Menopausal Hormone Therapy and Ovarian and Endometrial Cancers: Long-Term Follow-Up of the Women's Health Initiative Randomized Trials

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ABSTRACT

PURPOSE Menopausal hormone therapy's influence on ovarian and endometrial cancers remains unsettled. Therefore, we assessed the long-term influence of conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) and CEE-alone on ovarian and endometrial cancer incidence and mortality in the Women's Health Initiative randomized, placebo-controlled clinical trials.

MATERIALS AND METHODS Postmenopausal women, age 50-79 years, were entered on two randomized clinical trials evaluating different menopausal hormone therapy regimens. In 16,608 women with a uterus, 8,506 were randomly assigned to once daily 0.625 mg of CEE plus 2.5 mg once daily of MPA and 8,102 placebo. In 10,739 women with previous hysterectomy, 5,310 were randomly assigned to once daily 0.625 mg of CEE-alone and 5,429 placebo. Intervention was stopped for cause before planned 8.5-year intervention after 5.6 years (CEE plus MPA) and after 7.2 years (CEE-alone). Outcomes include incidence and mortality from ovarian and endometrial cancers and deaths after these cancers.

RESULTS After 20-year follow-up, CEE-alone, versus placebo, significantly increased ovarian cancer incidence (35 cases [0.041%] *v* 17 [0.020%]; hazard ratio [HR], 2.04 [95% CI, 1.14 to 3.65]; $P = .014$) and ovarian cancer mortality ($P = .006$). By contrast, CEE plus MPA, versus placebo, did not increase ovarian cancer incidence (75 cases [0.051%] *v* 63 [0.045%]; HR, 1.14 [95% CI, 0.82 to 1.59]; $P = .44$) or ovarian cancer mortality but did significantly lower endometrial cancer incidence (106 cases [0.073%] *v* 140 [0.10%]; HR, 0.72 [95% CI, 0.56 to 0.92]; $P = .01$).

CONCLUSION In randomized clinical trials, CEE-alone increased ovarian cancer incidence and ovarian cancer mortality, while CEE plus MPA did not. By contrast, CEE plus MPA significantly reduced endometrial cancer incidence.

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INTRODUCTION

Ovarian cancer and endometrial cancer are among the leading causes of cancer death for US women with 65,950 endometrial cancers and 12,550 related deaths and 19,880 ovarian cancers and 12,810 related deaths in 2022.[1] The association of menopausal hormone therapy with ovarian cancer and endometrial cancer has been a concern for nearly 50 years, with many questions unresolved.[2-4]

With respect to ovarian cancer in cohort studies, a Million Women Study report with 2,273 ovarian cancers found current hormone therapy users, regardless of formulation (estrogen-only or estrogen plus progestogen), are more likely to develop ovarian cancer ($P = .0002$) and die from the disease ($P = .0006$).[5] In a meta-analysis of findings from 52 observational studies, current or recent use of both estrogen-alone and estrogen plus progestogen was associated with higher ovarian cancer risk ($P < .0001$).[6] However, there are exceptions. In both a French cohort, evaluating estrogen-alone[7] and pooled analysis of five case-control studies evaluating estrogen plus progestin, no association with higher ovarian cancer risk was seen.[8] Thus, with rare exception,[7] while estrogen-alone is consistently associated with higher ovarian cancer risk in observational studies,

CONTEXT

Key Objective

As ovarian and endometrial cancer risk with menopausal hormone therapy has been unsettled, we examined the long-term influence of conjugated equine estrogen (CEE)–alone and CEE plus medroxyprogesterone acetate (MPA) on incidence and mortality of these cancers in the Women's Health Initiative randomized clinical trials.

Knowledge Generated

After 20-year follow-up, CEE-alone for 7.2 years significantly increased ovarian cancer incidence and ovarian cancer mortality; by contrast, CEE plus MPA for 5.6 years, did not, but did significantly lower endometrial cancer incidence. CEE plus MPA findings for endometrial cancer were concordant with observation studies, while ovarian cancer findings were discordant.

Relevance *(I. Cheng)*

The different impacts of the types of menopausal hormone therapies on ovarian and endometrial cancer incidence and mortality point to the importance of evaluating the risks versus benefits in the use of estrogen-alone and the combination of progesterone with estrogen.*

*Relevance section written by *JCO* Associate Editor Iona Cheng, PhD, MPH.

findings regarding estrogen plus progestin and ovarian cancer are mixed.

With respect to endometrial cancer, previous observational studies have established that estrogen-alone is associated with higher endometrial cancer risk[9] and progestin addition is associated with lower risk than estrogen-alone.[10] However, it is uncertain whether estrogen plus progestin provides lower endometrial cancer risk compared with no hormone use.[11,12]

Two Women's Health Initiative (WHI) randomized trials are addressing menopausal hormone therapy influence on these cancers. In the WHI trial where 16,608 postmenopausal women with a uterus were randomly assigned to daily conjugated equine estrogen (CEE) 0.625 mg plus medroxyprogesterone acetate (MPA) 2.5 mg, or placebo, there were more ovarian cancers in the CEE plus MPA group after 5.6 years of intervention,[13] and 13.0 years of cumulative follow-up (hazard ratio [HR], 1.24 [95% CI, 0.83 to 1.87]),[14] with neither findings statistically significant. There were fewer endometrial cancers in the CEE plus MPA group after 5.6 years of follow-up, a finding that became statistically significant after 13.0 years of follow-up (HR, 0.65 [95% CI, 0.48 to 0.89]).[14,15] Ovarian cancer findings have not been previously reported from the WHI randomized trial evaluating daily CEE-alone in 10,739 postmenopausal women with previous hysterectomy.

The current report updates findings with 20-year follow-up from the WHI randomized trial evaluating CEE plus MPA regarding ovarian and endometrial cancer incidence and mortality, and to our knowledge, for the first time, reports findings from the WHI randomized trial evaluating CEE-alone on ovarian cancer incidence and mortality.

MATERIALS AND METHODS

The WHI hormone therapy trial designs have been described.[16-18] Recruitment was at 40 US clinical centers between 1993 and 1998. Eligible were postmenopausal women, age 50-79 years, without suspicious mammogram and no baseline endometrial pathology for the combined hormone trial. Exclusions were previous breast cancer, anticipated survival of <3 years, and previous invasive cancer within 10 years. A 3-month washout period was required before random assignment for hormone users at screening. Demographic, medical, and reproductive history was collected at baseline using self-administered questionnaires. Previous postmenopausal hormone use was determined through a structured interview. Race and ethnicity were by self-reported against fixed categories. All participants provided written informed consent and study protocols were approved by all participating clinical centers.

For entry in the combined hormone therapy trial, for safety, pelvic examination with endometrial biopsy was required and performed by WHI-trained and WHI-certified staff. When biopsy was unsuccessful, vaginal ultrasounds were performed. An endometrial wall thickness of >0.5 cm, as evidence of pathologic findings,[19] precluded entry. Reports of endometrial cancer and complex adenomatous hyperplasia, with or without atypia, precluded entry. Women with simple hyperplasia could enter with abnormality resolution. After entry, women with heavy or persistent bleeding were referred to

TABLE 1. Baseline Characteristics of Participants in Two Women's Health Initiative Trials of Menopausal Hormone Therapy

	CEE-Alone Trial		CEE + MPA Trial	
Characteristic	CEE-Alone (n = 5,310)	Placebo (n = 5,429)	CEE + MPA (n = 8,506)	Placebo (n = 8,102)
Age at screening, years, mean (SD)	63.6 (7.3)	63.6 (7.3)	63.2 (7.1)	63.3 (7.1)
Age group at screening, years, No. (%)				
50-59	1,639 (30.9)	1,674 (30.8)	2,837 (33.4)	2,683 (33.1)
60-69	2,386 (44.9)	2,465 (45.4)	3,854 (45.3)	3,655 (45.1)
70-79	1,285 (24.2)	1,290 (23.8)	1,815 (21.3)	1,764 (21.8)
Hispanic,[a] No. (%)	353 (6.7)	361 (6.7)	519 (6.1)	461 (5.7)
Race,[a] No. (%)				
American Indian/Alaska Native	24 (0.5)	25 (0.5)	24 (0.3)	23 (0.3)
Asian/Pacific Islander	86 (1.6)	78 (1.4)	204 (2.4)	172 (2.1)
Black/African American	775 (14.6)	823 (15.2)	534 (6.3)	569 (7.0)
White	4,234 (79.7)	4,289 (79.0)	7,480 (87.9)	7,106 (87.7)
Multiracial, unknown, or not reported	191 (3.6)	214 (3.9)	264 (3.1)	232 (2.9)
College degree or higher, No. (%)	1,217 (23.2)	1,327 (24.6)	2,915 (34.4)	2,839 (35.3)
Body mass index, kg/m^2, median (IQR)	29.2 (8.1)	29.2 (7.8)	27.5 (7.5)	27.5 (7.4)
Smoking, No. (%)				
Never	2,723 (51.9)	2,705 (50.4)	4,178 (49.6)	3,999 (50.0)
Past	1,986 (37.8)	2,090 (38.9)	3,362 (39.9)	3,157 (39.5)
Current	542 (10.3)	571 (10.6)	880 (10.5)	838 (10.5)
Bilateral oophorectomy, No. (%)	1,938 (39.5)	2,111 (42.0)	29 (0.3)	24 (0.3)
Age at menopause, years, mean (SD)	44.5 (7.6)	44.4 (7.7)	50.0 (4.8)	50.0 (4.7)
Previous HT use, No. (%)				
Never used	2,769 (52.2)	2,769 (51.0)	6,277 (73.8)	6,022 (74.4)
Past user	1,871 (35.2)	1,947 (35.9)	1,671 (19.7)	1,587 (19.6)
Current user	669 (12.6)	709 (13.1)	554 (6.5)	490 (6.1)
Previous HT duration, No. (%)				
Never	2,769 (52.1)	2,769 (51.0)	6,277 (73.8)	6,022 (74.3)
<5 years	1,352 (25.5)	1,412 (26.0)	1,539 (18.1)	1,468 (18.1)
≥5 years	1,189 (22.4)	1,247 (23.0)	690 (8.1)	611 (7.5)
History of ovarian cancer, No. (%)	25 (0.5)	38 (0.7)	6 (0.1)	2 (0.0)
History of endometrial cancer, No. (%)	1 (0.0)	2 (0.0)	0	0

Abbreviations: CEE, conjugated equine estrogen; HT, menopausal hormone therapy; MPA, medroxyprogesterone acetate; SD, standard deviation.
[a]Ethnic group and race were self-reported by participants. Multiracial participants self-identified with more than one race. Participants with unknown race self-identified as other.

the study clinic gynecologist. The full gynecologic follow-up procedures have been described.[13,16] The participants' own physicians managed endometrial cancer and ovarian cancer therapy.

Participants were randomly allocated using a computerized, permuted-block algorithm at the WHI clinical coordinating center and stratified by age group and clinical center with double-blind study drug dispensing. In the trial involving 10,739 women with previous hysterectomy, random assignment was to daily 0.625 mg/d of CEE-alone or placebo. In the trial involving 16,608 women with a uterus, random assignment was to daily 0.625 mg/d of CEE plus 2.5 mg/d of MPA as a single tablet.

The hormone therapy interventions in both trials were stopped for cause before the planned 8.5-year intervention: after 5.6 years in the CEE plus MPA trial and after 7.2 years in the CEE-alone trial.[20] Follow-up for clinical outcomes continued per protocol through 2005. Follow-up for incidence outcomes beyond 2005 required two written consents as previously described[21] and was provided by over 78% of surviving participants on both occasions.[20] Characteristics of consenting participants by randomization group and extension study (I, II) have been provided.[20] For mortality findings, as all participants originally provided consent for survival linkage, long-term mortality follow-up was not restricted. Mortality information was enhanced by serial National Death Index

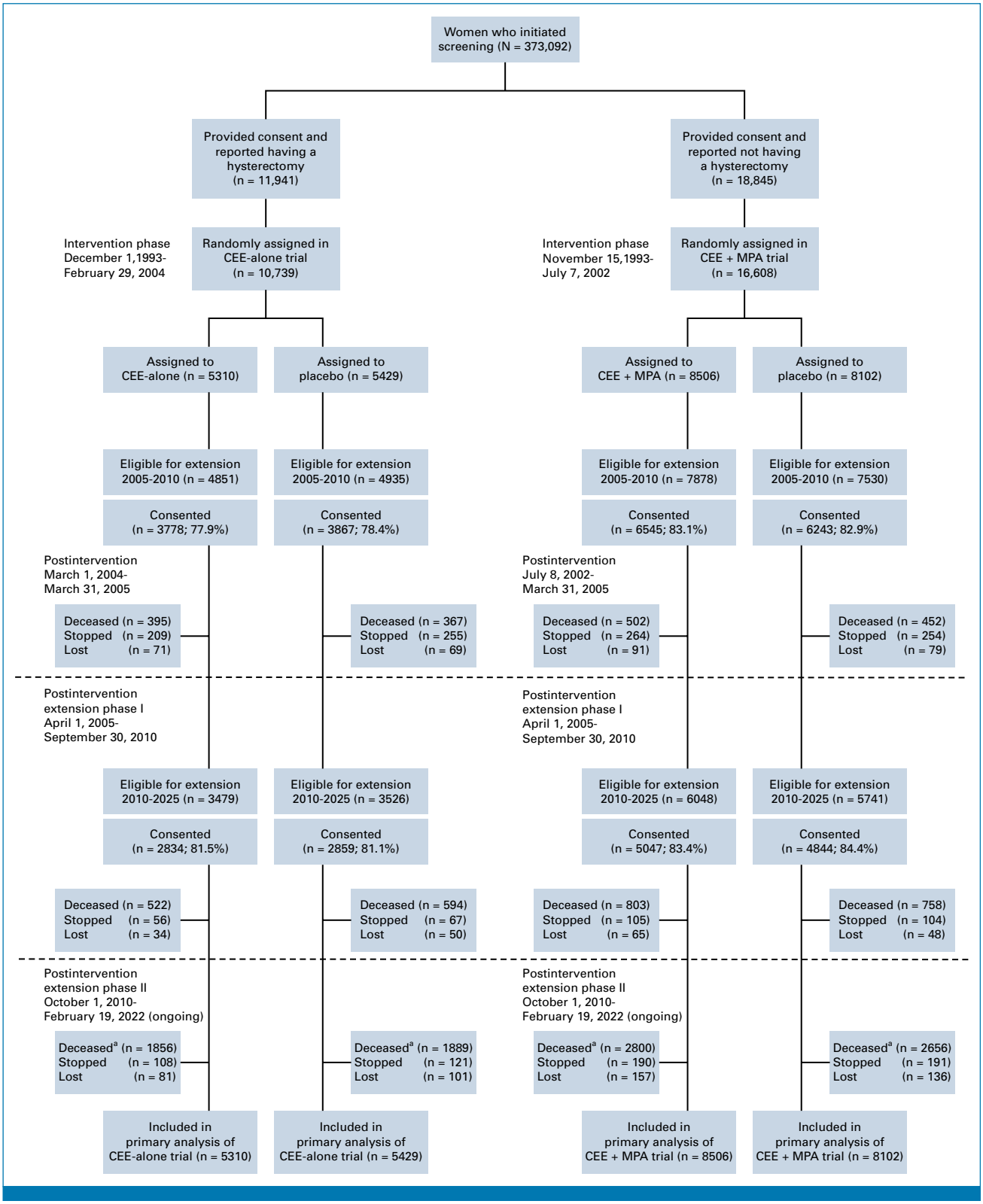

FIG 1. Flow of participants in two Women's Health Initiative trials of menopausal hormone therapy through extended follow-up. [a]Mortality data through December 31, 2020, and corresponds to most recent search of the National Death Index. CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate.

CEE-Alone Trial (n = 10,739) Clinical Outcome	Total Events (annualized rate, %[a]) CEE-Alone	Placebo	Diff/ 10K[b]	HR(95%CI)	P
Ovarian cancer	35 (0.041)	17 (0.020)	2	2.04 (1.14 to 3.65)	.014
Ovarian cancer mortality	25 (0.024)	9 (0.008)	2	2.79 (1.30 to 5.99)	.006
Death after ovarian cancer	30 (0.035)	12 (0.014)	2	2.47 (1.26 to 4.84)	.006
CEE + MPA Trial (n = 16,608) Clinical Outcome	**Total Events (annualized rate, %[a]) CEE + MPA**	**Placebo**	**Diff/ 10K[b]**	**HR(95%CI)**	**P**
Ovarian cancer	75 (0.051)	63 (0.045)	1	1.14 (0.82 to 1.59)	.44
Ovarian cancer mortality	65 (0.037)	52 (0.031)	1	1.21 (0.84 to 1.74)	.31
Death after ovarian cancer	68 (0.047)	48 (0.035)	1	1.37 (0.95 to 1.98)	.09
Endometrial cancer	106 (0.073)	140 (0.10)	−3	0.72 (0.56 to 0.92)	.010
Endometrial cancer mortality	13 (0.007)	21 (0.013)	−1	0.58 (0.29 to 1.16)	.12
Death after endometrial cancer	51 (0.035)	72 (0.052)	−2	0.68 (0.47 to 0.97)	.034

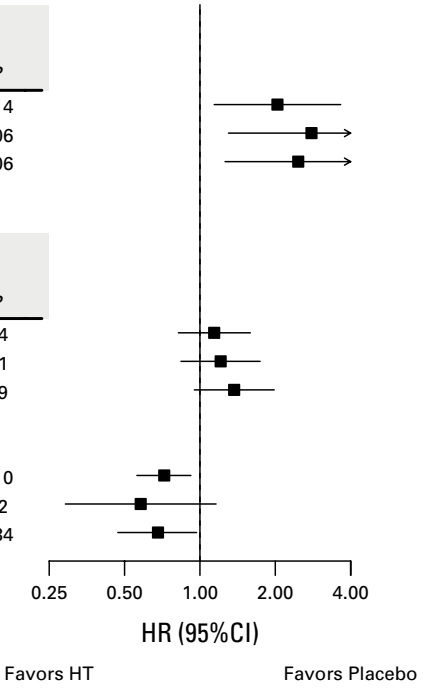

FIG 2. Association of hormone therapy with gynecologic cancer events during cumulative follow-up. [a]Annualized rates were calculated by dividing the total number of events by total follow-up time in years, and expressed as a percentage. [b]Difference in estimated absolute excess risks (HT minus placebo) for 10,000 person-years. CEE, conjugated equine estrogen; HR, hazard ratio; HT, menopausal hormone therapy; MPA, medroxyprogesterone acetate.

queries, which capture 98% of US deaths and provide ovarian and endometrial cancer mortality information regardless of reconsent status.[22]

Clinical outcomes included incident ovarian cancer, ovarian cancer mortality (ovarian cancer followed by death attributed to ovarian cancer), death after ovarian cancer (ovarian cancer followed by death from any cause), incident endometrial cancer, endometrial cancer mortality, and death after endometria cancer, as ascertained for all randomly assigned participants measured from random assignment through 2020.

Outcome assessment was every 6 months throughout the 8.5-year original trial period, with subsequent assessment annually. Cancers were confirmed by medical record review by trained clinical center physician-adjudicators at the clinical centers with adjudicators masked to random assignment and related symptoms. Final adjudication was performed at the clinical coordinating center. Deaths were documented with death certificate and medical record review with cause of death determined centrally by physician adjudicators.

For each trial, analyses included all participants by random assignment, using time-to-event methods. Participants contributed follow-up time until December 31, 2020, date of their first incident cancer, death, or loss to follow-up, whichever came first. HRs were estimated using Cox regression models with baseline hazard functions stratified by age group, randomization status in the WHI dietary modification trial, previous history of disease (for ovarian cancer outcomes), and study period (time-dependent), and complemented with annualized rates. The current analyses were not protocol-specified.

Statistical tests were based on a two-sided stratified score (log-rank) test, with nominal (unadjusted) $P \leq .05$ considered statistically significant. The potential for type I error because of sequential analyses is partially offset by plotting cumulative HRs to illustrate that findings are not a statistical aberration related to the specific length of follow-up used in these analyses. In addition, cumulative HRs graphically summarize temporal associations between the exposure (hormone therapy) and disease risk.[23] The use of cumulative HRs to complement the single HR summary for total cumulative follow-up was first introduced by Ross Prentice[23] and later advocated by Miguel Hernán.[24] Cumulative HRs (95% CIs) were calculated under proportional hazards assumptions and plotted as a function of increasing cumulative follow-up time from random assignment. The proportional hazards assumption was tested[25] and no compelling evidence against proportionality was found (all $P > .05$). Sensitivity analyses excluded participants who reported previous history of ovarian cancer, or bilateral oophorectomy at baseline. All events were measured from random

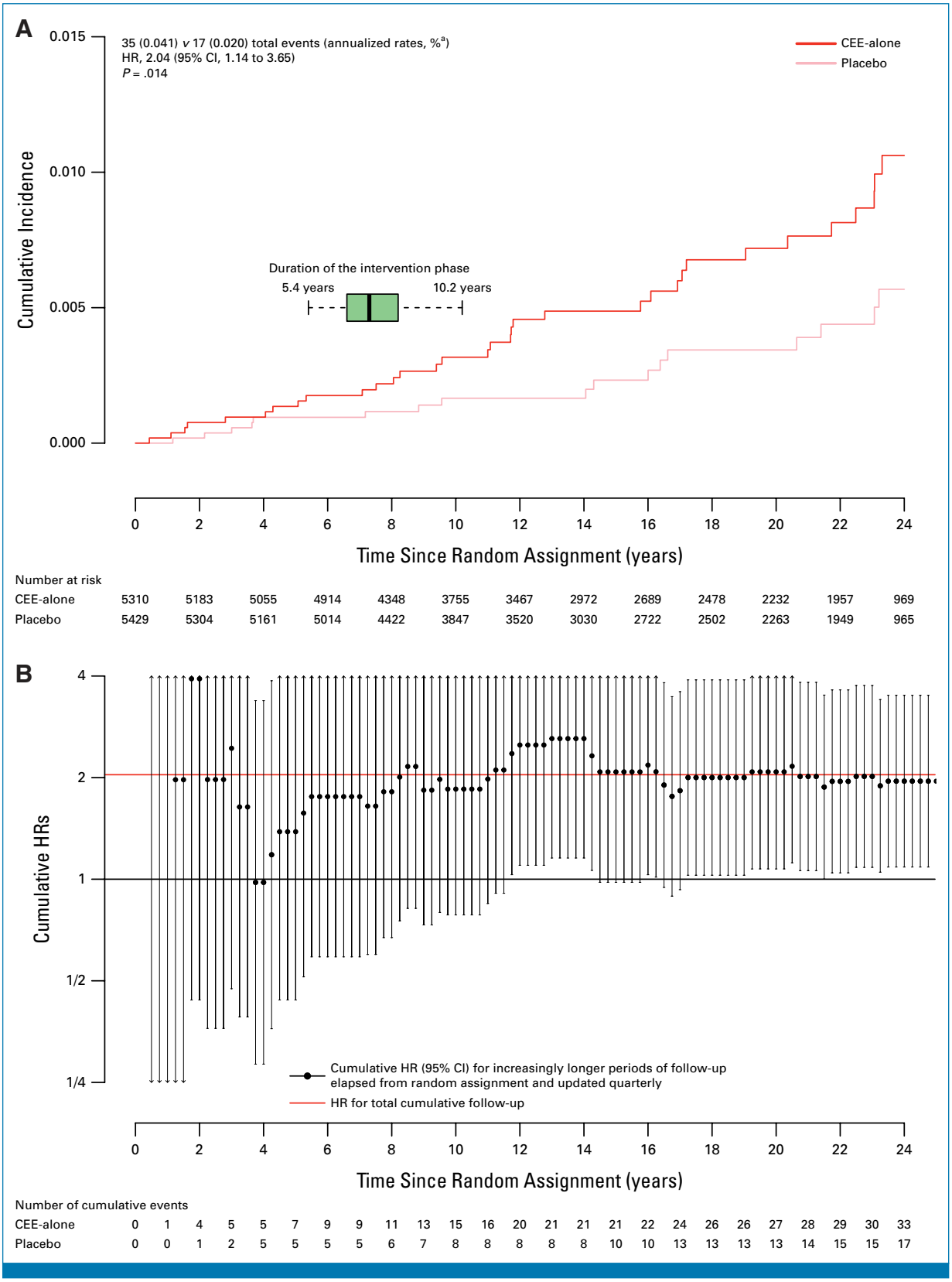

FIG 3. (A) Kaplan-Meier estimates, complemented by cumulative hazard ratios, for ovarian cancer in the CEE-alone trial. (B) Cumulative HRs (95% CI) were computed under the proportional hazards assumption, using increasingly longer cumulative follow-up elapsed from random assignment; Cox regression model was stratified by age group, randomization status in the dietary trial, previous history of ovarian cancer, and study phase (time-dependent). For example, if the trial had ended after only 3 years of follow-up, the resulting HR (95% CI), 2.44 (0.47 to 12.60) for five versus two events. The red reference (continued on following page)

FIG 3. (Continued). line indicates the estimated HR, 2.04 for total cumulative follow-up, and is essentially a weighted average of period-specific HR (95% CI), 2.01 (0.75 to 5.35), 2.91 (0.79 to 10.76), and 1.73 (0.72 to 4.15) for the intervention, early post-intervention (study, extension-1), and late postintervention (extension-2) periods, respectively. There was no evidence against proportionality (P = .92). [a]Annualized rates were calculated by dividing the total number of events by total follow-up time in years and expressed as a percentage. CEE, conjugated equine estrogen; HR, hazard ratio.

assignment including deaths after ovarian cancer and deaths after endometrial cancer, which used methodology developed by Prentice,[26] a special case of bivariate failure.[27]

Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc) and R software version 4.1 (R Foundation for Statistical Computing[28]; R-packages survival).

RESULTS

Baseline characteristics were balanced between randomization groups in both trials (Table 1). Although participants were similar in age, CEE-alone trial participants were more likely to be Black women, be obese, report previous hormone therapy use, and more commonly had bilateral oophorectomy than women in the CEE plus MPA trial.

Participant flow in both trials is outlined in Figure 1. Cumulative follow-up for mortality was a median of 23.0 years (IQR, 17.3-24.3 years). Follow-up for cancer incidence after 2005 required participant reconsent and had shorter cumulative median follow-up of 16.3 years (IQR, 9.1-23.5 years) for the CEE-alone trial and 19.4 years (IQR, 10.5-23.7 years) for the CEE plus MPA trial. Participants who provided consent to extended follow-up beyond September 30, 2010, had a cumulative median follow-up of 23.4 years (IQR, 21.1-24.4).

Hormone therapy associations with ovarian and endometrial cancers during cumulative follow-up are displayed in Figure 2. Use of CEE alone, compared with placebo, was associated with statistically significantly higher ovarian cancer incidence through cumulative follow-up (35 total events [0.041%, annualized %] *v* 17 [0.020%]; HR, 2.04 [95% CI, 1.14 to 3.65]; P = .01; Fig 3); tumor characteristics (histology, stage and grade) were descriptively summarized as events were limited (Appendix Table A1, online only). CEE-alone also significantly increased ovarian cancer mortality (HR, 2.79 [95% CI, 1.30 to 5.99]; P = .006) and deaths after ovarian cancer (Fig 2). KM estimates and cumulative HRs indicate a persistent effect of CEE-alone on ovarian cancer incidence that emerged after 12 years of follow-up and did not diminish (Fig 3).

By contrast, CEE plus MPA use, compared with placebo, was not associated with a statistically significantly higher ovarian cancer incidence through cumulative follow-up (75 cases [0.051%] *v* 63 [0.045%]; HR, 1.14 [95% CI, 0.82 to 1.59]; P = .44; Figs 2 and 4). Endometrial cancer characteristics are described in the Appendix (Table A2). Associations of hormone therapy with ovarian cancer by baseline subgroups and tumor characteristics are depicted in the Appendix (Fig A1), CEE plus MPA use, compared with placebo, was associated with statistically significantly lower endometrial cancer incidence through cumulative follow-up (106 cases [0.073%] *v* 140 [0.10%]; HR, 0.72 [95% CI, 0.56 to 0.92]; P = .01; Fig 5). CEE plus MPA also significantly decreased deaths after endometrial cancer, but not endometrial cancer mortality (Fig 2). KM estimates and cumulative HRs indicate a persistent effect that emerged after 10 years of follow-up and did not diminish (Fig 5).

Although bilateral oophorectomy history was uncommon for CEE plus MPA trial participants (n = 53; Table 1), nearly 38% (n = 4,049) of CEE-alone participants reported bilateral oophorectomy history. However, excluding participants with previous bilateral oophorectomy provided similar results (Appendix Fig A2). Additional sensitivity analyses that excluded women who reported previous ovarian cancer, all diagnosed >10 years before study entry (n = 63 and n = 8 in the CEE-alone and CEE + MPA trials, respectively; Table 1), provided essentially identical results (Appendix Fig A3).

Consent rates for extended follow-up were previously summarized by participant characteristics for each trial, with small differences for some characteristics associated with the target cancers (age, ethnicity, race, and previous menopausal hormone therapy duration). Consent rates were higher among patients with BMI ≥35 kg/m² randomly assigned to CEE plus MPA (84.5%) than those assigned to placebo (80.2%). However, incidence HRs were similar when using inverse probability weighting to account for those not providing extended follow-up consent. Specifically, the HR for endometrial cancer changed from HR, 0.72 (95% CI, 0.56 to 0.92) to HR, 0.70 (95% CI, 0.55 to 0.91) and for ovarian cancer changed from HR, 2.04 (95% CI, 1.14 to 3.65) to 1.98 (95% CI, 1.10 to 3.57), and from HR, 1.14 (95% CI, 0.82 to 1.59) to HR, 1.14 (95% CI, 0.82 to 1.60), for the CEE-alone and CEE plus MPA trials, respectively. Mortality results were based on NDI data, so are essentially complete regardless of reconsent status.

DISCUSSION

In long-term follow-up in randomized WHI clinical trials, CEE-alone, compared with placebo, was significantly associated with higher ovarian cancer incidence and higher ovarian cancer mortality. By contrast, CEE plus MPA, compared with placebo, was not significantly associated

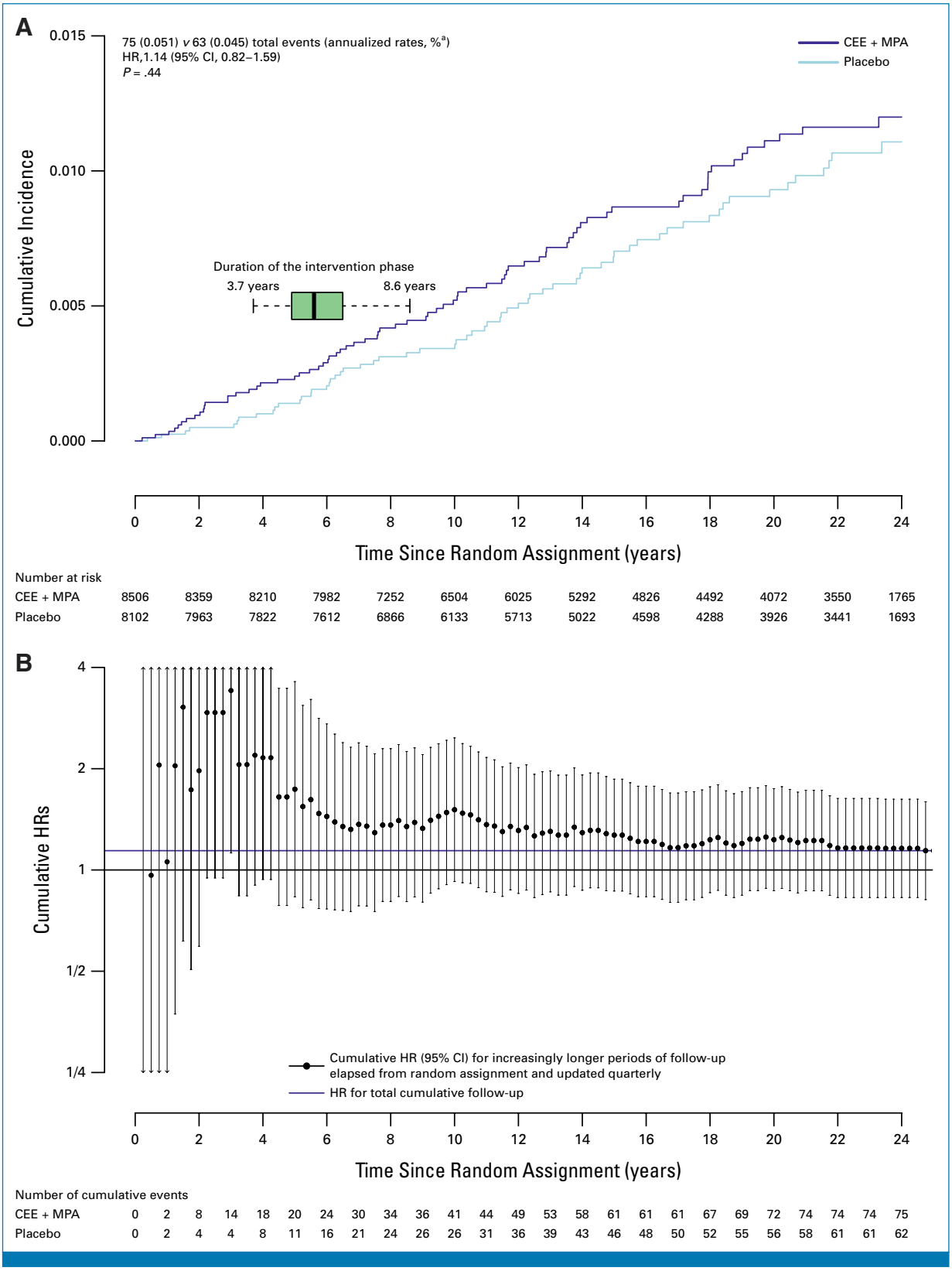

FIG 4. (A) Kaplan-Meier estimates, complemented by cumulative hazard ratios, for ovarian cancer in the CEE + MPA trial. The blue reference line indicates the estimated HR, 1.14, for total cumulative follow-up, and is essentially a weighted average of period-specific HR (95% CI), 1.41 (0.75 to 2.66), 1.14 (0.68 to 1.91), and 0.92 (0.49 to 1.72) for the intervention, early postintervention (study, extension-1), and late postintervention (extension-2) periods, respectively. There was no evidence against proportionality ($P = .13$). See the legend of Figure 3 for details. (B) Cumulative HRs (95% CI). [a]Annualized rates were calculated (continued on following page)

FIG 4. (Continued). by dividing the total number of events by total follow-up time in years and expressed as a percentage. CEE, conjugated equine estrogen; HR, hazard ratio; MPA, medroxyprogesterone acetate.

with higher ovarian cancer incidence or higher ovarian cancer mortality but was associated with significantly lower endometrial cancer incidence. The findings of CEE-alone having adverse influence on ovarian cancer incidence are consistent with most observational studies and we now add new, randomized trial information regarding CEE-alone increasing ovarian cancer mortality. The CEE plus MPA findings on endometrial cancer incidence are consistent with observational studies. By contrast, although observational studies generally associate combined hormone therapy use with higher ovarian cancer incidence and ovarian cancer mortality,[5,6] CEE plus MPA use in the WHI randomized trial did not significantly increase ovarian cancer incidence or ovarian cancer mortality.

Regarding ovarian cancer, in the WHI randomized, placebo-controlled trial, CEE-alone, in women with previous hysterectomy, significantly increased ovarian cancer incidence and significantly increased ovarian cancer mortality. The current report does not provide evidence for CEE plus MPA adverse effects on ovarian cancer incidence or mortality.

The value of providing cumulative hazards presentations is seen when considering CEE-alone and ovarian cancer incidence. In a series of cumulative HRs, for increasingly longer periods elapsed from random assignment, a HR of about 2 was seen after 8 years of cumulative follow-up, with statistical significance emerging after 12 years of cumulative follow-up, with significance persisting for more than a decade.

Now, after 20 years, with more total endometrial cancers (246 *v* 164[14,15]), the evidence for an association of significantly lower endometrial cancer risk with CEE plus MPA use is even stronger. The effect of MPA addition to CEE reducing, rather than simply mitigating, the adverse influence of exogenous estrogen on endometrial cancer suggests additional MPA effects on risk related to endogenous estrogen levels as well.

With respect to women's cancers, WHI randomized trial findings are discordant from cohort studies in several areas. The majority of cohort studies report estrogen plus progestin increases ovarian cancer incidence,[5,6] which was not seen in the WHI randomized trial. Cohort studies associate estrogen-alone with higher breast cancer incidence[29] and breast cancer mortality,[30] while in the WHI randomized trial, estrogen-alone significantly reduced breast cancer incidence and breast cancer mortality.[20] There are differences comparing cohort studies to randomized trials. In the cohort studies, women chose to either use hormone therapy or not, and use duration is commonly based on personal reports. In addition, selection bias can result in depletion of susceptible women with early cancer outcome, and those with intolerant side effects result in women excluded from findings for 5- or 10-year users. Thus, observational study findings are not easily compared with randomized trials involving women neutral to hormone use who were randomly assigned, in a double-blind process, to hormones or placebo. Cancer incidence and mortality findings are based on central medical record review, reported regardless of tolerance or compliance to study medications.

In 2002, when adverse health events were reported with CEE plus MPA in the WHI randomized trial,[17] a sharp, sustained decrease in menopausal hormone therapy occurred in the United States,[31] followed by a substantial decrease in breast cancer incidence.[32] In the CEE plus MPA trial, after intervention was abruptly ended, breast cancer incidence rapidly declined, but only in the intervention and not in the placebo group,[33] which supported a link between combined hormone use and breast cancer incidence. Further support was provided by 40-year trends in breast cancer incidence and hormone therapy use.[34] With respect to ovarian and endometrial cancers, the decrease in hormone therapy use beginning in 2002 has also been associated with a subsequent lower ovarian cancer incidence[35] and a higher endometrial cancer incidence.[36] These real-world findings support the WHI randomized clinical trial evidence whether they agree or disagree with the observational study results.

The current findings regarding CEE plus MPA effects on ovarian cancer are neutral and those on endometrial cancer are favorable. However, there are other considerations regarding estrogen plus progestin use. CEE plus MPA use increases breast density,[37] abnormal mammogram frequency, delays breast cancer detection,[38,39] significantly increases breast cancer incidence through 20 years,[20] and increases breast cancer mortality through 11 years ($P = .049$).[40] In addition, women required more endometrial biopsies (33% *v* 6%; $P < .001$) and diagnostic ultrasound examinations (13% *v* 4%; $P < .001$)[16] largely related to vaginal bleeding.

The role of endogenous estrogens compared with exogenous estrogens on women's cancers are complex.[41,42] A recent study found higher level of endogenous 17beta-estradiol (E2), the most potent estrogen, associated with higher risk of endometrial cancer, breast cancer, and endometroid ovarian cancer.[43] In the WHI randomized trials, while CEE-alone significantly increased ovarian cancer, CEE-alone significantly reduced breast cancer.[20] Thus, cancer associations with endogenous estrogens levels do not reliably predict cancer associations with exogenous estrogen use.

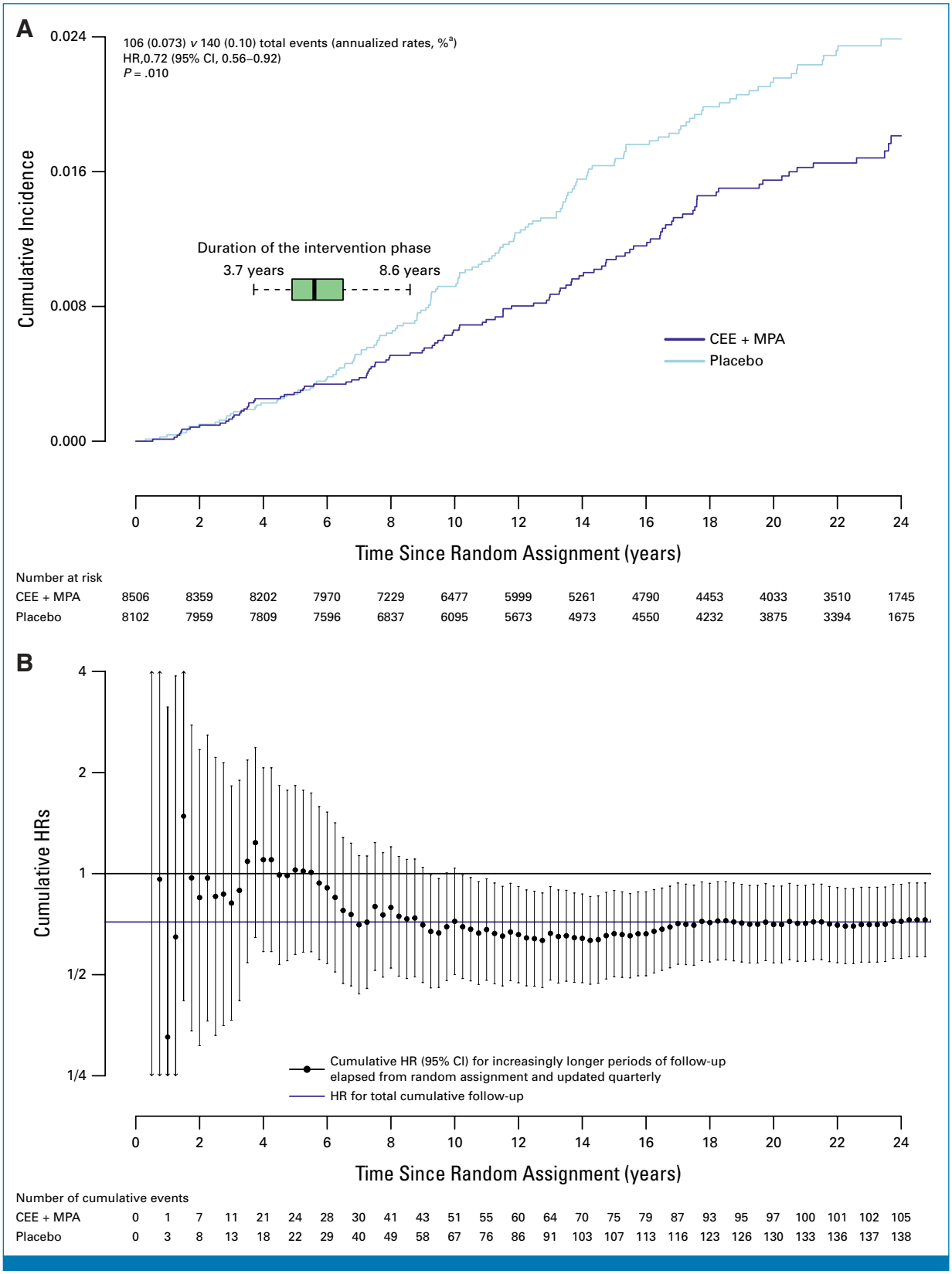

FIG 5. (A) Kaplan-Meier estimates, complemented by cumulative HRs, for endometrial cancer in the CEE + MPA trial. Cox regression model was stratified by age group, randomization status in the dietary trial, and study phase (time-dependent). The blue reference line indicates the estimated HR, 0.72, for total cumulative follow-up, and is essentially a weighted average of period-specific HR (95% CI), 0.83 (0.49 to 1.40), 0.57 (0.39 to 0.83), and 0.89 (0.57 to 1.39) for the intervention, early postintervention (study, extension-1), and late postintervention (extension-2) periods, respectively. There was no evidence against proportionality ($P = .80$). See the legend of Figure 3 for additional details. (B) Cumulative HRs (95% CI). [a]Annualized rates were calculated (continued on following page)

FIG 5. (Continued). by dividing the total number of events by total follow-up time in years and expressed as a percentage. CEE, conjugated equine estrogen; HR, hazard ratio; MPA, medroxyprogesterone acetate.

A number of recent observational studies have suggested that menopausal hormone therapy users before diagnosis of ovarian cancer have longer survival compared with those not using hormone therapy.[44-46] A Society of Gynecologic Oncology clinical practice statement concluded that despite a lack of level I evidence, the risk/benefit profile of hormone therapy appears favorable in many women with a history of high-grade serous ovarian cancer.[47] It is unclear how the WHI findings, which suggest that CEE-alone has an adverse influence on ovarian cancer in postmenopausal women, relate to younger premenopausal ovarian cancer survivors. However, in both the WHI randomized trial and in ovarian cancer survivors' status after oophorectomy, estrogen-alone is used in a low-estrogen environment. As short-term consequences of an ovarian cancer recurrence are grave, perhaps reconsideration of the evidence regarding general recommendation of estrogen-alone use in ovarian cancer survivors should be considered.

Study strengths include randomized, placebo-controlled designs, the large study populations with racial and ethnic diversity, long-term follow-up, and central cancer adjudication. A unique strength underlying the endometrial cancer outcomes is the entry requirement of no pathologic finding on clinical center examinations. Information on ovarian cancer and endometrial cancer mortality was enhanced by serial National Death Index queries.

This study has limitations. First, although endometrial cancer and ovarian cancer were specified secondary study outcomes,[48] long-term postintervention follow-up was not. In any event, limitations include those associated with secondary analyses. Second, use of two formulations, CEE-alone or CEE plus MPA, was evaluated. Although findings only apply to these agents, long-term randomized clinical trial findings for these cancers are not available for other hormone therapy formulations. Third, information on cancer recurrences or cancer therapy was not available. However, WHI participants commonly had health insurance, so access to appropriate cancer management would not be limited.

In conclusion, in randomized clinical trial settings, CEE-alone, in women with previous hysterectomy, increased ovarian cancer incidence and increased ovarian cancer mortality, while CEE plus MPA, in women with a uterus, in contrast to most observational studies, did not. However, CEE plus MPA reduced endometrial cancer incidence. These findings inform decisions regarding menopausal hormone therapy use.

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CLINICAL TRIAL INFORMATION

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DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at https://doi.org/10.1200/JCO.23.01918. The following data will be made available beginning July 1, 2025: the identified participant data and data dictionary (information about data sharing for the Women's Health Initiative can be found at: https://www.whi.org/doc/WHI-Data-Sharing-Statement.pdf). For these analyses, data will be publicly available 2 years after publication of this article. The following supporting documents are available: statistical/analytical and informed consent form https://www.whi.org/protocols-and-study-consents. The

study protocol and amendments for extended follow-up are found at the link below. https://www.whi.org/protocols-and-study-consents.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Menopausal Hormone Therapy and Ovarian and Endometrial Cancers: Long-Term Follow-Up of the Women's Health Initiative Randomized Trials

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No other potential conflicts of interest were reported.

APPENDIX

CEE-Alone Trial (n = 10,739) Clinical Outcome	Total Events (annualized rate, %[a]) CEE-Alone	Placebo	Diff/ 10K[b]	HR (95% CI)	P
Ovarian cancer	35 (0.041)	17 (0.020)	2	2.04 (1.14 to 3.65)	.014
Previous HT use					.79
Never	21 (0.048)	9 (0.021)	3	2.21 (1.01 to 4.83)	
Past	7 (0.023)	5 (0.016)	1	1.51 (0.48 to 4.78)	
Current	7 (0.058)	3 (0.023)	3	2.76 (0.69 to 11.08)	
Previous HT duration					.80
Never	21 (0.048)	9 (0.021)	3	2.21 (1.01 to 4.83)	
<5 years	3 (0.014)	3 (0.013)	0	1.22 (0.24 to 6.10)	
≥5 years	11 (0.055)	5 (0.024)	3	2.18 (0.76 to 6.30)	
Tumor histology[c]					.96
Serous	13 (0.015)	6 (0.007)	1	2.13 (0.81 to 5.61)	
Other	19 (0.022)	10 (0.011)	1	1.92 (0.89 to 4.13)	
Death only	3 (0.004)	1 (0.001)	0	2.67 (0.27 to 26.33)	
CEE + MPA Trial (n = 16,608) Clinical Outcome	**Total Events (annualized rate, %[a]) CEE+MPA**	**Placebo**	**Diff/ 10K[b]**	**HR (95% CI)**	***P***
Ovarian cancer	75 (0.051)	63 (0.045)	**1**	1.14 (0.82 to 1.59)	.44
Previous HT use					.46
Never	51 (0.048)	44 (0.043)	0	1.11 (0.74 to 1.66)	
Past	21 (0.073)	13 (0.048)	3	1.60 (0.80 to 3.21)	
Current	3 (0.028)	5 (0.053)	−2	0.64 (0.15 to 2.67)	
Previous HT duration					.82
Never	51 (0.048)	44 (0.043)	0	1.11 (0.74 to 1.66)	
<5 years	15 (0.055)	11 (0.043)	1	1.45 (0.66 to 3.16)	
≥5 years	9 (0.074)	8 (0.074)	0	1.04 (0.40 to 2.70)	
Tumor histology[c]					.23
Serous	32 (0.022)	21 (0.015)	1	1.46 (0.84 to 2.53)	
Other	31 (0.021)	35 (0.025)	0	0.84 (0.52 to 1.37)	
Death only	12 (0.008)	7 (0.005)	0	1.68 (0.66 to 4.26)	

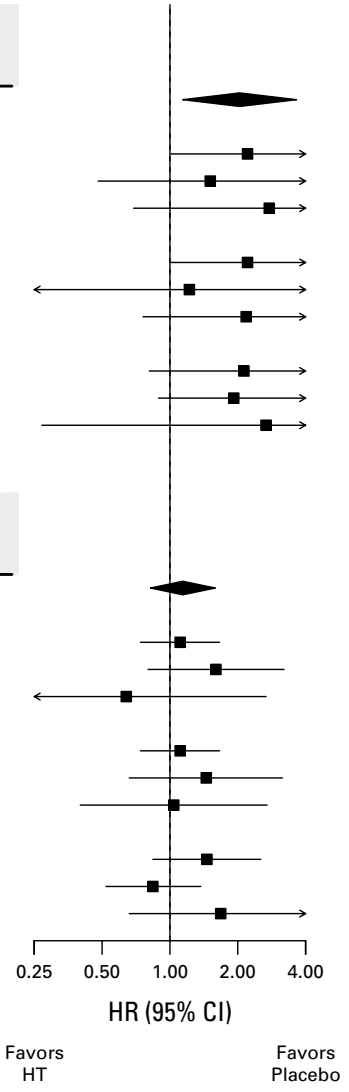

FIG A1. Association of hormone therapy with ovarian cancer by baseline subgroups and tumor characteristics during cumulative follow-up. [a]Annualized percentages were calculated by dividing the total number of events by total follow-up time in years. [b]Difference in estimated absolute excess risks (HT minus placebo) for 10,000 person-years. [c]Due to the limited number of cases, tumor histology was categorized as serous (serous papillary cystadenocarcinoma, or serous cystadenocarcinoma, not otherwise specified), other histology, or whether ascertainment of ovarian cancer was exclusively based on report of death. CEE, conjugated equine estrogen; HR, hazard ratio; HT, menopausal hormone therapy; MPA, medroxyprogesterone acetate.

CEE-Alone Trial (n = 6,690[a]) Clinical Outcome	Total Events (annualized rate, %[b]) CEE-Alone	Placebo	Diff/ 10K[c]	HR (95% CI)	*P*
Ovarian cancer	30 (0.055)	15 (0.028)	3	1.94 (1.04 to 3.62)	.03
Ovarian cancer mortality	23 (0.034)	7 (0.011)	2	3.22 (1.38 to 7.51)	
Death after ovarian cancer	27 (0.050)	10 (0.019)	3	2.64 (1.28 to 5.47)	
CEE + MPA Trial (n = 16,555[a]) Clinical Outcome	**Total Events (annualized rate, %[b]) CEE + MPA**	**Placebo**	**Diff/ 10K[c]**	**HR(95%CI)**	***P***
Ovarian cancer	75 (0.052)	63 (0.046)	1	1.14 (0.82 to 1.60)	.44
Ovarian cancer mortality	65 (0.038)	52 (0.032)	1	1.21 (0.84 to 1.74)	
Death after ovarian cancer	68 (0.047)	48 (0.035)	1	1.37 (0.95 to 1.98)	
Endometrial cancer	105 (0.073)	140 (0.10)	–3	0.71 (0.55 to 0.92)	.008
Endometrial cancer mortality	13 (0.008)	21 (0.013)	–1	0.58 (0.29 to 1.16)	
Death after endometrial cancer	50 (0.034)	72 (0.052)	–2	0.67 (0.47 to 0.96)	

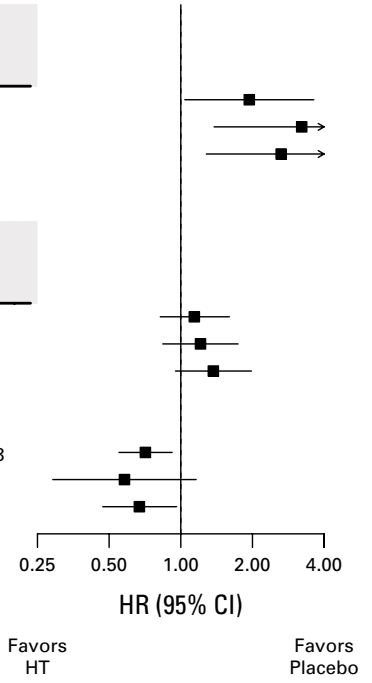

FIG A2. Sensitivity analysis that excluded participants who reported having had a bilateral oophorectomy at baseline. [a]There were 4,049 and 53 participants excluded in the CEE-alone and CEE+MPA trials, respectively. [b]Annualized percentages were calculated by dividing the total number of events by total follow-up time in years. [c]Difference in estimated absolute excess risks (HT minus placebo) for 10,000 person-years. CEE, conjugated equine estrogen; HR, hazard ratio; HT, menopausal hormone therapy; MPA, medroxyprogesterone acetate.

CEE-Alone Trial (n = 10,676[a]) Clinical Outcome	Total Events (annualized rate, %[b]) CEE-Alone	Placebo	Diff/ 10K[c]	HR (95% CI)	*P*
Ovarian cancer	35 (0.041)	17 (0.020)	2	2.04 (1.14 to 3.65)	.014
Ovarian cancer mortality	25 (0.024)	9 (0.008)	2	2.79 (1.30 to 5.99)	
Death after ovarian cancer	30 (0.035)	12 (0.014)	2	2.47 (1.26 to 4.84)	
CEE + MPA Trial (n = 16,600[a]) Clinical Outcome	**Total Events (annualized rate, %[b]) CEE + MPA**	**Placebo**	**Diff/ 10K[c]**	**HR(95%CI)**	***P***
Ovarian cancer	75 (0.051)	63 (0.045)	1	1.14 (0.82 to 1.59)	.44
Ovarian cancer mortality	65 (0.037)	52 (0.031)	1	1.21 (0.84 to 1.74)	
Death after ovarian cancer	68 (0.047)	48 (0.035)	1	1.37 (0.95 to 1.98)	
Endometrial cancer	106 (0.073)	140 (0.10)	−3	0.72 (0.56 to 0.92)	.010
Endometrial cancer mortality	13 (0.007)	21 (0.013)	−1	0.58 (0.29 to 1.16)	
Death after endometrial cancer	51 (0.035)	72 (0.052)	−2	0.68 (0.47 to 0.97)	

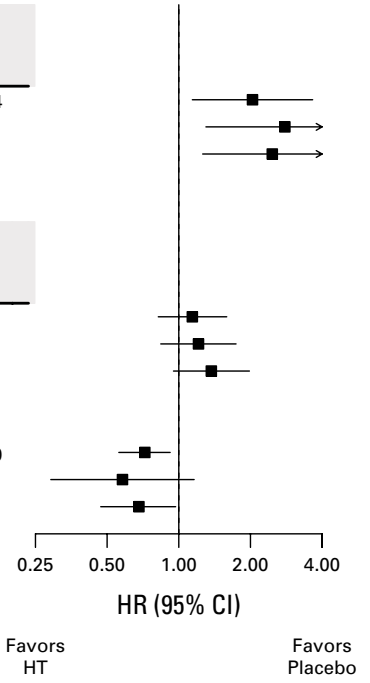

FIG A3. Sensitivity analysis that excluded participants who reported history of ovarian cancer at baseline. [a]There were 63 and 8 participants excluded in the CEE-alone and CEE+MPA trials, respectively. [b]Annualized percentages were calculated by dividing the total number of events by total follow-up time in years. [c]Difference in estimated absolute excess risks (HT minus placebo) for 10,000 person-years. CEE, conjugated equine estrogen; HR, hazard ratio; HT, menopausal hormone therapy; MPA, medroxyprogesterone acetate.

TABLE A1. Distribution of Tumor Characteristics for Ovarian Cancers by Randomization Group

	CEE-Alone Trial (n = 52[a]), No. (%)		CEE + MPA Trial (n = 138[a]), No. (%)	
Tumor Characteristic	CEE-Alone (n = 35)	Placebo (n = 17)	CEE + MPA (n = 75)	Placebo (n = 63)
Tumor characteristics available[a]	32 (91.4)	16 (94.1)	63 (84.0)	56 (88.9)
Histology[b,c]				
Serous papillary cystadenocarcinoma	8 (25.0)	4 (25.0)	19 (30.2)	12 (21.4)
Serous cystadenocarcinoma, NOS	5 (15.6)	2 (12.5)	13 (20.6)	9 (16.1)
Adenocarcinoma, NOS	6 (18.8)	1 (6.3)	8 (12.7)	4 (7.1)
Endometrioid carcinoma	3 (9.4)	1 (6.3)	3 (4.8)	5 (8.9)
Carcinoma, NOS	1 (3.1)	1 (6.3)	0	8 (14.3)
Mucous adenocarcinoma	2 (6.3)	1 (6.3)	1 (1.6)	3 (5.4)
Neoplasm malignant	1 (3.1)	0	3 (4.8)	3 (5.4)
Clear cell adenocarcinoma, NOS	0	0	2 (3.2)	3 (5.4)
Mucinous cystic tumor-borderline malignancy	0	1 (6.3)	3 (4.8)	1 (1.8)
Serous papillary cystic tumor-borderline malignancy	2 (6.3)	0	0	2 (3.6)
Other, specified	4 (12.5)	5 (31.3)	10 (15.9)	6 (10.7)
Unknown/not done/missing	0	0	1 (1.6)	0
Stage[c]				
Local	4 (12.5)	3 (18.8)	10 (15.9)	10 (17.9)
Regional	4 (12.5)	1 (6.3)	9 (14.3)	8 (14.3)
Distant	24 (75.0)	12 (75.0)	43 (68.3)	38 (67.9)
Unknown/not done/missing	0	0	1 (1.6)	0
Grade[c]				
Well differentiated	0	2 (12.5)	0	3 (5.4)
Moderately differentiated	2 (6.3)	2 (12.5)	8 (12.7)	7 (12.5)
Poorly differentiated	19 (59.4)	4 (25.0)	20 (31.7)	22 (39.3)
Unknown/not done/missing	11 (34.4)	8 (50.0)	35 (55.6)	24 (42.9)

Abbreviations: CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate; NOS, not otherwise specified.

[a]Tumor characteristics were not available for n = 4 (7.7%) participants in the CEE-alone trial (three CEE *v* one placebo; 8.6 *v* 5.9%) as ascertainment and adjudication of ovarian cancer was exclusively on the basis of report of death. Likewise, tumor characteristics were not available and exclusively on the basis of report of death for n = 19 participants in the CEE + MPA trial (12 CEE + MPA *v* seven placebo; 16.0 *v* 11.1%). Availability did not statistically differ between randomization groups for the CEE-alone trial ($P > .99$) or CEE + MPA trial ($P = .46$); *P* values based on Fisher's exact test.

[b]Histologic classifications with overall frequency >2% are separately shown in decreasing order; other, specified combined remaining classifications.

[c]Excludes participants whose ascertainment and adjudication of ovarian cancer was exclusively on the basis of report of death as data were 100% missing.

TABLE A2. Distribution of Tumor Characteristics for Endometrial Cancers by Randomization Group

	CEE + MPA Trial (N = 246)	
Tumor Characteristic	CEE + MPA (n = 106[a])	Placebo (n = 140[a])
Tumor characteristics available[a]	106 (100.0)	140 (100.0)
Histology[b]		
Endometrioid carcinoma	58 (54.7)	93 (66.4)
Adenocarcinoma, NOS	22 (20.8)	13 (9.3)
Serous cystadenocarcinoma, NOS	7 (6.6)	4 (2.9)
Mullerian mixed tumor	6 (5.7)	2 (1.4)
Carcinosarcoma, NOS	1 (0.9)	6 (4.3)
Clear cell adenocarcinoma, NOS	0	7 (5.0)
Other, specified	12 (11.3)	15 (10.7)
Stage		
In situ	1 (0.9)	0
Local	85 (80.2)	100 (71.4)
Regional	14 (13.2)	30 (21.4)
Distant	5 (4.7)	10 (7.1)
Unknown/not done/missing	1 (0.9)	0
Grade		
Well differentiated	22 (20.8)	21 (15.0)
Moderately differentiated	40 (37.7)	51 (36.4)
Poorly differentiated	39 (36.8)	62 (44.3)
Unknown/not done/missing	5 (4.7)	6 (4.3)

Abbreviations: CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate; NOS, not otherwise specified.
[a]Tumor characteristics were available for all participants diagnosed with endometrial cancer
[b]Histologic classifications with overall frequency >2% are separately shown in decreasing order; other, specified combined remaining classifications.