## APPENDIX (SUPPLEMENTAL ONLINE MATERIALS)

### Secondary and Patient-Reported Outcomes in the Two Trials

***Other symptoms and health-related quality of life outcomes*:** Several other symptoms have been examined in the WHI HT trials and results have been previously reported. Changes in menopausal symptoms and treatment-related effects were analyzed after 1 year (estrogen-progestin[1] and estrogen alone[2]), at trial closure (treatment-compliant women in the estrogen-alone trial[2]), and after stopping HT (treatment-compliant women in the estrogen-progestin[3] and estrogen-alone trials[2]). In addition to the effects on vasomotor symptoms and other endpoints reported in the main text, CEE+MPA provided significantly greater relief than placebo at 1 year for vaginal or genital dryness (74.1 *v*. 54.6%; RR=2.40 [1.90-3.02]), joint pain or stiffness (47.1 *v*. 38.4%; RR=1.43 [1.24-1.64]), and general aches or pains (49.3 *v*. 43.7%; RR=1.25 [1.08-1.44]). However, it also raised the risk for vaginal or genital discharge (4.1 *v*. 1.0%; RR=4.47 [3.44-5.81]), vaginal or genital irritation (4.2 *v*. 2.8%; RR=1.52 [1.27-1.81]), headaches (5.8 *v*. 4.7%; RR=1.26 [1.08-1.46]), and breast tenderness (9.3 *v*. 2.4%; RR=4.26 [3.59-5.04]). Vaginal bleeding, mostly spotting, was commonly reported in the estrogen-progestin trial, occurring in 51% of women in the treatment group at month 6 and declining to 13% at year 5. Among women in the placebo group, 86.6% never reported bleeding. CEE+MPA also increased the risk for hysterectomy (3.1% *v*. 2.5%; RR=1.26 [1.03-1.48]) and dilation and curettage procedures (5.4 *v*. 2.4%; RR=2.23 [1.88-2.63]).

At 1 year, CEE alone, compared with placebo, improved vaginal dryness (34.3 *v*. 42.9%; RR=0.80 [0.68-0.93]), but increased the risk for breast tenderness (8.4 *v*. 3.4%; RR=2.48 [2.08-2.97]) CEE alone was also associated with a small but significant (p=0.04) reduction in joint pain in an analysis that combined women with and without joint pain at baseline. Assignment to CEE alone was associated with a reduced risk for knee or hip replacement by the end of the intervention period (RR=0.84 [0.70-1.00]; p=0.05),[4] suggesting a favorable influence on joint health. Such a reduction was not seen for CEE+MPA.[4]

Among a subgroup of nondisabled participants aged ≥65 who completed performance-based assessments of physical function (grip strength, chair stands, and timed walk) at baseline and at 1, 3, and 6 years, neither CEE+MPA nor CEE alone reduced the risk for decline in physical function.[5]

### Additional Analyses Addressing Risk Stratification

A detailed presentation of biomarker findings and analyses stratified by baseline risk factor status and other clinical characteristics is beyond the scope of this manuscript. However, three sets of analyses are highlighted in this section due to their potential relevance to clinical decision making about HT. Women with more favorable baseline CHD risk factor status (lower LDL-cholesterol levels, lower ratios of total cholesterol:HDL-C, and absence of metabolic syndrome criteria) tended to have more favorable CHD outcomes on HT than women at higher baseline risk of CHD.[6-9] For breast cancer, women closer to the onset of menopause or with shorter gap times (interval between menopause and start of HT use) tended to have higher breast cancer risk on estrogen-progestin than women with longer gaps times.[10] Finally, because some clinicians prescribe HT for fracture prevention, analyses stratifying women by their baseline risk of fracture (low, moderate, and high) were conducted, to assess the global index for each group. No group had a favorable global index in either trial (HRs were 1.20, 1.23, and 1.03, respectively, for CEE+MPA and 0.81, 1.09, 1.04, respectively, for CEE alone), indicating that the benefit in reducing fracture risk was offset or exceeded by other risks associated with HT, even among women at the highest risk for fracture.[11, 12]

### Additional Discussion of the Breast Cancer Findings

Breast cancer results differed between the two trials. Women on CEE+MPA had more abnormal mammograms and required more breast biopsies.[13] CEE+MPA interfered with breast cancer detection,[13] increased breast

cancer incidence, with cancers diagnosed at a more advanced stage, likely reflecting diagnostic delay.[14] As women closer to menopause may have higher risk with estrogen plus progestin use,[10, 15-17] the slightly elevated HRs seen with CEE+MPA in WHI may underestimate breast cancer in this group. In addition, deaths from breast cancer were significantly increased after 11 years of follow-up.[14, 18] Analyses adjusting for time from menopause, mammography patterns, and prior HT use before enrollment can reconcile many of the discrepancies between observational and clinical trial findings for breast cancer.[15] While the post-intervention findings for CEE+MPA on breast cancer show some persistent elevation in risk, the year-to year reductions in HRs after stopping suggests possible influence of a carry over effect due to reduced diagnostic interference on mammography once HT ended. In contrast to the findings with CEE+MPA, the significant reduction in breast cancer seen with CEE was unexpected.[19,20] Further study of the relationship between different HT regimens and breast cancer is warranted.

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