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Comparison of Clinical Outcomes among Users of Oral and Transdermal Estrogen Therapy in the Women's Health Initiative Observational Study

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Abstract

Objective—To examine associations of estrogen preparations with an index of health risks vs. benefits.

Methods—Using data from 45,112 participants of the Women's Health Initiative Observational Study (average follow-up 5.5 years), we examined associations of estrogen type and oral conjugated equine estrogens [CEE] dose with time to first global index event [GIE], defined as coronary heart disease, breast cancer, stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer, or death.

Results—Oral CEE <0.625 mg/d + progestogen (P) users had a lower risk of a GIE (adjusted HR hazard ratio [aHR] 0.74, 95% CI 0.56–0.97) than oral CEE 0.625 mg/d + P users. GIE risk in oral CEE 0.625 mg/d + P users was greater with ≥5 years (aHR 1.22, 95% CI 1.06–1.41) than with <5 years use. In women with prior hysterectomy, compared with women taking oral CEE 0.625 mg/d for <5 years, GIE risk was similar with oral CEE <0.625 mg/d, oral E_2, and transdermal E_2, whether used for < 5 years or ≥ 5 years. There was no difference in GIE risk between users of: oral CEE + P vs. oral E_2+ P; oral CEE + P vs. transdermal E_2+ P; oral estradiol + P vs. transdermal E_2+ P. Findings were similar among women with hysterectomy taking estrogen alone.

Conclusions—The summary index of risks vs. benefits was similar for oral CEE- versus oral or transdermal E_2-containing regimens. CEE + P containing less than 0.625 mg/d of CEE (vs. 0.625 mg/d) for <5 years appeared safer.

Keywords

estrogen; progestogen; menopausal hormone therapy; progesterone; estradiol

Introduction

During the intervention phase of the Women's Health Initiative [WHI] Hormone Therapy (HT) Trials, the use of oral conjugated equine estrogens (CEE, 0.625mg/d without medroxyprogesterone acetate) was associated with increased risk of stroke, decreased risk of hip fracture, and, possibly, decreased risk of breast cancer, whereas the use of the same CEE regimen combined with medroxyprogesterone acetate (MPA, 2.5mg/d) was associated with

increased risk of invasive breast cancer, stroke, and pulmonary embolism, but decreased risk of colorectal cancer and hip fracture [1]. Within the first year of therapy, there was a higher risk of coronary heart disease (CHD) among women assigned to CEE + MPA [2]. However, at the time of discontinuation of both HT trials, neither CEE alone nor CEE + MPA significantly influenced all-cause mortality in the WHI HT Trials. The hazard ratio (95% confidence interval) for the global index, defined as the time to the earliest of CHD, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, endometrial cancer, hip fracture, and death from any cause, was 1.12 (1.02–1.24) for CEE + MPA vs. placebo, and 1.03 (0.93–1.13) for CEE alone vs. placebo. Although the global indices were more favorable for younger than older women who were assigned to CEE alone (p for trend by age = 0.02), there was no age subgroup that derived statistically significant reduction in global index events with either CEE alone or CEE + MPA in the intervention phases of WHI HT Trials [1].

It is possible that estrogen formulations, doses, and routes other than the oral CEE regimens used in the WHI have different balances of risks and benefits. For example, the recent American College of Obstetricians and Gynecologists opinion regarding deep vein thrombosis states that oral estrogen may exert a pro-thrombotic effect, whereas transdermal estrogen has little or no effect on pro-thrombotic markers and may have beneficial actions on pro-inflammatory markers [3]. Similarly, a systematic review concluded that compared to transdermal estrogen therapy, oral estrogen therapy may be associated with increased risk of venous thromboembolism[4]. No large-scale randomized controlled trials of transdermal HT vs. placebo (or vs. oral estrogen) have examined major clinical events such as myocardial infarction (MI), stroke, pulmonary embolism, cancer, or hip fracture. Moreover, the overall balance of risks and benefits with the use of transdermal estradiol compared to oral estradiol or oral CEE has not been previously examined. Also unknown are the potential overall risks vs. benefits of using a low-dose of CEE (0.3 or 0.45 mg daily) or oral estradiol instead of a conventional (0.625 mg daily) CEE dose. Further scrutiny of the overall health effects of the various types and routes of menopausal HT is important, especially for women with elevated baseline health risks, including obesity, diabetes mellitus, or cardiovascular disease (CVD).

It is highly unlikely that a trial that is as large in scale as the WHI HT Trials will be conducted to perform head-to-head comparisons of the effects of transdermal estradiol, oral estradiol, low-dose CEE, and traditional-dose CEE. However, the longitudinal WHI Observational Study (WHI-OS) data provide a unique opportunity to compare clinical outcomes in a large cohort of postmenopausal women using various HT regimens. The WHI HT trials developed a global event index (GIE) as a summary index of risks vs. benefits of clinical outcomes of HT [2]. In the current report, using WHI-OS data, we used the same index to compare the risk of a global index event according to HT type (oral CEE, oral estradiol, or transdermal estradiol), duration, and CEE dose.

Methods

The Women's Health Initiative (WHI) Study

Between the years 1993 and 1998, the WHI enrolled 161,808 postmenopausal women aged 50–79 years at 40 clinical centers. WHI Extension Study I continued annual follow-up for an

additional five years (2005–2010) among the 76% of participants who were alive and consented. Mean (standard deviation) follow-up duration was 5.5 (2.8) years during HT use; for the CEE dose comparison analyses, mean follow-up duration was 4.2 (1.7) years. The institutional review boards of each participating institution approved the study protocol. Each study participant provided written informed consent

The WHI Observational Study (WHI-OS), a subset of the WHI, was designed to examine important causes of morbidity and mortality in postmenopausal women [5, 6]. 93,676 participants enrolled in the WHI-OS. To ensure that HT use preceded the medical outcomes of interest, we excluded data from 1) participants who had prevalent medical conditions prior to enrollment (MI in past 6 months, any past history of deep vein thrombosis or pulmonary embolism, any past history of breast cancer or endometrial cancer, and any invasive cancer within 10 years prior to enrollment) (n= 11,450); 2) participants who did not provide information regarding HT use or hysterectomy status (n=454) at baseline (n=461); and 3) participants who did not provide follow-up data (n = 473) (Figure 1). 88,824 participants provided complete information regarding HT use during follow-up and were free of prevalent exclusionary medical conditions. Because this study is focused on women who used HT, we excluded data from the 34,637 women who had never used HT, and excluded data from the 1,075 women who had used HT regimens that do not reflect usual clinical practice (i.e. estrogen alone with intact uterus or estrogen + progestogen [P] therapy after hysterectomy). Therefore, our final analytic sample was composed of 45,112 participants who reported use of oral CEE, oral estradiol, or transdermal estrogen, with or without progestogen. Some women underwent hysterectomy before study enrollment or during the study follow-up; the analytic sample of 45,112 women included 22,311 participants with intact uterus throughout the study, and 23,505 participants who had undergone hysterectomy before baseline or during study follow-up.

For analyses that examined HT dosage, the sample size was 21,914 participants with intact uterus and 22,660 participants with prior hysterectomy who provided information regarding HT dosage.

Outcome: Global Index Event

We defined the global index event (GIE) as the time to first occurrence of CHD (nonfatal MI or CHD death), invasive breast cancer, stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer, or death from any cause through the end of WHI Extension I [2]. (See Supplement for details of outcome ascertainment).

Main predictor: HT Type and CEE Dose

Questionnaire items assessed HT usage patterns at baseline and annual visits 3 through 8. Questionnaire items assessed whether participants had used estrogen with or without progestogen since the last questionnaire, the type of preparation (e.g. estradiol, CEE), and the route of administration (oral, transdermal) (Supplement eTables 1–4). We could not compare progestogen types and doses because of the wording of the questionnaire items.

Other measurements

Baseline questionnaires were used to collect information regarding demographic information, smoking, physical activity level, alcohol intake, medication use, and medical, family, reproductive, and surgical histories. Gail breast cancer risk score was calculated for each participant [7].

Blood pressure, height, and weight were directly measured at baseline. Body mass index (BMI) was calculated as body weight in kilograms (kg) divided by the square of height in meters.

Statistical analysis

We used Cox proportional hazards models stratified by 5-year age intervals to examine associations between HT type, route, and duration and risk of GIE. HT use was time-varying. Follow-up time was calculated from the start of HT use to the date of the first event (among the events included in the GIE), or last available follow-up visit, or end of study follow-up period (2.5 years after last report of HT use), whichever occurred first.

We grouped participants into two groups based on whether they had undergone prior hysterectomy. For women with prior hysterectomy, the main potential predictors were time-varying exposure to transdermal estradiol (patch) alone, oral estradiol alone, or oral CEE alone (reference). For women with an intact uterus, the main potential predictors were time-varying exposure to transdermal estradiol + progestogen (P), oral estradiol + P, and oral CEE + P (reference).

In dose comparison analyses, the main potential predictors for women with prior hysterectomy were oral high-dose CEE (>0.625 mg/d) alone, low-dose oral CEE (<0.625 mg/d) alone, oral estradiol alone, and transdermal estradiol alone, and conventional-dose oral CEE (0.625 mg/d, reference). For women an intact uterus, the main potential predictors were oral high-dose CEE (>0.625 mg/d) + P, low-dose oral CEE (<0.625 mg/d) + P, oral estradiol + P, and transdermal estradiol + P, vs. conventional-dose CEE) and conventional-dose oral CEE+P (reference).

We adjusted the regression models for covariates assessed on baseline questionnaires: age (linear), race/ethnicity (Black or African-American, Hispanic/Latino, non-Hispanic white, other/unknown), education (high school or less, some college, college degree or higher), income (<$10,000, $10,000 to $19,999, $20,000 to $34,999, $35,000 to $49,999, $50,000 to $74,999, $75,000 to $99,999, $100,000 to $149,999, ≥ $150,000), smoking (never, former, current), BMI, physical activity (metabolic equivalent of task [MET] hours/week), alcohol (servings/week), diabetes mellitus, systolic blood pressure, diastolic blood pressure, aspirin, statins, history of CVD (MI, stroke, or revascularization), history of cancer, Gail breast cancer risk score, family history of breast cancer, age at menopause, age at first birth, and bilateral oophorectomy.

We stratified our results by <5 years vs. ≥5 years duration of HT use [8], age at time of HT initiation (<60 years, 60–69 years, and ≥70 years) [9], years since menopause, and BMI.

Because prior studies have reported differences in breast cancer and venous thromboembolism in users of oral vs. transdermal estradiol, we decided *a priori* to determine whether exclusion of breast cancer and pulmonary embolism from the GIE calculation accentuated the differences in the GIE risk across preparations. In additional sensitivity analyses, we excluded participants who reported a history of stroke or colorectal cancer prior to the WHI baseline visit.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

On average, participants were 62 years-old and the mean duration of follow-up was 8.6 years (average HT duration 5.5 years). Characteristics of the participants using oral CEE-containing regimens were similar to those using oral or transdermal regimens (Table 1). Compared with oral CEE + P users, a higher proportion of oral and transdermal estradiol + P users were younger (aged <60 years) and leaner (BMI < 35 kg/m^2). Specifically, a higher proportion of oral estradiol + P (78%) and transdermal estradiol + P users (80%) than oral CEE + P users (68%) were aged <60 years; this pattern was similar in women with prior hysterectomy. Also, compared with oral CEE + P users (50%), a higher proportion of oral estradiol + P users (56%) and transdermal estradiol + P users (56%) had BMI <25 kg/m^2. Statin use, self-reported diabetes (treated with medication), antihypertensive medication use, and aspirin use were slightly more frequent among CEE + P users than among oral or transdermal estradiol + P users. Absolute event rates for the individual components of the GIE are displayed in eFigure 1.

Compared with participants whose data regarding covariates was complete, those for whom some covariate data were missing were: slightly older, less likely to be white, less educated, more likely to smoke, and had lower Gail breast cancer risk scores. These differences between the two groups were all small in magnitude (data not shown).

HT type and risk of GIE

In women with an intact uterus using estrogen with progestogen, the risk of a GIE was not statistically significantly different in oral estradiol + P users or in transdermal estradiol + P users compared with oral CEE + P users (reference group) (Table 2). There was no difference in GIE risk between oral estradiol + P users and transdermal estradiol + P users.

In women with previous hysterectomy, compared with women taking oral CEE alone (reference), we found no significant difference in the risk of a GIE among women taking oral estradiol alone or transdermal estradiol alone (Table 2). There was also no difference in GIE risk between users of oral estradiol alone and users of transdermal estradiol alone.

HT route, CEE dose, and risk of GIE

In adjusted models, in women with an intact uterus, low-dose oral CEE + P users had a lower risk of a GIE (adjusted HR [aHR] 0.74, 95% CI 0.56–0.97) than did users of oral conventional-dose CEE + P (reference) (Table 3). After we removed breast cancer events from the GIE, the decreased GIE risk of in women taking low-dose oral CEE + P compared

with women taking conventional-dose oral CEE + P became even more pronounced (aHR 0.46, 95% CI 0.29–0.72) and was not further reduced by additional exclusion of pulmonary emboli from the GIE (eTable 5). Compared with women using conventional-dose CEE + P, GIE risk was not significantly different in women using high-dose CEE + P, transdermal estradiol + P, or oral estradiol + P (Table 3).

In women with a hysterectomy, GIE risk did not differ among women using high-dose oral CEE, oral estradiol, transdermal estradiol, or low-dose oral CEE compared with women using conventional-dose CEE (Table 3).

HT preparation, duration of use, and GIE

We examined HT duration of use and CEE dose simultaneously (Table 4). In women with an intact uterus, the risk of a GIE in conventional-dose CEE + P users was greater with ≥5 years duration (aHR 1.22, 95% CI 1.06–1.41) than with <5 years duration of use (reference). Compared with women taking conventional-dose oral CEE + P for < 5 years, the GIE risk did not differ for women taking: low-dose oral CEE + P <5 years or ≥5 years, high-dose oral CEE + P <5 years or ≥5 years, oral estradiol + P ≥5 years or ≥5 years, or transdermal estradiol + P <5 years or ≥ 5 years (Table 4).

In women with prior hysterectomy, the risk of a GIE was greater in women who used oral high-dose CEE for <5 years (aHR 1.56, 95% 1.12–2.18) than in women who used conventional-dose CEE for < 5 years (Table 4). Compared with women taking conventional-dose CEE for <5 years, GIE risk was similar in women taking conventional-dose oral CEE for ≥5 years, low-dose oral CEE for < 5 years or ≥5 years, oral estradiol for <5 years or ≥ 5 years, or transdermal estradiol for < 5 years or ≥ 5 years.

HT dose, route, and GIE by age group, baseline BMI category, and years since menopause

In women with an intact uterus <60 years, the risk of a GIE was 33% lower in women using oral estradiol + P (aHR 0.67, 95% CI 0.48–0.96) than in women using conventional-dose oral CEE + P (reference)(eTable 6). However, HRs for pairwise comparisons of HT types among users aged <60 years were similar: oral low dose CEE +P vs. oral estradiol +P aHR 1.14 (0.68–1.90); transdermal estradiol +P vs. oral estradiol +P aHR 1.10 (0.62–1.94); oral low dose CEE +P vs. transdermal estradiol +P aHR 1.03 (0.56–1.89). GIE risk was no different in users of high-dose oral CEE + P, low-dose oral CEE + P, or transdermal estradiol + P (eTable 6). In contrast, in women aged >60 years, the risk of a GIE was similar in users of conventional-dose oral CEE + P and users of other preparations.

Within users of each category of HT type, the risk of a GIE was similar in women who had BMI between 25–<30 kg/m^2 or ≥30 kg/m^2 and in women with BMI <25 kg/m^2 (eTable 7). However, among users of oral CEE + P, GIE risk was greater in women with BMI ≥30 kg/m^2 (aHR 1.21, 1.03–1.42) than in women with BMI <25 kg/m^2 (reference). Analyses of GIE stratified by years since menopause are displayed graphically in eFigure2.

Sensitivity analysis

When we excluded participants with history of any CHD, stroke, coronary revascularization or history of any cancer (including colorectal) prior to WHI study enrollment, the magnitudes of the hazard ratios were very similar to those of the primary analysis. The hazard ratio for the risk of GIE in users of low-dose CEE + progestogen was similar in magnitude but was no longer statistically significant in the sensitivity analysis: 0.74 (95% CI 0.56–0.97) in the primary analysis vs. 0.81 (HR 0.62–1.08) in the sensitivity analysis..

Discussion

In this large observational cohort of postmenopausal women (mean HT use 5.5 years). The risk of global index events varied by dose, duration, and BMI in women using CEE + P. Specifically, we found that women taking low-dose CEE + P had a 26% lower risk of a GIE than did users of conventional-dose CEE + P. Among women with intact uterus, longer duration of oral conventional-dose CEE+P use (≥5 years) was associated with 22% higher risk of a GIE than <5 years of use, but the risk with other formulations (transdermal estradiol + P, oral estradiol + P), whether <5 years or ≥5 years in duration, was similar to that of oral CEE + P for <5 years. In contrast, in women with a prior hysterectomy, compared with <5 years of oral CEE alone, the GIE risk was similar for ≥5 years of conventional-dose oral CEE alone, oral estradiol alone (≥5 years or <5 years) or transdermal estradiol alone (≥5 years or <5 years). Among users of oral CEE + P, GIE risk was greater in women with BMI ≥30 kg/m^2 (aHR 1.21, 1.03–1.42) than in women with BMI <25 kg/m^2.

In the current study, the longer duration of oral CEE+P use (≥5 years), but not oral CEE alone, was associated with a 22% higher risk of a GIE than was <5 years of use, but this was not true for oral CEE alone, where risk was similar for <5 years and ≥5 years of duration of use. Our findings are consistent with the results of the WHI randomized controlled trial of conventional-dose CEE + medroxyprogesterone acetate. In the HT trials, the global index was balanced for oral CEE alone, but was unfavorable for CEE + MPA[8, 10]. Based on the WHI HT Trial findings, the U.S. Food and Drug Administration labeling recommends that the duration of estrogens with or without progestins “should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman” [11]. Our current results for CEE + P are consistent with these recommendations.

We found that GIE risks in transdermal estradiol + P users and oral estradiol + P users were similar. As noted by Cochrane systematic reviews [12], clinical trial evidence is lacking regarding transdermal estradiol’s effects on clinical events, and the recent Cochrane systematic review on CVD reviewed only oral HT [13]. In a prior WHI-OS study, compared with oral CEE (and adjusted for progestogen use), oral estradiol was associated with 36% lower risk of stroke, and transdermal estradiol was associated with a 37% lower risk of CHD, but these differences were not statistically significant [14]. A case-control study found that both the use of transdermal estradiol ≥50 μg/d and the use of oral CEE (≤0.625 mg/d or >0.625mg/d) were associated with increased stroke risk[15]. Observational studies also suggest that, unlike oral estrogen (CEE + P and estradiol + P), transdermal estrogen is not

associated with an increased risk of venous thromboembolism, and that some types of progestogen are thrombogenic while others are not [16–24].

There are no clinical trials comparing breast cancer incidence during therapy with oral vs. transdermal estrogen preparations, and results of observational studies are not consistent [25–3027, 31–33]. Therefore, it is unclear whether breast cancer risk varies by route of estradiol administration. However, after removing breast cancer events from the GIE, we found that the decreased GIE risk in women taking low-dose oral CEE + P compared with women taking conventional-dose oral CEE + P was even more pronounced.

Limitations of our study include that we could not compare various progestogen type/dose because of the wording of questionnaire items. Most HT users were taking CEE, reflecting current clinical practice at the time that WHI was initiated. In addition, pulmonary embolism events were self-reported. We performed multiple statistical comparisons, so some of our findings may have been due to chance. Although we adjusted for multiple covariates, the observational study design has potential for survival bias and selection bias; however, a head-to-head trial to compare various HT formulations would not be feasible. Our results may not apply to low-dose oral and transdermal estradiol preparations that became available recently, after WHI began. Strengths of our study include a large cohort of postmenopausal women with longitudinal follow-up, medical record adjudication of most outcomes, and the availability of detailed information regarding important covariates.

Conclusions

In conclusion, in this study, the risks of global index outcomes were similar across the HT formulations. Our results suggest that the use of CEE at a dose of <0.625 mg/d instead of 0.625 mg/d, limiting the duration of use of CEE + P to <5 years, and avoiding the use of CEE + P in women with BMI ≥ 30 could result in fewer adverse events. We did not identify notable differences in overall risk vs. benefit in users of oral estradiol- or transdermal estradiol-containing regimens compared with users of oral CEE-containing regimens. These findings will help to inform HT clinical decision-making.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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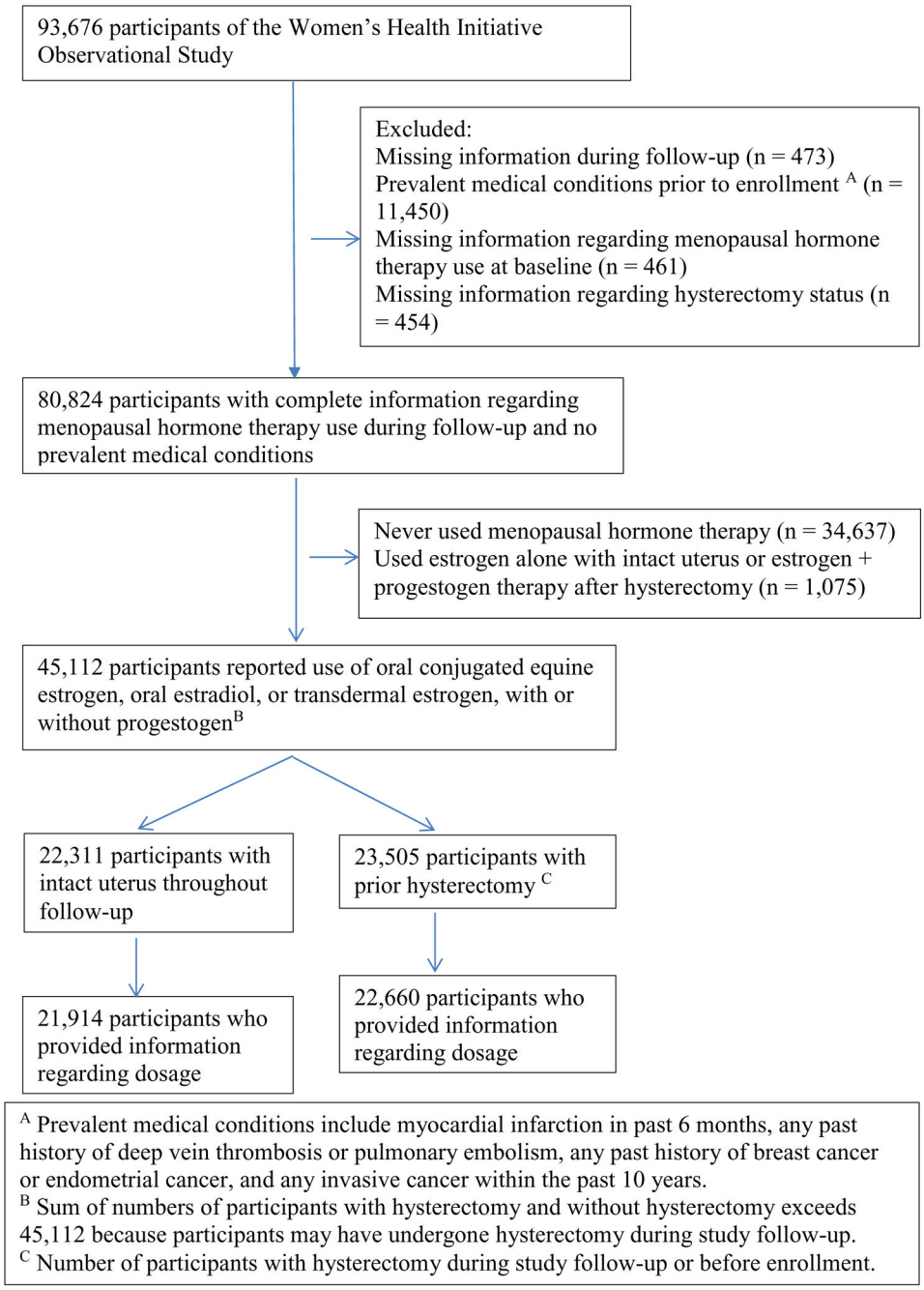

Figure 1.
Analytic Sample Flow Diagram

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Table 1

Baseline characteristics by hormone therapy formulation for those with intact uterus and those with hysterectomy, both hysterectomy and formulation allowed to change over time

	Intact Uterus			**Hysterectomy**		
	Oral CEE + P[a]	**Oral Estradiol +P**	**Transdermal estradiol +P**	**Oral CEE alone**	**Oral Estradiol alone**	**Transdermal estradiol alone**
N[b]	**20,114**	**2,843**	**1,336**	**19,413**	**3,470**	**2,753**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Age, years						
<65	13,658 (67.9)	2,229 (78.4)	1,063 (79.6)	10,783 (55.5)	2,351 (67.8)	2,052 (74.5)
65–69	3,754 (18.7)	359 (12.6)	166 (12.4)	4,498 (23.2)	603 (17.4)	433 (15.7)
70–75	2,046 (10.2)	202 (7.1)	87 (6.5)	2,996 (15.4)	377 (10.9)	216 (7.8)
≥75	656 (3.3)	53 (1.9)	20 (1.5)	1,136 (5.9)	139 (4.0)	52 (1.9)
Ethnicity						
Black or African-American	758 (3.8)	54 (1.9)	38 (2.9)	1,472 (7.6)	188 (5.4)	238 (8.7)
Hispanic/Latino	660 (3.3)	67 (2.4)	38 (2.9)	776 (4.0)	132 (3.8)	99 (3.6)
White (not of Hispanic origin)	17,597 (87.7)	2,600 (91.7)	1,214 (91.2)	16,321 (84.3)	3,009 (86.8)	2,322 (84.5)
Other/unknown	1,052 (5.2)	113 (4.0)	41 (3.1)	803 (4.1)	136 (3.9)	90 (3.3)
Education						
High school or less	2,854 (14.3)	290 (10.2)	123 (9.3)	4,147 (21.5)	636 (18.5)	434 (15.9)
Some college	6,506 (32.6)	912 (32.2)	427 (32.2)	7,696 (39.9)	1,383 (40.1)	1,130 (41.4)
College degree or higher	10,595 (53.1)	1,628 (57.5)	777 (58.6)	7,422 (38.5)	1,428 (41.4)	1,165 (42.7)
Income						
Less than $10,000	382 (2.0)	27 (1.0)	12 (0.9)	611 (3.3)	66 (2.0)	64 (2.4)
$10,000 to $19,999	1,276 (6.6)	132 (4.8)	52 (4.1)	1,806 (9.7)	276 (8.2)	171 (6.4)
$20,000 to $34,999	3,430 (17.8)	403 (14.6)	170 (13.4)	4,254 (22.8)	702 (21.0)	484 (18.2)
$35,000 to $49,999	3,823 (19.8)	508 (18.4)	214 (16.8)	3,899 (20.9)	679 (20.3)	516 (19.4)
$50,000 to $74,999	4,503 (23.3)	679 (24.6)	336 (26.4)	3,895 (20.9)	741 (22.1)	630 (23.6)
$75,000 to $99,999	2,406 (12.5)	410 (14.8)	180 (14.2)	1,769 (9.5)	346 (10.3)	306 (11.5)
$100,000 to $149,999	1,955 (10.1)	348 (12.6)	168 (13.2)	1,259 (6.7)	281 (8.4)	252 (9.5)

	Intact Uterus			Hysterectomy		
	Oral CEE + P[a]	Oral Estradiol +P	Transdermal estradiol +P	Oral CEE alone	Oral Estradiol alone	Transdermal estradiol alone
N[b]	20,114	2,843	1,336	19,413	3,470	2,753
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
$150,000 or more	1,089 (5.6)	197 (7.1)	115 (9.0)	690 (3.7)	183 (5.5)	170 (6.4)
Don't know	441 (2.3)	59 (2.1)	25 (2.0)	471 (2.5)	75 (2.2)	72 (2.7)
Smoking status						
Never Smoked	9,635 (48.6)	1,317 (46.9)	625 (47.2)	9,884 (51.6)	1,774 (51.8)	1,302 (48.0)
Past Smoker	9,090 (45.8)	1,376 (49.0)	625 (47.2)	8,208 (42.9)	1,482 (43.3)	1,251 (46.1)
Current Smoker	1,107 (5.6)	115 (4.1)	74 (5.6)	1,062 (5.5)	167 (4.9)	159 (5.9)
Body mass index (Kg/m^2)						
<25	9,912 (49.9)	1,580 (56.3)	740 (56.1)	7,856 (40.9)	1,489 (43.4)	1,150 (42.2)
25–<30	6,433 (32.4)	844 (30.1)	415 (31.5)	6,839 (35.6)	1,196 (34.9)	978 (35.9)
≥30	3,536 (17.8)	384 (13.7)	163 (12.4)	4,535 (23.6)	744 (21.7)	598 (21.9)
Diabetes treated (pills or shots)	430 (2.1)	32 (1.1)	21 (1.6)	662 (3.4)	80 (2.3)	82 (3.0)
Systolic blood pressure						
Mean (SD)	123.7 (17.0)	121.0 (16.7)	119.6 (15.7)	127.9 (17.9)	125.0 (17.6)	123.1 (16.9)
Diastolic blood pressure						
Mean (SD)	74.2 (9.0)	73.9 (9.0)	73.7 (8.7)	75.0 (9.2)	74.9 (9.0)	74.9 (9.1)
History of Cancer	743 (3.7)	123 (4.3)	47 (3.5)	1,385 (7.1)	240 (6.9)	180 (6.5)
History of cardiovascular disease[a]	519 (2.6)	51 (1.8)	25 (1.9)	816 (4.2)	116 (3.3)	80 (2.9)
Age at menopause						
Mean (SD)	50.4 (4.7)	50.2 (4.4)	50.3 (4.5)	45.3 (7.0)	45.8 (6.7)	45.7 (6.8)
Age at First Birth						
Never had term pregnancy	2,719 (14.8)	440 (16.6)	191 (15.5)	2,009 (11.4)	363 (11.3)	274 (11.0)
< 20	1,708 (9.3)	249 (9.4)	98 (7.9)	2,850 (16.2)	507 (15.8)	401 (16.1)
20–29	12,229 (66.4)	1,725 (65.0)	812 (65.9)	11,713 (66.5)	2,151 (67.1)	1,669 (66.9)

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	Intact Uterus			Hysterectomy		
	Oral CEE + P[a]	Oral Estradiol +P	Transdermal estradiol +P	Oral CEE alone	Oral Estradiol alone	Transdermal estradiol alone
N[b]	20,114	2,843	1,336	19,413	3,470	2,753
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
30+	1,773 (9.6)	238 (9.0)	132 (10.7)	1,053 (6.0)	183 (5.7)	149 (6.0)
Gail breast cancer risk score (5-year risk) Mean (SD)	1.7 (0.9)	1.6 (0.8)	1.6 (0.8)	1.8 (1.0)	1.7 (0.9)	1.6 (0.9)
Bilateral Oophorectomy	99 (0.5)	11 (0.4)	9 (0.7)	9,171 (48.9)	1,599 (47.2)	1,246 (46.1)
Aspirin use	3,998 (19.9)	538 (18.9)	216 (16.2)	4,179 (21.5)	722 (20.8)	473 (17.2)
Statin use	1,310 (6.5)	135 (4.7)	66 (4.9)	1,559 (8.0)	249 (7.2)	214 (7.8)
Antihypertensive med use	1,593 (7.9)	171 (6.0)	86 (6.4)	2,389 (12.3)	368 (10.6)	227 (8.2)

[a] CEE – conjugated equine estrogen, P - progestin or progesterone

[b] Number by HT type adds up to more than total study population because women can change categories over the follow-up period

[a] Cardiovascular disease history includes a past history of myocardial infarction, stroke, or revascularization

Table 2

Risk of global index event[a] by menopausal hormone therapy type

	N events	Events/1,000 person-years[b]	N events (fully-adjusted model)	HR (95% CI) [c]
Intact Uterus				
Oral CEE + P[d]	1484	16.4 (15.6–17.2)	1181	1.0 (ref)
Oral Estradiol + P	126	15.4 (11.5–19.4)	100	0.86 (0.70–1.06)
Transdermal E + P	60	14.6 (10.6–18.7)	47	0.89 (0.66–1.19)
Oral estradiol + P	126	15.4 (11.5–19.4)	100	1.0 (ref)
Transdermal E + P	60	14.6 (10.6–18.7)	47	1.03 (0.73–1.46)
Hysterectomy				
Oral CEE alone	1710	14.0 (13.3–14.7)	1349	1.0 (ref)
Oral Estradiol alone	195	14.0 (12.0–16.0)	150	0.96 (0.81–1.14)
Transdermal E alone	162	14.4 (12.1–16.8)	122	0.93 (0.77–1.13)
Oral estradiol alone	195	14.0 (12.0–16.0)	150	1.0 (ref)
Transdermal E alone	162	14.4 (12.1–16.8)	122	0.97 (0.77–1.24)

[a] Time to risk of global index is defined as time to first coronary heart disease, breast cancer, stroke, pulmonary embolism, hip fractures, colorectal cancer, endometrial cancer, or death. Outcomes are through the end of extension 1.

[b] Age- and race/ethnicity-adjusted rate

[c] HR denotes hazard ratio; 95% CI denotes 95% confidence interval. Cox hazard model stratified by baseline 5-year age intervals, adjusted for age, race/ethnicity, education, income, smoking, body mass index, physical activity (metabolic equivalent of task [MET] hours/week), alcohol (servings/week), diabetes, systolic blood pressure, diastolic blood pressure, aspirin, statins, history of cardiovascular disease (myocardial infarction, stroke, or revascularization), history of cancer, Gail breast cancer risk score, family history of breast cancer, age at menopause, age at first birth, in those with hysterectomy also adjusted for bilateral oophorectomy

[d] CEE – conjugated equine estrogen, P - progestin or progesterone. Menopausal hormone therapy is entered into the models as a time-varying covariate.

Table 3

Risk of global index event[a] by menopausal hormone therapy route and CEE dose[b]

	N events	Events/1,000 person-years[c]	N events Fully adjusted model	HR (95% CI)[d]
Intact Uterus				
Oral CEE				
High-dose +P	48	16.4 (11.4–21.3)	39	1.14 (0.82–1.57)
Conventional-dose +P	1040	16.5 (15.5–17.5)	826	1.0 (ref)
Low-dose +P	73	11.8 (9.0–14.6)	56	**0.74 (0.56–0.97)**
Oral Estradiol +P	83	12.6 (9.7–15.5)	64	0.81 (0.63–1.05)
Transdermal +P	35	11.6 (7.5–15.8)	28	0.78 (0.54–1.14)
Hysterectomy				
Oral CEE				
High-dose	167	14.8 (12.5–17.1)	134	1.09 (0.90–1.31)
Conventional-dose	887	12.9 (12.1–13.8)	700	1.0 (ref)
Low-dose	105	12.4 (9.6–15.3)	82	0.92 (0.73–1.16)
Oral Estradiol	121	13.8 (11.3–16.3)	92	1.03 (0.83–1.28)
Transdermal	97	13.0 (10.3–15.8)	72	0.89 (0.70–1.14)

[a] Global index event is defined as time to first CHD, breast cancer, stroke, pulmonary embolism, hip fractures, colorectal cancer, endometrial cancer, or death. Outcomes are through the end of extension 1.

[b] CEE – conjugated equine estrogen, P - progestin or progesterone. CEE doses were defined as follows: conventional-dose 0.625 mg/day, low-dose < 0.625 mg/day, high-dose >0.625 mg/day. Menopausal hormone therapy is entered into the models as a time-varying covariate. Statistically significant values are represented in **boldface** type.

[c] Age- and race/ethnicity-adjusted rate

[d] HR denotes hazard ratio; 95% CI denotes 95% confidence interval. Cox hazard model stratified by baseline 5-year age intervals, adjusted for age, race/ethnicity, education, income, smoking, body mass index, physical activity (metabolic equivalent of task [MET] hours/week), alcohol (servings/week), diabetes, systolic blood pressure, diastolic blood pressure, aspirin, statins, history of cardiovascular disease (myocardial infarction, stroke, or revascularization), history of cancer, Gail breast cancer risk score, family history of breast cancer, age at menopause, age at first birth, in those with hysterectomy also adjusted for bilateral oophorectomy.

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Table 4

Joint effects of menopausal hormone therapy type[a], duration, and CEE dose on risk of global index event[b]

	Duration	N Events	Events/1,000 person-years[c]	N events Fully-adjusted model	HR[d] (95% CI)	HR (95% CI)
Intact uterus						
Oral CEE +P	<5 years	566	15.4 (14.1–16.7)	427	1.0 (ref)	
Oral CEE +P	≥5 years	918	16.9 (15.8–18.0)	754	**1.14 (1.01–1.29)**	
Oral Estradiol +P	<5 years	71	15.0 (11.2–18.7)	57	0.95 (0.72–1.26)	1.0 (ref)
Oral Estradiol +P	≥5 years	55	14.2 (10.1–18.2)	43	0.92 (0.67–1.26)	0.97 (0.65–1.44)
Transdermal estradiol +P	<5 years	30	13.4 (8.0–18.8)	25	0.98 (0.66–1.48)	1.04 (0.65–1.66)
Transdermal estradiol +P	≥5 years	30	16.3 (10.0–22.5)	22	0.95 (0.62–1.46)	1.00 (0.61–1.64)
Hysterectomy						
Oral CEE alone	<5 years	389	15.2 (13.7–16.7)	292	1.0 (ref)	
Oral CEE alone	≥5 years	1321	13.7 (12.9–14.5)	1057	0.89 (0.78–1.02)	
Oral Estradiol alone	<5 years	89	13.7 (10.9–16.6)	65	0.80 (0.61–1.05)	1.0 (ref)
Oral Estradiol alone	≥5 years	106	14.3 (11.6–17.1)	85	0.95 (0.74–1.21)	1.19 (0.86–1.64)
Transdermal estradiol alone	<5 years	67	13.5 (10.2–16.9)	48	0.85 (0.63–1.16)	1.06 (0.73–1.55)
Transdermal estradiol alone	≥5 years	95	14.7 (11.6–17.8)	74	0.86 (0.66–1.11)	1.07 (0.77–1.50)
Intact uterus						
Oral CEE High-dose +P	<5 years	24	14.5 (8.3–20.8)	21	1.13 (0.73–1.75)	
Oral CEE High-dose +P	≥5 years	24	20.6 (11.4–29.8)	18	1.50 (0.93–2.41)	
Oral CEE Conventional-dose +P	<5 years	452	15.4 (14.0–16.9)	339	1.0 (ref)	
Oral CEE Conventional-dose +P	≥5 years	588	17.2 (15.7–18.6)	487	**1.22 (1.06–1.41)**	
Oral CEE Low-dose +P	<5 years	43	13.3 (9.3–17.3)	34	0.91 (0.64–1.30)	
Oral CEE Low-dose +P	≥5 years	30	10.9 (6.5–15.2)	22	0.72 (0.47–1.11)	
Oral Estradiol +P	<5 years	44	13.4 (9.2–17.7)	34	0.92 (0.65–1.31)	
Oral Estradiol +P	≥5 years	39	13.1 (8.7–17.5)	30	0.91 (0.62–1.32)	
Transdermal estradiol +P	<5 years	16	9.5 (4.3–14.7)	14	0.87 (0.51–1.49)	
Transdermal estradiol +P	≥5 years	19	13.5 (6.9–20.0)	14	0.88 (0.52–1.51)	
Hysterectomy						

	Duration	N Events	Events/1,000 person-years[c]	N events Fully-adjusted model	HR[d] (95% CI)	HR (95% CI)
Oral CEE High-dose alone	<5 years	53	20.4 (14.6–26.1)	44	**1.56 (1.12–2.18)**	
Oral CEE High-dose alone	≥5 years	114	13.0 (10.6–15.4)	90	0.97 (0.75–1.26)	
Oral CEE Conventional-dose alone	<5 years	244	14.2 (12.4–16.0)	173	1.0 (ref)	
Oral CEE Conventional-dose alone	≥5 years	643	12.5 (11.5–13.5)	527	1.03 (0.87–1.23)	
Oral CEE Low-dose alone	<5 years	46	11.8 (8.1–15.5)	36	0.85 (0.59–1.22)	
Oral CEE Low-dose alone	≥5 years	59	13.3 (8.4–18.2)	46	1.03 (0.74–1.44)	
Oral Estradiol alone	<5 years	52	13.6 (9.8–17.3)	37	0.99 (0.69–1.41)	
Oral Estradiol alone	≥5 years	69	14.0 (10.7–17.3)	55	1.11 (0.82–1.51)	
Transdermal estradiol alone	<5 years	43	13.2 (9.1–17.3)	29	0.94 (0.64–1.40)	
Transdermal estradiol alone	≥5 years	54	12.1 (8.7–15.5)	43	0.90 (0.64–1.26)	

[a] CEE doses were defined as follows: conventional-dose 0.625 mg/day, low-dose < 0.625 mg/day, high-dose >0.625 mg/day.

[b] CEE – conjugated equine estrogen, P - progestin or progesterone. Time to global index event was defined as time to first CHD, breast cancer, stroke, pulmonary embolism, hip fractures, colorectal cancer, endometrial cancer, or death. Outcomes are through the end of extension 1. Models were stratified by baseline 5-year age intervals and adjusted for age, race/ethnicity, education, income, smoking, physical activity (metabolic equivalent of task [MET] hours/week), alcohol intake (servings/week), diabetes, systolic blood pressure, diastolic blood pressure, aspirin, statins, history of cardiovascular disease (myocardial infarction, stroke, or revascularization), history of cancer, Gail breast cancer risk score, family history of breast cancer, age at menopause, age at first birth, in those with hysterectomy also adjusted for bilateral oophorectomy. Menopausal hormone therapy is entered as a time-varying covariate. Statistically significant values are represented in **boldface** type.

[c] Age-adjusted rate.

[d] HR = hazard ratio