Title

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Journal

Annals of Internal Medicine, 171(6)

ISSN

1056-8751

Authors

Manson, JoAnn E
Aragaki, Aaron K
Bassuk, Shari S
et al.

Publication Date

2019-09-17

DOI

10.7326/m19-0274

Peer reviewed

HHS Public Access

Author manuscript

Ann Intern Med. Author manuscript; available in PMC 2021 May 14.

Published in final edited form as:

Ann Intern Med. 2019 September 17; 171(6): 406–414. doi:10.7326/M19-0274.

Menopausal Estrogen-Alone Therapy and Health Outcomes in Women with and without Bilateral Oophorectomy: A Randomized Trial

JoAnn E. Manson, MD, DrPH, **Aaron K. Aragaki, MS**, **Shari S. Bassuk, ScD**, **Rowan T. Chlebowski, MD, PhD**, **Garnet L. Anderson, PhD**, **Jacques E. Rossouw, MD**, **Barbara V. Howard, PhD**, **Cynthia A. Thomson, PhD**, **Marcia L. Stefanick, PhD**, **Andrew M. Kaunitz, MD**, **Carolyn J. Crandall, MD, MS**, **Charles B. Eaton, MD**, **Victor W. Henderson, MD**, **Simin Liu, MD, ScD**, **Juhua Luo, PhD**, **Thomas Rohan, MBBS, PhD**, **Aladdin H. Shadyab, PhD**, **Gretchen Wells, MD, PhD**, **Jean Wactawski-Wende, PhD**, **Ross L. Prentice, PhD**, **WHI Investigators**

Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (Drs. Manson and Bassuk); Fred Hutchinson Cancer Research Center, Seattle, WA (Mr. Aragaki and Drs. Anderson and Prentice); City of Hope National Medical Center, Duarte, CA and Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA (Dr. Chlebowski); Division of Public Health Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD (Dr. Rossouw); MedStar Health Research Institute and Georgetown/Howard Universities (Dr. Howard); Mel & Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ (Dr. Thomson); Stanford Prevention Research Center, Stanford, CA (Dr. Stefanick); University of Florida College of Medicine Jacksonville – Jacksonville, FL (Dr. Kaunitz); Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine at University of California, Los Angeles (Dr. Crandall); Department of Family Medicine and Epidemiology, Alpert Medical School of Brown University, Providence, PI (Dr. Eaton); Departments of Health Research & Policy (Epidemiology) and of Neurology & Neurological Sciences, Stanford University (Dr. Henderson); Departments of Epidemiology and Medicine, Brown University, Providence, RI (Dr. Liu); Departments of Epidemiology and Biostatistics, School of Public Health, Indiana University, Bloomington, Indiana (Dr. Luo); Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY (Dr. Rohan); Department of Family Medicine and Public Health, School of Medicine, University of California, San Diego, La Jolla, CA (Dr. Shadyab); University of Kentucky, Lexington (Dr. Wells); University at Buffalo, the State University of New York, Buffalo, NY (Dr. Wactawski-Wende).

Abstract

Correspondence and reprint requests to: JoAnn E. Manson, MD, DrPH, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Avenue, 3rd Fl., Boston, MA; phone: 617-278-0871; fax: 617-731-3843; jmanson@rics.bwh.harvard.edu.

Conflict of Interest Disclosures: All authors will complete and submit the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Supplementary Material
Protocol
Appendix

Background: Whether health outcomes of menopausal estrogen therapy differ between women with and without bilateral salpingo-oophorectomy (BSO) is unknown.

Objective: To examine estrogen therapy outcomes by BSO status, with additional stratification by 10-year age groups.

Design: Subgroup analyses of Women's Health Initiative estrogen-alone randomized trial.

Setting: 40 U.S. clinical centers.

Participants: 9,939 women aged 50–79 years with prior hysterectomy and known oophorectomy status.

Intervention: Conjugated equine estrogens (CEE, 0.625 mg/day) or placebo for 7.2 years (median).

Measurements: Incidence of coronary heart disease and invasive breast cancer (the trial's two primary endpoints), all-cause mortality, and a "global index" (these endpoints plus stroke, pulmonary embolism, colorectal cancer, and hip fracture) during the intervention phase and 18-year cumulative follow-up.

Results: The effects of CEE alone did not differ significantly according to BSO status. However, age modified the effect of CEE among women with prior BSO. During the intervention phase, CEE was significantly associated with adverse effects (hazard ratio for global index=1.42, 95% confidence interval 1.09–1.96) among older women (aged ≥70), but the global index was not elevated in younger women (p, trend by age=0.016). During cumulative follow-up, women aged 50–59 with BSO experienced a treatment-associated reduction in all-cause mortality (hazard ratio=0.68 [0.48–0.96]), whereas older women with BSO had no mortality reduction (p, trend by age=0.034). There was no significant association between CEE and outcomes among women with conserved ovaries, regardless of age.

Limitation: CEE timing in relation to BSO varied; multiple comparisons without adjustment for multiple testing.

Conclusion: The effects of CEE were not significantly different by BSO status in the overall cohort, but some findings varied by age. Among women with prior BSO, CEE led to adverse effects during the treatment period in women aged ≥70, whereas women randomized before age 60 appeared to derive mortality benefit over the long term.

Trial registration: clinicaltrials.gov identifier: NCT00000611

Keywords

estrogen therapy; mortality; benefit-risk assessment; oophorectomy; clinical trial

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Each year an estimated 425,000 U.S. women have a hysterectomy for benign gynecologic conditions (1,2), and one third (3) to one half (4) of these women undergo concurrent oophorectomy to minimize ovarian cancer risk. However, several observational studies have found that, although it does reduce subsequent risk of ovarian (5–7) and breast (5,8) cancer, bilateral salpingo-oophorectomy (BSO) also confers long-term health risks beyond those resulting from hysterectomy itself, especially when ovary removal occurs early (before age

45–50 years). Observational studies also suggest that BSO-associated elevations in all-cause mortality (5,9–12), coronary heart disease (CHD) (10,13–15), and other adverse outcomes are attenuated among women treated with menopausal estrogen therapy (4). Given the acute declines (16,17) and sustained reductions (18,19) in endogenous sex hormones that occur following BSO, it is biologically plausible that estrogen therapy might confer long-term benefits, including a reduction in all-cause mortality, in women who have undergone this procedure, and that such benefits may be greater than in women with conserved ovaries. The Women's Health Initiative (WHI) estrogen-alone trial, a large-scale randomized trial of estrogen therapy in 10,739 women aged 50–79 who entered the trial with prior hysterectomy with or without BSO, provides a unique opportunity to investigate these issues, which have not been previously examined in a randomized trial setting. Because prior analyses of the benefits and risks of estrogen therapy in the WHI study population indicate variation by age at randomization (20,21), assessing the effects of such therapy not only according to BSO status but also jointly by BSO status and age is of interest. Results of such analyses have the potential to inform clinical decision making regarding estrogen therapy.

METHODS

Study Design

The WHI estrogen-alone trial, including the design, compliance, and outcome adjudication procedures, is described elsewhere (20–23). Briefly, 10,739 postmenopausal women ages 50 to 79, with prior hysterectomy, were recruited from 1993 to 1998 at 40 U.S. clinical centers and randomized to oral conjugated equine estrogens (CEE [Premarin], 0.625 mg/day) or placebo. Primary outcomes were incident CHD and invasive breast cancer. Each center obtained institutional review board approval, and all participants provided written informed consent. The intervention phase was stopped on February 29, 2004 (after a median of 7.2 years [interquartile range, 6.4–8.1 years]), earlier than planned, because of an increased stroke risk not offset by lower CHD risk in the CEE group (23). Post-intervention follow-up was available through December 31, 2014 (median 18 years of cumulative follow-up) for mortality endpoints and September 30, 2014 for other incident events. Mortality endpoints were ascertained by regular surveillance of the cohort through the National Death Index and by next-of-kin or postal service reports (20,22). Summary statistics may differ slightly from those in previous publications because of more complete endpoint ascertainment in this report. After the trial ended, participants were told their randomization assignment; fewer than 4% reported personal post-trial use of systemic estrogen.

WHI investigators and representatives of the National Heart, Lung, and Blood Institute (NHLBI), the trial's sponsor, collaborated on the design and conduct of the trial; data interpretation; management, analysis, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Statistical Analysis

Intervention-phase analyses included all randomized participants with known oophorectomy status (n=9,939), stratified by whether or not they reported having undergone surgical removal of both ovaries (BSO) prior to randomization. Women reporting no BSO, and those

reporting single or partial oophorectomy, were classified as not having undergone BSO (of these, nearly three quarters had both ovaries intact, one quarter had one ovary removed, and 3% had part of an ovary removed). Participants were analyzed according to their randomization assignment until last intervention contact, using time-to-event methods based on the intention-to-treat principle. A composite "global index" of monitored clinical events was calculated as time to first event for CHD, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, and death. Results are presented for the trial's primary outcomes (CHD and invasive breast cancer), all-cause mortality, and the global index. Analyses of other endpoints in the global index and of other major endpoints (total MI, coronary revascularization, total cancer, total fractures, total cardiovascular mortality, and total cancer mortality), as in previous reports (20,21,24,25), are presented in the appendix, and should be interpreted cautiously due to multiple comparisons.

Hazard ratios (HRs) were estimated using Cox proportional hazards models, stratified by BSO status (yes/no) at enrollment, age, randomization status in the WHI Dietary Modification trial, prior cardiovascular or other disease (if appropriate), and study phase (time-dependent strata). Preplanned analyses included presentation of intervention-phase and cumulative follow-up HRs and forest plots for women with and without BSO separately, then additionally stratified by 10-year age group. HRs may exhibit within- or between-phase time dependencies (20,21). HRs for varying cumulative follow-up periods have been previously reported (20,21,24,25), with additional follow-up time and extended cumulative incidence curves (26) included in the present analyses. Cumulative incidence curves were standardized using inverse probability weighting (26) and computed for the full cohort so that BSO and randomization groups were balanced with respect to age and other variables above (as used to stratify the baseline hazard functions for the primary analysis). Incidence curves by 10-year age group were then computed using these weights.

Within each BSO stratum, interactions between randomization group and age group were assessed with a 1 degree-of-freedom test for linear trend, with each age group assigned an integer value (0,1,2). Exploratory analyses were also stratified by age at BSO. In addition, we examined whether the overall influence of CEE depended on time elapsed (<10; 10 -< 20; ≥20 years) from age at BSO to age at randomization to CEE (defined as "gap-time"), by including gap-time interaction parameters.

Statistical tests were based on a two-sided stratified score (log rank) test, with nominal (unadjusted) p-values ≤0.05 considered statistically significant. P-values should be interpreted cautiously due to multiple comparisons. Sensitivity analyses censored participants who took fewer than 80% of study pills over the preceding follow-up period; excluded women who reported unilateral or partial oophorectomy; stratified by pre-randomization use of hormone therapy; and adjusted for characteristics that differed by BSO status or age group. The latter analysis included the baseline variables of age, clinic-measured baseline body mass index (BMI), systolic and diastolic blood pressure as linear covariates, and indicator variables for medications inventoried at baseline (aspirin and medications for diabetes, hypertension, and hyperlipidemia) to account for differences in cardiovascular and mortality risk factors associated with BSO status (27), with additional stratification of the baseline hazard functions by race/ethnicity. This select list of covariates

maintained the integrity of the randomization by excluding less than 0.5% of randomized participants because of missing covariates. Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina) and R software version 3.4 (R Foundation for Statistical Computing, http://www.r-project.org/; R-packages 'survival' (28) and 'rmeta' (29)).

RESULTS

Baseline characteristics

The flow of participants in the WHI estrogen-alone trial through the 18-year cumulative follow-up period is presented in Figure 1.

Within each BSO stratum, baseline characteristics were well balanced in the CEE and placebo groups (Table 1). However, women with BSO were slightly older (by ~1 year) and more likely to be white and to have certain cardiovascular risk factors, particularly hypertension, diabetes, and a smoking history, as well as higher BMI, than women without BSO (Appendix Table 1). They were also more likely to have had an earlier age at menopause and prior hormone therapy use.

Treatment effects in women with and without BSO

During the intervention phase, the effects of CEE therapy on health outcomes did not differ significantly between women with and without BSO in the total cohort of women aged 50–79 (Figure 2). In each group, when examined separately, CEE was not associated with a statistically significant increase or decrease in CHD, breast cancer, all-cause mortality, or the global index. Similarly, during cumulative 18-year follow-up, CEE was not significantly associated with these four outcomes in women with and without BSO in the overall cohort aged 50–79.

Treatment effects in women with and without BSO, age-stratified analyses

Intervention phase.—In age-stratified analyses of women with BSO, younger women (aged 50–59) and those aged 60–69 had treatment effects that were in a non-adverse direction, whereas older women (age 70–79) had treatment effects that were generally adverse (Figure 3). Compared with their older counterparts, younger individuals with BSO experienced significantly less adverse treatment effects for breast cancer (p, trend by age=0.010) and the global index (p, trend by age=0.016). For the global index, treatment-associated HRs were 0.85 (95% confidence interval 0.54–1.34), 0.94 (0.74–1.19), and 1.42 (1.09–1.86) in women aged 50–59, 60–69, and 70–79, respectively.

In contrast, age did not significantly influence the association between CEE and health outcomes in women without BSO (Figure 3). The p-values for the trend tests by age were nonsignificant for all four major outcomes.

Cumulative follow-up.—In the BSO group, some age differences in the effect of CEE were evident during cumulative follow-up, with significantly reduced all-cause mortality and a trend toward a more favorable benefit-risk balance as assessed by the global index in

younger than in older women (Figure 3). For all-cause mortality, the treatment-associated HRs were 0.68 (0.48–0.96), 0.88 (0.74–1.05), and 1.02 (0.86–1.21) for those aged 50–59, 60–69, and 70–79, respectively (p, trend by age=0.034); for the global index, these HRs were 0.85 (0.64–1.13), 0.95 (0.81–1.11), and 1.12 (0.94–1.34) (p, trend=0.072). Age-stratified results for the individual outcomes in the global index are provided in Appendix Figure 1, Panel A, but these results should be interpreted cautiously due to multiple comparisons.

Among women without BSO, there continued to be little influence of age on the CEE effect during cumulative follow-up (Figure 3). Again, the p-values for the trend tests by age were nonsignificant for all four major outcomes. The results by age group for individual outcomes included in the global index are presented in Appendix Figure 1, Panel B.

The Kaplan-Meier estimates for cumulative incidence of the four major outcomes by age group (50–59, 60–69, and 70–79) are shown in Appendix Figure 2. A progressive divergence of the curves for CEE vs. placebo among women aged 50–59 was more apparent among the women with BSO than those without BSO, especially for breast cancer, all-cause mortality, and the global index.

Regarding a potential modifying effect of age at time of BSO, women who underwent BSO before age 45 and were also below age 60 at time of randomization had a cumulative CEE-associated HR for all-cause mortality of 0.60 (0.38–0.95); other women did not have a significant reduction in this endpoint (p, interaction=0.34) (Appendix Figure 3). Moreover, there was a significant interaction between CEE and gap-time for all-cause mortality during cumulative follow-up (p=0.001); women who were randomized to CEE <10 years after BSO experienced a substantial mortality reduction (HR=0.66 [0.48–0.92]) whereas those randomized ≥20 years after BSO had no reduction (HR=1.02 [0.90–1.17]).

Sensitivity analyses

Analyses that adjusted for prior hormone therapy use or other baseline characteristics that differed according to BSO status (as shown in Appendix Table 1) or age group did not appreciably change the main results, indicating that these characteristics did not confound the BSO-stratified or the joint BSO- and age-stratified associations between randomized treatment assignment and health outcomes. In addition, although statistical power was low, analyses stratified by prior hormone therapy use found that this variable did not modify the effect of randomized treatment in younger women (aged 50–59) with or without BSO—groups for whom hormone therapy decision making is most relevant (Figure 4). Analyses excluding women who reported unilateral or partial oophorectomy did not alter the findings. In analyses that censored participants who became non-compliant with study pills, smaller sample sizes led to imprecise and generally uninformative results.

DISCUSSION

In the overall cohort of 50- to 79-year-old women with hysterectomy in the WHI estrogen-alone trial, randomized assignment to CEE for a median of 7 years was associated with a similar pattern of benefits and risks in women with and without BSO. However, age at

randomization to CEE more strongly influenced the effect of treatment, especially on all-cause mortality, among those with a history of BSO than among those with ovarian conservation. Younger women (aged 50–59) with BSO who were randomized to CEE experienced a statistically significant 32% reduction in all-cause mortality over 18 years of cumulative follow-up, whereas younger women without BSO and older women with or without BSO did not have a mortality reduction. The CEE-associated reduction in all-cause mortality experienced by younger women with BSO was most apparent among those who had had this procedure before age 45. In addition, older women (aged 70–79) with BSO who were randomized to CEE had a significantly unfavorable balance of benefits and risks (elevated global index) during the intervention phase; this adverse result was not observed among younger women with BSO or among women with ovarian conservation in any age group. The reasons for these findings are unclear. Women with BSO entered the trial with a more adverse cardiovascular risk profile and slightly higher BMI than did women with conserved ovaries, and the older women presumably had longer durations of exposure to these risk factors than the younger. However, adjustment for these risk factors did not materially alter the results. In addition, older women with BSO were far more distant from exposure to premenopausal endogenous estrogen levels, and also had many more years of oophorectomy-related reductions in sex-hormone levels (18,19), than either younger women with or without BSO or older women without BSO. Women with BSO in the remote past may gradually adapt to these lower levels, with downregulation of estrogen receptors, such that late perturbation of the hormonal milieu precipitates adverse events. Indeed, the effect of CEE therapy on all-cause mortality was highly dependent on the length of time that had elapsed between BSO and WHI trial entry; women who were randomized to CEE within 10 years experienced a significant 34% reduction in this endpoint, whereas those randomized to CEE ≥20 years after BSO did not have reduced risk.

The findings may have relevance to clinical practice. Initiation of estrogen therapy after early BSO and continuation until at least the average age of natural menopause (age 51) has been the traditional standard of care, but recent studies suggest changing practice patterns, with marked declines in the prevalence and duration of estrogen use in affected women (30–32) since the initial findings of the WHI hormone therapy trials (23, 33) were published in the early 2000s. The WHI was not designed to examine the health effects of initiation of estrogen therapy shortly after BSO, but the results reported here indicate that women below age 60 and with a history of BSO, regardless of pre-trial hormone therapy use, had neutral or potentially beneficial effects from CEE treatment. (The findings also suggest that women with hysterectomy and BSO should not start CEE after age 60 or 70, but this scenario is rare in clinical practice.) This provides some reassurance to clinicians and their younger patients with BSO that, in the absence of contraindications, the use of estrogen beyond the average age of natural menopause to manage menopausal symptoms or—in women at high risk of fracture who cannot tolerate alternative osteoporosis therapies—to lower osteoporosis risk (34) should not have net adverse effects. Women with BSO randomized to CEE while in their fifties did not experience statistically significant increases in risk of any of the four major outcomes examined. Moreover, in long-term follow-up, these women had a significant 32% reduction in all-cause mortality and nonsignificant 15–33% risk reductions in CHD, breast cancer, and the global index. These findings are consistent with the results of long-

term observational studies suggesting that estrogen therapy attenuates all-cause mortality (5,9,11) and coronary risks (10,13–15) after BSO (4), and also support the absence of an increase in cancer risk. Although they did not derive a long-term mortality benefit, younger women without BSO had a net treatment result (global index) similar to that of younger women with prior BSO. This suggests that, in the absence of contraindications, younger women without BSO also should not have an unfavorable benefit-risk balance from using estrogen for menopausal symptom relief throughout their fifties or later. That said, previous WHI analyses indicate that oral CEE increases venous thromboembolic risk, even in younger women (20). The use of transdermal estrogen may avert this excess risk (35), but the long-term effects of such therapy on breast cancer and CHD remain unclear and require elucidation in future trials.

The results of this study fill an important knowledge gap regarding randomized assessment of the benefits and risks of estrogen therapy in women with and without elective BSO, but several limitations warrant consideration. First, as noted above, although gap-time analyses were conducted, the WHI could not rigorously examine health effects of estrogen therapy initiated immediately following BSO. Second, only one dose, formulation, and route of administration of estrogen was assessed; thus, the results do not necessarily generalize to other estrogen preparations or routes of delivery. Third, nonadherence to randomized treatment may have diluted effect estimates. However, during the intervention phase, adherence rates for CEE vs. placebo were similar among women with and without BSO and could not explain the stronger trends by age among women with BSO. In addition, as noted above, fewer than 4% of women reported personal hormone therapy use during the post-trial period. Fourth, hysterectomy and BSO were self-reported by participants, and outside validation was not conducted. However, a study of the validity of self-reported gynecologic surgery among patients in an integrated group practice in Washington State found sensitivity of 91% and positive predictive value of 97% for hysterectomy and sensitivity of 64% and positive predictive value of 100% for BSO (36). Misclassification of BSO in the WHI would tend to attenuate the results, although sensitivity analyses excluding women with unilateral oophorectomy did not show such an effect. Fifth, subgroup analyses should be interpreted with caution due to multiple comparisons. Sixth, although sensitivity analyses that adjusted for measured baseline characteristics that differed by BSO status did not materially change the results, it remains possible that unmeasured or unknown factors that co-vary with BSO status may confound the results. Finally, recommendations regarding the use of BSO have changed since WHI enrollment, which occurred more than two decades ago. Growing consensus is that BSO, particularly prior to the average age at menopause, should be considered only in women at high risk of ovarian and/or breast cancer, such as those with high-risk BRCA gene variants, but not in women at usual risk of these outcomes (37). Thus, results regarding the effects of estrogen therapy in WHI women with BSO may not generalize to a higher-risk BSO population. Moreover, the fact that estrogen therapy may offset risks of BSO should not be used to justify performing this procedure in women at average risk of cancer.

In conclusion, menopausal estrogen-alone therapy taken for a median of 7 years was associated with reduced mortality and a generally favorable safety profile when initiated before age 60 in women with prior BSO. Such therapy was not significantly associated with

mortality or other major outcomes in women without BSO. Increasing age was associated with more adverse treatment effects in women with BSO than in those with conserved ovaries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

WHI Investigators and Study Participants

The authors thank the WHI investigators, staff, and the trial participants for their outstanding dedication and commitment.

Dr. Manson and Mr. Aragaki had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding/Support:

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. Wyeth Ayerst donated the study drugs.

Short List of WHI Investigators

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller

Clinical Coordinating Center: Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg.

Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker

Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker

For a list of all the investigators who have contributed to WHI science, see: https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf

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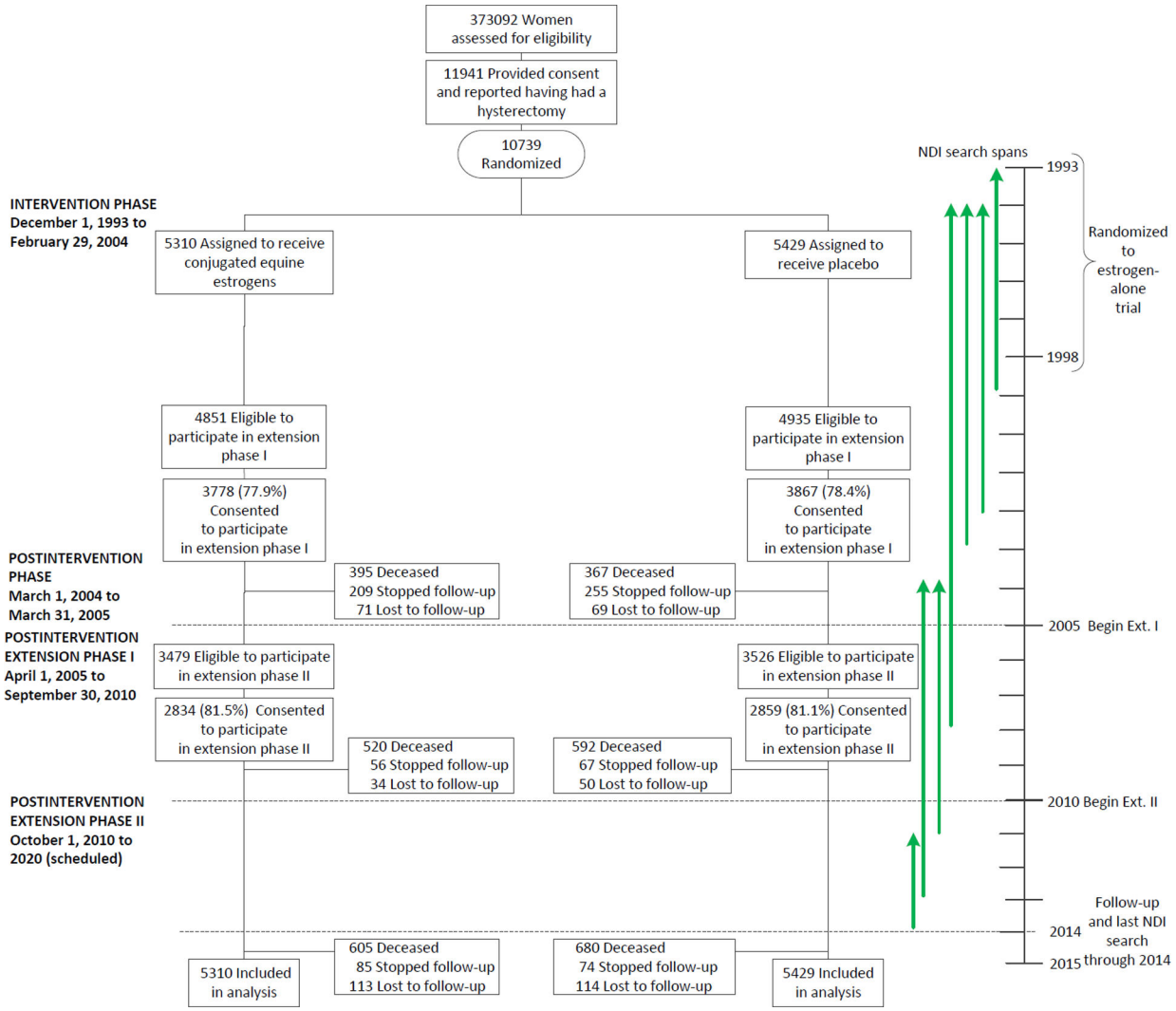

Figure 1.

Flow of participants in the Women's Health Initiative trial of estrogen-alone therapy vs placebo through extended follow-up.

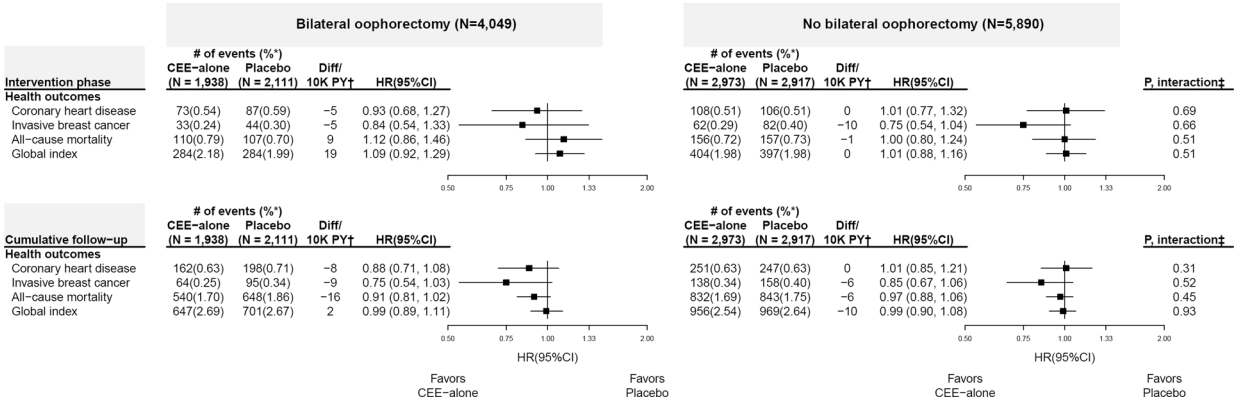

Figure 2.

Number of events (annualized rates, %), difference in estimated absolute risks, and hazard ratios (95% confidence intervals) for select health outcomes in the overall study population of women aged 50 to 79 in the Women's Health Initiative conjugated equine estrogens (CEE)-Alone Trial, according to oophorectomy status during the intervention phase and cumulative follow-up.

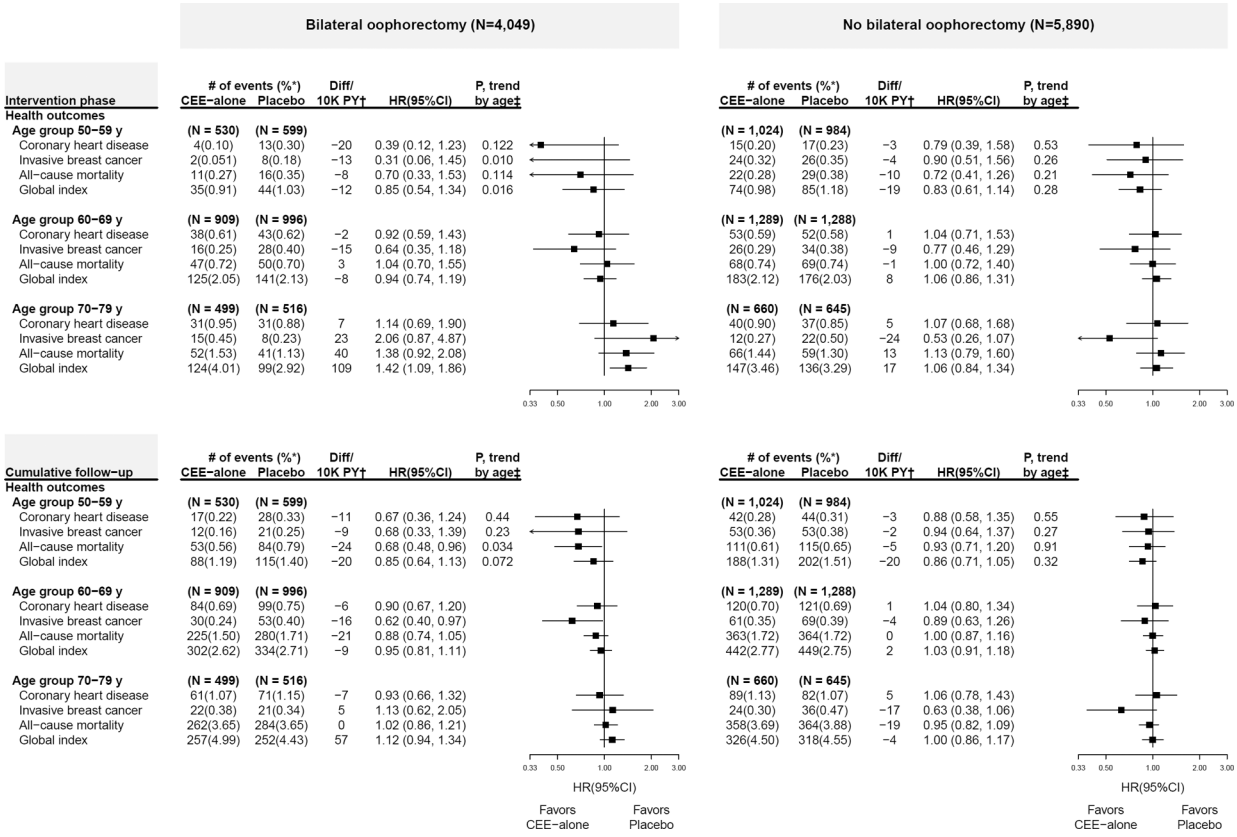

Figure 3.

Number of events (annualized rates, %), difference in estimated absolute risks, and hazard ratios (95% confidence intervals) for select health outcomes in the overall study population of women aged 50 to 79 in the Women's Health Initiative CEE-Alone Trial, according to oophorectomy status and 10-year age group during the intervention phase and cumulative follow-up.

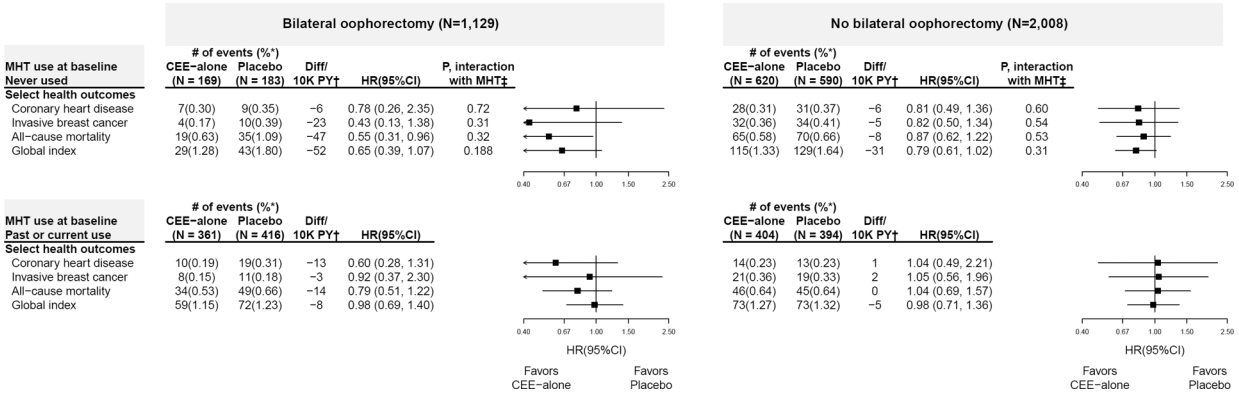

Figure 4.

Select health outcomes during cumulative follow-up stratified by BSO status and prior menopausal hormone therapy (MHT) use among women aged 50–59 years

Table 1.

Baseline characteristics of CEE-alone trial participants stratified by bilateral salpingo-oophorectomy (BSO) status

	BSO				No BSO			
	CEE-alone (N=1938*)		Placebo (N=2111)		CEE-alone (N=2973)		Placebo (N=2917)	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Age at screening, y, mean, (SD)	64.2	(7.0)	64.1	(7.2)	62.9	(7.4)	63.1	(7.4)
Age group at screening, y, (%)								
50–59	530	(27.3)	599	(28.4)	1024	(34.4)	984	(33.7)
60–69	909	(46.9)	996	(47.2)	1289	(43.4)	1288	(44.2)
70–79	499	(25.7)	516	(24.4)	660	(22.2)	645	(22.1)
Race/ethnicity, (%)								
White	1513	(78.1)	1620	(76.7)	2251	(75.7)	2219	(76.1)
Black	260	(13.4)	304	(14.4)	427	(14.4)	410	(14.1)
Hispanic	92	(4.7)	109	(5.2)	196	(6.6)	197	(6.8)
American Indian	20	(1.0)	10	(0.5)	16	(0.5)	18	(0.6)
Asian/Pacific Islander	31	(1.6)	34	(1.6)	41	(1.4)	39	(1.3)
Unknown	22	(1.1)	34	(1.6)	42	(1.4)	34	(1.2)
>High school diploma or GED, (%)†‡	1294	(67.4)	1405	(66.9)	1984	(67.3)	2018	(69.8)
Family income ≥$50,000, (%)†‡	416	(22.6)	445	(22.3)	678	(24.2)	674	(24.6)
Hormone use, (%)†‡								
Never	737	(38.0)	829	(39.3)	1787	(60.1)	1699	(58.3)
Past	893	(46.1)	968	(45.9)	862	(29.0)	855	(29.3)
Current§	308	(15.9)	313	(14.8)	323	(10.9)	361	(12.4)
Vasomotor symptoms, (%)†‡								
None	1126	(58.6)	1198	(57.2)	1602	(54.5)	1592	(55.4)
Mild	470	(24.5)	561	(26.8)	818	(27.8)	768	(26.7)
Moderate/Severe	325	(16.9)	334	(16.0)	522	(17.7)	514	(17.9)
Smoking, (%)†‡								
Never	967	(50.2)	1040	(49.8)	1546	(52.5)	1480	(51.3)
Past	766	(39.8)	843	(40.4)	1090	(37.0)	1099	(38.1)
Current	193	(10.0)	206	(9.9)	307	(10.4)	307	(10.6)
Treated Diabetes, (%)†‡	156	(8.0)	169	(8.0)	214	(7.2)	203	(7.0)
Hypertension or BP ≥ 140/90, (%)†‡	1009	(55.3)	1072	(54.3)	1421	(51.1)	1361	(50.7)
High cholesterol requiring medication, (%)	309	(15.9)	304	(14.4)	393	(13.2)	460	(15.8)
Statin use, (%)	158	(8.2)	157	(7.4)	200	(6.7)	238	(8.2)
Aspirin use (≥ 80 mg/d), (%)	400	(20.6)	403	(19.1)	579	(19.5)	610	(20.9)
Medical History, (%)								
Myocardial infarction	67	(3.5)	63	(3.0)	82	(2.8)	99	(3.4)
Angina†‡	160	(8.3)	157	(7.5)	211	(7.1)	197	(6.8)

	BSO				No BSO			
	CEE-alone (N=1938*)		Placebo (N=2111)		CEE-alone (N=2973)		Placebo (N=2917)	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
CABG or PCI†‡	55	(2.9)	42	(2.0)	50	(1.7)	65	(2.3)
Stroke	35	(1.8)	33	(1.6)	35	(1.2)	42	(1.4)
DVT or pulmonary embolism	34	(1.8)	37	(1.8)	48	(1.6)	37	(1.3)
Fracture age 55+†‡	266	(17.8)	255	(16.3)	359	(17.0)	330	(16.1)
Family history of breast cancer†‡//	319	(17.6)	353	(17.6)	512	(18.3)	460	(16.9)
Body mass index, median, (IQR)†‡¶	29.3	(8.1)	29.4	(7.7)	29.1	(8.0)	29.0	(7.9)
Systolic BP, mm Hg, mean, (SD)	130.9	(17.5)	130.9	(17.6)	129.7	(17.3)	129.6	(17.6)
Diastolic BP, mm Hg, mean, (SD)†‡	76.8	(9.0)	76.5	(9.6)	76.3	(9.4)	76.4	(9.2)

Abbreviations: BP, blood pressure; BSO, bilateral salpingo-oophorectomy; CABG, coronary artery bypass graft; CEE, conjugated equine estrogens; DVT, deep vein thrombosis; GED, general equivalency diploma; IQR, interquartile range; PCI, percutaneous coronary intervention.

*Values are reported as No. (%) unless otherwise indicated.

†Missing data among BSO group: education (n = 30), income (n = 208), hormone use (n = 1), vasomotor symptoms (n = 35), smoking (n = 34), diabetes (n = 2), hypertension (n = 250), history of angina (n = 22), CABG or PCI (n = 53), fracture (n = 575), family history of breast cancer (n = 227), body mass index (n = 26) and diastolic BP (n = 1).

‡Missing data among no BSO group: education (n = 51), income (n = 348), hormone use (n = 3), vasomotor symptoms (n = 74), smoking (n = 61), diabetes (n = 8), hypertension (n = 426), history of angina (n = 36), CABG or PCI (n = 77), fracture (n = 822), family history of breast cancer (n = 368), body mass index (n = 29) and diastolic BP (n = 1)

§Required a 3-month washout period prior to randomization.

//Indicates occurrence in paticipant's mother, sister, daughter, or grandmother.

¶Calculated as weight in kilograms divided by height in meters squared.