	Estrogen alone and estrogen plus progestin both associated with higher breast cancer risk
1997	Collaborative Group on Hormonal Factors in Breast Cancer[8]	Collaborative reanalysis of 51 case-control studies	Hormone therapy (80% estrogen alone) associated with higher breast cancer risk
2003	Beral[9]	Cohort analysis with mammography at entry	Estrogen alone and estrogen plus progestin both associated with higher breast cancer risk. Trend for higher breast cancer mortality in estrogen-plus-progestin users
2019	Beral[10]		Estrogen-alone and estrogen plus progestin both associated with higher breast cancer mortality
2019	Collaborative Group on Hormonal Factors in Breast Cancer[11]		Estrogen-alone and estrogen plus progestin both associated with higher breast cancer risk

breast cancer, 51% had used menopausal HT. Every menopausal HT type (including estradiol and CEE), except vaginal estrogen, was associated with excess breast cancer risk, which increased with duration of use and was greater for estrogen plus progestin compared with estrogen-alone preparations. Even short-duration (1–4 years) use was associated with excess risk in current users, and some excess risk persisted for more than 10 years after use.[11] The Million Women Study was also updated in 2019 with analyses on 907,167 postmenopausal women who were free from breast cancer at recruitment. Follow-up was approximately 20 years after

TABLE 2. Changing Concepts Regarding Menopausal HT and Breast Cancer

Concepts in 2002

Combined estrogen-plus-progestin use

- Estrogen plus progestin increases breast cancer risk

Estrogen-alone use

- Estrogen alone increases breast cancer risk but may require longer-duration exposure than combined estrogen plus progestin for an effect

Hormone therapy*

- Breast cancers associated with hormone therapy are diagnosed at earlier stage, are mainly hormone receptor–positive, and have a favorable prognosis

Current concepts based on WHI randomized clinical trial evidence

Combined CEE plus MPA use

CEE plus MPA use for 5.6 y broadly increases breast cancer risk with the increase not limited to hormone receptor–positive cancers†

- CEE plus MPA interferes with breast cancer mammographic detection resulting in cancers diagnosed at more advanced stage†
- CEE plus MPA increases breast cancer mortality through 7-y follow-up, but the mortality effect subsequently attenuated and was no longer statistically significant†

Estrogen-alone (CEE) use

- CEE-alone use for 7.2 y reduces breast cancer risk with greatest effect on poor-prognosis, estrogen receptor–positive, progesterone receptor–negative breast cancers†
- CEE alone does not substantially interfere with breast cancer detection by mammography†
- CEE-alone reduces breast cancer mortality through 20-y follow-up

Findings for CEE-alone on breast cancer incidence and mortality differ from observational study findings.

*Hormone therapy concepts refer to findings that are similar for estrogen-alone and estrogen-plus-progestin use or findings where estrogen alone and estrogen plus progestin were combined in analyses.

†Findings that differ from concepts in 2002.

recruitment, and 7086 (0.8%) of women died of breast cancer. Both estrogen-alone and estrogen-plus-progestin use were associated with excess breast cancer mortality ($P < 0.0001$).[10] Concepts regarding menopausal hormone therapy and breast cancer prevalent in 2002 are summarized in Table 2.

In 2020, the 2 WHI randomized clinical trials, which involved 27,347 postmenopausal women, evaluating menopausal HT were updated with cumulative 20-year follow-up. Findings for estrogen-alone use were discordant from those from the Collaborative Group and The Million Women Study.[25] Potential reasons for the discrepancies between these 2 observational studies and randomized trials will be addressed following the discussion of the WHI trial results below.

DESIGN AND CONDUCT OF THE WHI RANDOMIZED TRIALS OF MENOPAUSAL HT

When the 2 WHI randomized, placebo-controlled clinical trials were initiated in 1993, millions of women in the United States were using HT for menopausal symptom management and chronic disease prevention. However, despite decades of observational study evidence, the balance of risks and benefits of HT use was uncertain, as no randomized clinical trial evidence was available. The focus of the current presentation is on breast cancer findings in the 2 WHI randomized trials of HT that addressed this important question.

The design and conduct of the trials evaluating CEE-alone and the trial evaluating CEE plus MPA were similar and have been previously described[26] and are depicted in Figure 1. Postmenopausal women, aged 50 to 79 years, with anticipated survival greater than 3 years, with a mammogram not suggestive of cancer, and without a prior breast cancer history were eligible. Eligibility for the CEE-alone trial additionally required prior hysterectomy. The trials were approved by institutional review boards at the clinical centers and participants provided written informed consent. Annual mammography was required for ongoing study pill distribution. Breast cancer incidence was a protocol-specified primary safety outcome, as the primary monitoring outcome for harm.

Breast cancers were verified by central medical record/pathology report review. Deaths and causes of death were documented with death certificates and medical records. Information on mortality by cause were enhanced by serial National Death Index queries, which capture 95% of deaths.[27]

In the trial involving 16,608 women with a uterus, randomization was to 0.625 mg/d of CEE plus 2.5 mg/d of MPA. In the trial involving 10,749 women with prior hysterectomy, randomization was to 0.625 mg/d of CEE alone or placebo. Intervention in the CEE plus MPA trial was stopped after 5.6 years. Intervention in the CEE-alone trial was stopped after 7.2 years.

CEE PLUS MPA AND BREAST CANCER

The CEE plus MPA intervention was stopped when the protocol-specified, weighted log-rank test static for breast cancer crossed the boundary prompting a review of global index, which indicated overall harm.[12] At that time, CEE plus MPA significantly increased breast cancer incidence (hazard ratio [HR], 1.24, nominal $P = 0.003$), and the cancers were significantly larger and at more advanced stage.[24] These findings challenged the then prevalent concept that hormone therapy would lead to earlier diagnosis of breast cancers with more favorable characteristics.[18,28]

Women in the CEE plus MPA group had significantly more abnormal mammograms (35.0% vs. 23.0%), which had less sensitivity for cancer detection and had a higher rate of breast biopsies (10.6% vs. 6.1%, all $P < 0.001$[24,29]) with potential emotional and economic cost.[30,31] Taken together, the findings of inferior mammogram performance and larger cancers, suggested that CEE plus MPA stimulates breast cancer growth and delays breast cancer diagnosis.[24]

MAMMOGRAPHIC DENSITY CHANGE AS A POTENTIAL MEDIATOR

As higher mammographic breast density is predictive of breast cancer risk,[32] breast density change was examined as potential physiologic mediator of the breast cancer increase and delay in diagnosis seen with CEE plus MPA use.[24] In an initial study in a subset of 413 randomized women, after 1 year, combined HT significantly increased mammographic breast density by 6%.[33] Subsequently, in an ancillary nested case-control study in the WHI CEE plus MPA trial, with 174 women diagnosed with breast cancer and 733 cancer-free women as controls, 1-year change in mammographic breast density was predictive of future breast cancer; women in the highest quintile of density were at 3.6-fold higher breast cancer risk (95% confidence interval [CI], 1.52–8.56). When an analysis adjusted for the mammographic density change, all of the increased

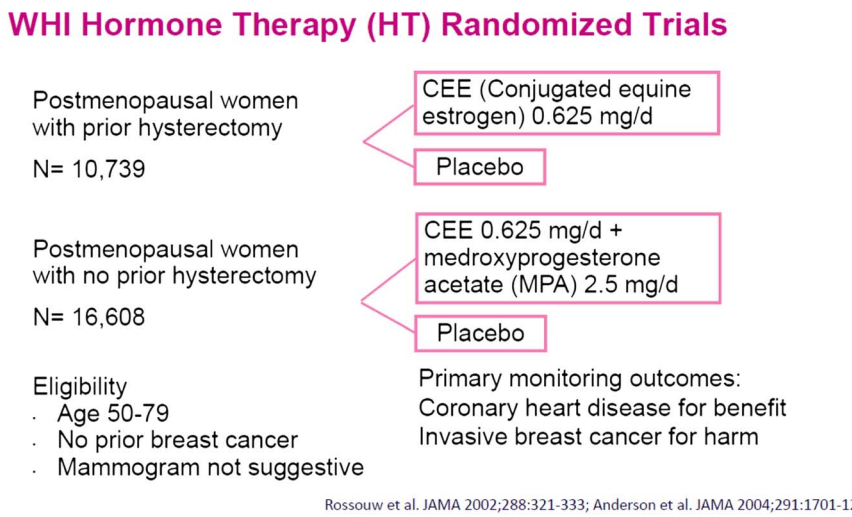

FIGURE 1. Women's Health Initiative HT randomized trials.

breast cancer risk was accounted for.[34] These findings had potential to influence clinical management of combined HT use.

CEE PLUS MPA: POSTINTERVENTION FOLLOW-UP

Breast cancer mortality findings from the WHI trial evaluating CEE plus MPA were initially reported after mean follow-up of 11.0 (SD, 2.7) years and 5.6 years' mean intervention. At that time, the increase in breast cancer incidence in the combined hormone therapy group persisted (HR, 1.25; 95% CI, 1.07–1.46; $P = 0.004$), and there were more deaths from breast cancer (HR, 1.96; 95% CI, 1.00–4.04; $P = 0.049$) and more deaths after breast cancer (HR, 1.57; 95% CI, 1.01–2.48; $P = 0.045$).[35]

In the most recent report, after more than 20 years' cumulative follow-up, a significant increase in breast cancer incidence continued for women in the CEE plus MPA group (HR, 1.28; 95% CI, 1.13–1.45; $P < 0.001$). Although there were more deaths from breast cancer in women from the hormone therapy group, the finding was no longer statistically significant (HR, 1.35; 95% CI, 0.94–1.95; $P = 0.11$).[25] The most likely basis for the persistent increase in breast cancer risk is that a progestin-induced increase in the breast epithelium stem cell pool, a signal for breasts to enlarge during pregnancy, may leave estrogen-plus-progestin users with a long-term elevation in breast cancer risk.[36]

Findings regarding breast cancer incidence with CEE plus MPA use were similar in Black women (HR, 1.35; 95% CI, 0.79–2.30). Although some have suggested that estrogen plus progestin can be used by obese women with "minimal breast cancer risk,"[37] HRs for incidence were higher than 1 and were comparable in women with body mass index <25 kg/m^2 and in women with higher body mass index.[38] Some have questioned whether estrogen plus progestin did increase breast cancer incidence,[39] because no significant increase was seen in women with no prior hormone use through 11-year follow-up, and the breast cancer incidence was low in prior hormone users randomized to placebo. With long-term follow-up, CEE plus MPA increased breast cancer incidence in both prior hormone users (HR, 1.52; 95% CI, 1.16–1.98) and never prior users (HR, 1.21; 95% CI, 1.05–1.40) with no significant interaction ($P = 0.14$).[25] The low incidence rate in prior users was likely related to estrogen-withdrawal apoptosis.[40]

In summary, postmenopausal women with an intact uterus considering therapy for menopausal vasomotor symptoms should be aware of the full range of risks and benefits of estrogen-plus-progestin use. These include a short-term increase in abnormal mammogram findings and breast biopsies and a persistent, long-term increase in breast cancer incidence.

CEE ALONE AND BREAST CANCER

In the WHI estrogen-alone trial, 10,739 postmenopausal women with prior hysterectomy were randomized to CEE-alone or placebo and followed for clinical outcomes. The CEE-alone intervention was stopped early by the National Institutes of Health because stroke incidence was increased without a corresponding reduction in coronary heart disease.[41] At that time, there were fewer breast cancers in the CEE-alone versus placebo groups (annualized rates, 0.28% and 0.43%, respectively) but the difference was not statistically significant (HR, 0.80; 95% CI, 0.62–1.04; $P = 0.09$). Although not a primary outcome, the subgroup of invasive ductal carcinomas was significantly reduced in the CEE-alone group (HR, 0.71; 95% CI, 0.52–0.99). Use of CEE alone was also associated with a reduced breast cancer incidence in women at lower breast cancer risk, namely, those with no prior breast biopsy (HR, 0.57; 95% CI, 0.41–0.78) or a first-degree relative with breast cancer (HR, 0.68; 95% CI, 0.52–0.90).[42]

Women in the CEE-alone versus placebo group had significantly more abnormal mammograms with abnormalities requiring follow-up throughout the intervention (36.2% and 28.1%, respectively; $P < 0.001$); however, mammograms suggestive or highly suggestive of cancer were not increased.[42] Unlike findings with CEE plus MPA, where there was strong evidence of diagnostic delay,[24] CEE-alone use did not substantially compromise mammogram performance.[43] In a subset of randomized trial participants, CEE-alone use resulted in a 2.6% higher mammographic breast density compared with placebo use after 1 year,[44] whereas CEE plus MPA use resulted in a 6.9% higher density compared with placebo.[33]

CEE ALONE: POSTINTERVENTION FOLLOW-UP

Breast cancer findings from the WHI trial evaluating CEE alone were updated after a median follow-up of 11.8 years' (interquartile range, 9.1–12.9) and 7.1 years' intervention.[45] At that time, the use of CEE-alone was associated with lower breast cancer incidence (151 cases, 0.27% per year) compared with placebo (199 cases, 0.355 per year), which was statistically significant (HR, 0.77; 95% CI, 0.62–0.95; $P = 0.02$). As seen during the intervention period, the CEE-alone effect was greatest in women without a prior breast biopsy ($P = 0.01$) or breast cancer family history ($P = 0.02$). Fewer women died of breast cancer in the CEE-alone group (6 vs. 16 deaths; HR, 0.37; 95% CI, 0.13–0.91; $P = 0.03$), and there were fewer deaths after breast cancer as well (HR, 0.62; 95% CI, 0.39–0.97; $P = 0.04$). To our review, this is the first pharmacologic intervention to report such a finding on breast cancer mortality,[45] as documented in the latest American Society of Clinical Oncology review of breast cancer prevention. There, commenting on tamoxifen, raloxifene, and aromatase inhibitors in prevention trials, guideline authors report "there is no evidence for a survival advantage given for primary prevention"; namely, there was no reduction in deaths from breast cancer seen in the prevention trials.[46]

CEE ALONE AND BREAST CANCER IN BLACK WOMEN

Clinical outcomes in Black women receiving any menopausal HT have been rarely reported. In the WHI CEE-alone trial, 1616 Black women were randomized (15% of 10,739) with findings reported after 13 years' cumulative follow-up. Black women in the CEE-alone group had fewer breast cancers compared with women in the placebo group (HR, 0.47; 95% CI, 0.26–0.82).[47] An interesting interaction of CEE alone by race was seen as CEE alone increased mean blood pressure in White women but not in Black women (interaction $P < 0.001$).[48]

CEE ALONE: LONG-TERM FOLLOW-UP

In the most recent report, after more than 20 years' cumulative follow-up, a significant decrease in breast cancer incidence continued for postmenopausal women with prior hysterectomy in the CEE-alone group (HR, 0.78; 95% CI, 0.65–0.93; $P = 0.005$), which was associated with significantly reduced breast cancer mortality (HR, 0.60; 95% CI, 0.37–0.97; $P = 0.04$).[25]

One hypothesis for the reduction in breast cancer seen with CEE alone was that a period of estrogen deprivation changes the sensitivity of the tumor to estrogen-induced apoptosis.[49] In early analyses of the CEE-alone trial,[43] breast cancer reduction was greater in women with gap time (time from menopause to first hormone therapy use) of 5 or more years. However, with longer follow-up, no significant interaction ($P = 0.30$) was seen in women by gap time,[25] suggesting other mechanisms, besides estrogen deprivation, are involved. A likely mediator of the breast cancer

mortality reduction with CEE alone was the significant reduction in poor-prognosis, estrogen-receptor–positive, progesterone receptor–negative cancers[50] (HR, 0.44; 95% CI, 0.27–0.74).[25]

In the WHI Dietary Modification trial, where 48,835 postmenopausal women were randomized to a low-fat dietary pattern or a usual-diet comparison group, outcomes after 8.8.5 years of dietary intervention and 19.6 years' cumulative follow-up paralleled those in the CEE-alone trial; namely, a statistically significant reduction in poor-prognosis, estrogen receptor–positive, progesterone receptor–negative breast cancers was seen (HR, 0.77; 95% CI, 0.64–0.94), which was associated with a statistically significant reduction in breast cancer mortality (HR, 0.79; 95% CI, 0.64–0.97; $P = 0.02$).[51] Thus, in these 2 WHI randomized trials, the study interventions, CEE-alone and a low-fat dietary pattern, reduced the incidence of a subgroup of poor prognosis breast cancers, with associated significant decrease in breast cancer mortality.

In the CEE-alone trial, in postmenopausal women 50 to 59 years of age, CEE-alone use was associated with a decrease in all-cause mortality.[52,53] Taken together with the breast cancer findings, randomized trial evidence provides reassurance for postmenopausal women with prior hysterectomy who are close to menopause considering estrogen alone for menopausal symptom management.

OBSERVATIONAL STUDIES, RANDOMIZED CLINICAL TRIALS, AND BREAST CANCER

Findings from observational studies in the Collaborative Group on Hormonal Factors in Breast Cancer[11] and The Million Women's Study cohort[10] are largely congruent with findings from the WHI randomized trial evaluating CEE plus MPA.[25] In both the Collaborative Group and the WHI trial, estrogen-plus-progestin use was associated with significantly increased long-term breast cancer risk. The Million Women Study found CEE plus MPA associated with a significant increase in breast cancer mortality.[10] In the WHI randomized trial, although there were more deaths from breast cancer in the hormone group, the finding was only significant through 11 years of follow-up.[25,35]

The findings are discordant regarding estrogen-alone use and breast cancer. The Collaborative Group[11] and The Million Women Study found estrogen alone associated with increased breast cancer. In contrast, in the WHI randomized trial, CEE alone was associated with reduced breast cancer incidence and a 40% decrease in breast cancer mortality.[25] This discordance is difficult to reconcile. Although WHI participants are older, there was not a significant interaction in terms of breast cancer incidence effect by age, gap time, or time from menopause to CEE-alone initiation (<5 vs. ≥5 years) after 11.8 years'[45] and after 20 years'[25] follow-up.

The WHI investigators provided data from the WHI randomized trials evaluating menopausal HT to the Collaborative Group investigators. The WHI results were presented only in Supplementary Appendix S17 and S18[11] and were included in a meta-analysis of 5 smaller randomized trials evaluating estrogen alone, where information on breast cancer was available.[11] In a narrative review, the findings from these 5 smaller trials[54–58] were outlined along with the most recent clinical trial results. The combined results from the smaller randomized trials of estrogen alone on breast cancer incidence had a relative risk of 0.61 (95% CI, 0.34–1.09; $P = 0.15$) and when combined with the WHI CEE-alone result with 384 breast cancers (relative risk, 0.77; 95% CI, 0.64–0.93; $P = 0.01$).[59] Consideration of the smaller randomized trials evaluating estrogen alone with breast cancer provides support for the WHI randomized trial findings of lower breast cancer incidence and lower breast cancer mortality (HR, 0.60; 95% CI, 0.37–0.97; $P = 0.04$).[25]

PUBLIC HEALTH IMPLICATIONS OF THE WHI MENOPAUSAL HT TRIALS

Following the presentation of the WHI randomized clinical trial findings of CEE plus MPA adverse effects on chronic disease outcomes in 2002 and on breast cancer specifically in 2003,[24] there was a rapid and substantial decline in hormone therapy use, with a 66% decrease for combined CEE and MPA use in the United States.[60] Subsequently, a decrease in breast cancer incidence was reported in women 50 years or older from the Surveillance, Epidemiology, and End Results registry. Ravdin and colleagues[61] then proposed that the breast cancer decrease, the first in the previous 20 years, resulted from the decrease in CEE plus MPA use.

The issue remained controversial, with decline in mammography use an alternative explanation.[62,63] The issue was definitively addressed when WHI investigators reported findings from the CEE plus MPA trial. There, after women were documented to suddenly stop study pill use, breast cancer incidence sharply declined, while mammography use did not differ between randomization groups.[64] The age-adjusted lower breast cancer incidence seen in White women has been largely sustained through 2015.[65] By one estimate, compared with 2002, there have been 126,000 fewer breast cancers through 2012 than might have occurred if the WHI trial were not conducted.[66]

The potential public health impact of CEE alone for postmenopausal women 50 to 59 years of age with prior hysterectomy is yet to be determined, as the remarkable 40% reduction in breast cancer mortality with CEE alone does not seem to have been fully embraced by the breast cancer prevention community.

CONCLUSIONS

Comprehensive findings on the full range of risks and benefits associated with estrogen alone for women with prior hysterectomy and estrogen-plus-progestin use are beyond the scope of the current presentation but have been reported.[52,67] With respect to breast cancer, combined use of CEE plus MPA is associated with interference in breast cancer detection and increased risk of breast cancer, which can persist long-term after discontinuation. In contrast, CEE-alone use, in postmenopausal women with prior hysterectomy, is associated with reduced breast cancer risk and substantial reduction in breast cancer mortality, also persisting long-term. Taken together with other outcomes, randomized trial evidence provides reassurance for postmenopausal women with prior hysterectomy who are close to menopause and considering estrogen alone for menopausal symptom management.

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