HHS Public Access

Author manuscript

Menopause. Author manuscript; available in PMC 2019 September 01.

Published in final edited form as:

Menopause. 2018 September ; 25(9): 985–991. doi:10.1097/GME.0000000000001115.

Estrogen-alone Therapy and Invasive Breast Cancer Incidence by Dose, Formulation, and Route of Delivery: Findings from the WHI Observational Study

Chrisandra Shufelt, MD, MS[1], **C. Noel Bairey Merz, MD**[1], **Mary B. Pettinger, MS**[2], **Lydia Choi, MD**[3], **Rowan Chlebowski, MD, PhD**[4], **Carolyn J. Crandall, MD, MS**[5], **Simin Liu, MD, ScD**[6], **Dorothy Lane, MD, MPH**[7], **Ross Prentice, PhD**[2], **JoAnn E. Manson, MD, DrPH**[8], and **for the Women's Health Initiative Investigators**

[1]Barbra Streisand Women's Heart Center, Cedars-Sinai Heart Institute, Los Angeles, CA

[2]Fred Hutchinson Cancer Research Center, Seattle, WA

[3]Karmanos Cancer Institute Wayne State University, Detroit, MI

[4]Department of Medical Oncology and Developmental Therapeutics, City of Hope National Medical Center, Duarte, CA

[5]Department of Medicine, University of California, Los Angeles, Los Angeles, CA

[6]Departments of Epidemiology, Brown University, Providence, RI

[7]Department of Family, Population and Preventive Medicine, Stony Brook University School of Medicine, Stony Brook, NY

[8]Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Abstract

Objective—Research on the relationships between different hormone therapy doses, formulation and routes of delivery and subsequent breast cancer incidence has been limited. This study directly compared different estrogen doses, formulations, and route of delivery of estrogen alone among women with a hysterectomy in relation to invasive breast cancer incidence.

Methods—The Women's Health Initiative Observational Study (WHI-OS) is a large multi-center prospective cohort study conducted at 40 US sites. Analyses included 26,525 postmenopausal

Corresponding Author: Chrisandra Shufelt, MD, MS (Chrisandra.Shufelt@cshs.org) 8631 W. Third Street, Suite 740 East, Los Angeles, CA 90048.

Women's Health Initiative Investigators: A full listing of Women's Health Initiative investigators can be found at http://whiscience.org/publications/WHI_investigators_longlist

Presentation: This research was presented as an oral abstract at the 2016 North American Menopause Society annual meeting, Orlando, Florida by Dr. Shufelt.

Conflicts of Interest/Financial Disclosure: Dr Chlebowski reports receipt of consulting fees or honoraria from Novartis, Genentech, Amgen, and Astra-Zeneca, Novo Nordisk, and Genomic Health; fees for participation in review activities from Pfizer; payment for lectures from Novartis; and payment for educational activities from Educational Concepts Group. All other authors report no conflicts of interest/disclosures.

women with a hysterectomy, aged 50–79 years at study entry recruited between September 1993 – December 1998, with annual follow-up through September 12, 2005.

Results—Average follow up was 8.2 years. For conjugated equine estrogen (CEE) users, no difference was observed between low-dose CEE (<0.625 mg) compared to conventional-dose CEE (0.625mg) for breast cancer [HR 0.99 (95% CI 0.65, 1.48)]. Compared to conventional-dose CEE, transdermal estrogen was associated with a non-significant lower risk of invasive breast cancer [HR 0.75 (0.47, 1.19)]. The low prevalence of transdermal use likely limited power for this comparison as well as for a comparison of oral estradiol to conventional-dose CEE [HR 1.20 (95% CI 0.84, 1.39)].

Conclusion—Our results indicate that invasive breast cancer risk did not differ appreciably in women with a hysterectomy using estrogen-alone when directly comparing different doses, formulations, and routes of delivery to the conventional oral CEE. These findings suggest that the lower breast cancer risk found in the WHI estrogen-alone trial may extend to lower doses of CEE. Additional research is needed to confirm these hypotheses.

Keywords

Menopause Hormone Therapy; Invasive breast cancer; estradiol; transdermal

INTRODUCTION

Observational epidemiological studies have consistently reported increased breast cancer risk associated with post-menopausal hormone therapy (HT) use.[1,2] However, Women's Health Initiative (WHI) results indicate that breast cancer risks differ between estrogen plus progestin[3] and estrogen alone.[4] There is limited research on the relationship between estrogen dose, route of delivery, and formulation (bioidentical vs synthetic) and the risk of breast cancer.

In the WHI clinical trials (WHI-CT), breast cancer risk during the intervention phase (ended March 31, 2005) was increased in the estrogen plus progestin arm (hazard ratio [HR] 1.25, 95% confidence interval [CI] 1.07–1.46)[3] but not in the estrogen-alone arm (RR 0.77, 95% CI 0.57–1.01).[4,5] In follow up analysis of the health outcomes from the estrogen-alone trial after 10.7 years (including a median 5.9 years for the intervention phase), women on estrogen therapy alone had a significantly lower breast cancer risk compared to placebo (HR 0.77, 95% CI 0.62–0.95).[6] Furthermore, in women who developed breast cancer, the risk of dying was lower in women who took estrogen compared to placebo. More recently, breast cancer mortality results for women randomized to CEE-alone were found to have statistically significant lower mortality rates after 18-years in follow up versus placebo (HR 0.55 [95% CI 0.33–0.92]).[7] It is unknown whether the lower breast cancer risk in the estrogen-alone trial extends to other doses, routes of delivery and formulations.

To date, no randomized clinical trials have provided head-to-head comparisons of different doses or formulations of estrogen (e.g., CEE vs 17-β estradiol [E2]), in relation to breast cancer outcomes. Animal models have suggested that the standard doses of CEE may result in less estrogen-induced epithelial proliferation in the breast compared with E2 but these

results have yet been replicated in humans.[8] One Finnish study assessed the incidence of breast cancer in women using oral or transdermal estradiol and did not find a difference in observed risk by route of delivery; although this study did not control for confounders such as parity, age at first birth and weight.[9] Even though these questions are of great clinical interest, it remains unknown whether HT dose, formulations or route of delivery influence breast cancer incidence.

The purpose of this study was to evaluate relationships between different estrogen doses, formulations, and route of delivery in women with a hysterectomy on estrogen-alone HT in relation to invasive breast cancer incidence in the WHI-OS. Further, a goal was to determine whether results varied by time since menopause onset (<10 years, ≥10 years) for estrogen initiation, as current menopause guidelines recommend initiating HT within 10-years in healthy menopausal women for menopause related symptoms.[10]

METHODS

The WHI-OS is a large multi-center prospective cohort study conducted at 40 US sites. The details of the scientific rationale, eligibility criteria, and design of the WHI-OS have been previously published.[11] Briefly, 93,676 postmenopausal women aged 50–79 years were recruited between September 1, 1993 and December 31, 1998. Annual follow-up by mailed self-administered questionnaires and completed annual medical histories, confirmed by medical record review, and detailed assessments of hormone use were obtained through September 12, 2005. Data were uniformly collected from participants according to a standardized institutional review board-approved protocol by trained study staff. All participants provided written informed consent for this research study at the time of enrollment.

For these analyses, 39,147 women had a hysterectomy prior to baseline. Study participants were excluded if they had a history of breast cancer (n=2,206), no mammogram reported within 2 years of baseline (n=6,224), missing information regarding baseline hormone therapy use (n=45) and those reporting current use of both estrogen plus progestin by women with previous hysterectomy (n=792). Additional exclusion that occurred at baseline or during follow up included: use of estrogen with testosterone (n=1,507), use of dehydroepiandrosterone (DHEA) (n=620), phytoestrogen pills or creams (n=1,395), yam pill (n=176), or progesterone creams (n=747). The number of women remaining was 26,525.

For this study, breast cancer was defined as invasive breast cancer and did not include breast cancer in situ. Information on breast cancer was collected at annual contacts. Breast cancers were initially verified by medical record review by centrally trained physician adjudicators at each clinical center with final adjudication and coding performed centrally by WHI cancer coders.

Oral HT estrogen doses were defined as: low-dose CEE < 0.625 mg; conventional-dose CEE dose = 0.625 mg; and high-dose CEE > 0.625 mg. Hormone formulation categories were defined as oral estradiol and oral CEE. Transdermal estrogen categorization included all

dose formulations. Mean duration of HT use prior to enrollment plus years of use of current formulation at baseline through follow-up was calculated for each formulation.

Statistical Analysis

Descriptive statistics of the study sample characteristics were reported using mean ± standard deviation or frequency, by HT type and dose. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals between different doses, routes of delivery and formulations of HT and breast cancer incidence directly compared to conventional CEE dose. Time to breast cancer incidence was computed from date of enrollment to date of first breast cancer event, and censored by date of death, date of last study follow-up or September 12, 2005, whichever occurred first. Annual follow up data were collected on HT with a mean follow-up time of 8.2 years. For each follow-up year, the type of hormone used was categorized as non-user, oral estradiol, transdermal, oral low dose CEE, oral conventional dose CEE, oral high dose CEE, and other. The HT exposure begins with the baseline information, and at each subsequent data collection, the type and dose is updated; if HT was stopped, the participant becomes a former user, and remains a never user if no use is reported during follow-up. To increase the precision of the standard error estimates, the models include all participants including the never and former users. All analyses were stratified by baseline 5-year age intervals.

Variables considered as potential confounders or effect modifiers were included as covariates in the model and included age (linear), race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, Other), smoking (never, former, current), quartiles of total recreational physical activity measured in MET-hours/week, body mass index (BMI) categories (<25, 25-<30, ≥30 kg/m^2), BMI (linear kg/m^2), treated diabetes (no, yes), oophorectomy (no, partial, bilateral), education (5 categories, table 1) and household income (6 categories, table 1), alcohol consumption (6 categories, table 1), parity (6 categories, table 1), cumulative frequency of mammography, Gail risk score for breast cancer (this takes into account family history, menarche, and age at 1st birth), and prior HT use (no, yes). Analyses were adjusted for frequency of mammography during follow-up using a time-dependent cumulative count of annually reported mammography. Hazard ratios and 95% confidence intervals were estimated by years since menopause (<10 versus >10) and gap time, where years since menopause is the difference between age at menopause and age at WHI enrollment, and gap time is the difference between age at menopause and age first used HT. All analyses were conducted using SAS 9.2 (SAS Institute, Inc., Cary, North Carolina). All p-values were two-sided tests and values less than 0.05 were considered statistically significant.

RESULTS

Table 1 summarizes the demographic characteristics of the analytic sample of women with hysterectomy at baseline (study enrollment), stratified by the comparison groups according to dose of CEE, HT formulation, and route of delivery. Mean duration of follow up for the WHI-OS in these analyses was 8.2 years. Mean duration of HT use was 18.5 years for

conventional dose CEE, 17.4 years for low dose CEE, 19.3 years for high dose CEE, 14.7 years for oral estradiol and 14.0 years for transdermal use.

At baseline, 5,990 (22.5%) women with a hysterectomy had never used HT. Among women with a hysterectomy using high dose CEE, the age at menopause was younger (43.1 yrs) with higher rates of bilateral oophorectomy. Women using low dose CEE had a higher mean baseline Gail score [2.08] (5-year risk of breast cancer) compared to conventional or high dose CEE [1.68]. Among the women using CEE formulation, 846 (7%) were on low-dose CEE, 2,004 (16%) were on high dose CEE, and the remainder (9,903 [77%]) were on conventional-dose CEE. There were 1,134 women using transdermal estrogen, a number similar to women using oral estradiol. The mean age at enrollment was 65.4 (7.3) years for the never users and slightly lower in the hormone users, with the lowest age at follow up seen in the transdermal E users, 60.6 (6.8) years. Women who used HT tended to have lower body mass index (BMI), higher educational and household income levels, and were more likely to have had bilateral oophorectomy. These and other variables were included in multivariate models.

Overall, the absolute risk of invasive breast cancer was 43 per 10,000 person-years in women with hysterectomy using CEE-alone over the 8 year follow up. The risk was slightly higher in women using CEE alone <10 yr since menopause compared (45 per 10,000 person-years) compared to >10 yr since menopause (42 per 10,000 person-years) however, this difference was not statistically significant.

Direct Comparison: Route of Delivery

After adjustment for age, breast cancer risk factors, education, and household income, the transdermal route of delivery was associated with a slight but non-significant reduction in risk of breast cancer compared to oral conventional dose CEE (RR 0.75, 95% CI 0.47, 1.19) (Table 2). Although the relatively small number of transdermal users likely limited power, this finding was consistent regardless of years since menopause.

Direct Comparison: Oral HT Dose

After adjustment for breast cancer risk factors, women with a hysterectomy who used oral low dose CEE had similar rates of breast cancer compared to women who used oral conventional dose of CEE. (Table 3) There was also no difference in breast cancer risk when stratified by years since menopause in women with a hysterectomy (<10 yrs vs. ≥10 yrs). There was also no difference in invasive breast cancer risk in the use of high dose CEE when compared to the conventional dose CEE overall and based on years since menopause. (Table 3) However, for all analyses, due to the limited sample size among the groups, statistical power was likely greatest for conventional-dose CEE, and limited for the high and low dose HT.

Direct Comparison: HT Formulation

Analysis by estrogen type, estradiol vs. CEE, suggested that oral estradiol may be associated with higher rates of breast cancer incidence in women with a hysterectomy than conventional-dose CEE (HR 1.20, 95% CI 0.84, 1.39), but the differences were not

statistically significant (Table 4). This difference was more pronounced <10 years since menopause but still not significant (HR 1.46, 95% CI 0.78, 2.73).

For HT dose, formulation and route of delivery analyses were conducted to compare HT by gap time from menopause to first use of HT (< 5 years versus ≥ 5 years). HRs were not significantly increased or decreased, relative to conventional dose CEE, for women in either gap-time group and interaction tests by gap time were not statistically significant (see Appendix A). Statistical power for these analyses, however, was limited.

DISCUSSION

Our results indicate that invasive breast cancer risk did not differ in women with a hysterectomy using estrogen-alone when directly comparing different estrogen doses, formulations, and routes of delivery to the conventional oral CEE dose. Low dose CEE was associated with a similar risk when compared to conventional dose, regardless of years since menopause. Our results suggest that transdermal estradiol may confer a slightly less risk of breast cancer than oral conventional dose, however sample size likely contributed to this analysis being underpowered. Oral estradiol compared to conventional dose CEE was associated with a trend toward higher breast cancer incidence specifically within the first 10 years since menopause, further work is needed in larger sample sizes. The totality of these findings support the hypothesis that the lower breast cancer risk found in the WHI CEE-alone trial may extend to lower doses of CEE-alone as well as transdermal route of delivery.

To date, many observational and clinical studies have found higher rates of breast cancer using estrogen-alone even stratified by dose, formulation or route of delivery. In the Million Women's Study, breast cancer risk using estrogen-alone compared to never users was increased regardless of route of delivery or CEE dose [transdermal E-alone RR 1.24 (1.11–1.39) vs. oral E-alone RR 1.32 (1.21–1.45)] and [CEE<0.625mg RR 1.25 (1.11–1.41) vs CEE>0.625mg RR 1.36 (1.14–1.61)].[12] In the French E3N Cohort study, there was no difference between route of delivery comparing oral and transdermal and both had a non-significant increased risk [Oral E-alone RR 1.32 (0.76–2.29) vs transdermal E-alone RR 1.28 (0.98–1.69)], with a follow up of 8.1 years.[13] In a Finnish registry report of 85,000 women, oral and transdermal estrogen-alone had similar breast cancer risk with no increased risk <5 yrs of use [overall HR 0.93 (95% CI 0.80–1.04)] however after >5 years regardless of dose, both oral and transdermal estrogen-alone had increased risk for breast cancer [overall HR 1.44 (95% CI 1.29–1.59)].[14]

A majority of breast cancers (80%) are estrogen receptor positive, so the concept that estrogen-alone therapy may decrease the risk of invasive breast cancer appears contradictory.[15] Menopause HT after breast cancer has also been associated with more invasive breast cancer and increased rates of recurrence.[16–18] Furthermore, anti-estrogen drugs used to block estrogen production (aromatase inhibitors), block ovarian function (gonadotropin-relating hormone agonists) or block the effect at the estrogen receptor (selective estrogen receptor modulators) are current standards of care for breast cancer treatment.[19] However, prior to development of these agents, the standard of care for metastatic postmenopausal breast cancer treatment was high-dose synthetic estrogen therapy (estradiol 6–30mg/d).[20,21]

The remission of breast cancer with high dose estrogen therapy increased relative to the number of years since menopause when treatment was initiated, leading to the hypothesis that the mechanism of action is antitumor activity through apoptosis in long-term estrogen-deprived breast cancer cells.[21,22]

Recent attention has focused on the difference between oral estrogen compared to transdermal delivery with respect to first pass metabolism, pharmacokinetics and inflammatory markers in the liver.[23–25] Oral estrogens first metabolize in the liver sinusoids resulting in higher conversion of estradiol to estrone as opposed to transdermal estrogens which avoid first pass metabolism providing a lower and constant dose of estrogen with a more physiologic ratio of estradiol to estrone.[24] While the association with “first pass” has been evaluated with respect to cardiovascular outcomes,[26] the association with breast cancer remains unclear.

The limitation of our study includes the observational design which cannot address causal inferences. We cannot exclude to possibility of confounding due to selection bias related to the type of HT used. Another limitation includes the small number of women using transdermal or low-dose estrogen resulting in large confidence intervals making interpretation of these results challenging. Finally, we recognize that adjusting for breast cancer related characteristics such as Gail risk score at baseline may potentially lead to residual confounding in our observation cohort and may underestimate breast cancer risk.

CONCLUSION

To date, our analysis is one of the largest studies to address the relation of dose, formulation, and route of delivery with estrogen-alone and invasive breast cancer. Our results suggest that invasive breast cancer risk does not differ appreciably in users of low-dose versus conventional-dose CEE. We did not observe differences in invasive breast cancer risk between oral estradiol or transdermal estradiol users; compared to conventional-dose oral CEE however relatively low prevalence of transdermal use likely limited power for this comparison. These findings suggest that the lower risk of breast cancer found in the WHI CEE-alone trial may extend to lower doses of CEE as well as transdermal route of delivery, however we recognize that this study finding is limited by sample size. Future investigation should be focused on different doses of CEE and comparative analyses with transdermal and oral estradiol.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: The Women’s Health Initiative program is funded by the National Heart, Lung, and Blood Institute, the National Institutes of Health, and the US Department of Health and Human Services through contracts through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. This work was also supported by K23HL127262-01A1, GCRC grant MO1-RR00425 from the National Center for Research Resources, and the Edythe L. Broad Women’s Heart Research Fellowship, Cedars-Sinai Medical Center, Los Angeles, California, and the Barbra Streisand Women’s Cardiovascular Research and Education Program, Cedars-Sinai Medical Center, Los Angeles.

Additional Contributions: We thank the Women's Health Initiative investigators, staff, and study participants for their outstanding dedication and commitment.

References

1. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. The Lancet (British edition). 1997; 350(9084):1047–1059.
2. Collins JA, Blake JM, Crosignani PG. Breast cancer risk with postmenopausal hormonal treatment. Human Reproduction Update. 2005; 11(6):545–560. [PubMed: 16150813]
3. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The women's health initiative randomized trial. JAMA. 2003; 289(24):3243–3253. [PubMed: 12824205]
4. Stefanick ML, Anderson GL, Margolis KL, et al. EFfects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA. 2006; 295(14):1647–1657. [PubMed: 16609086]
5. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The women's health initiative randomized controlled trial. JAMA. 2004; 291(14):1701–1712. [PubMed: 15082697]
6. LaCroix Az CRTMJE. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: A randomized controlled trial. JAMA. 2011; 305(13):1305–1314. [PubMed: 21467283]
7. Manson JE, Aragaki AK, Rossouw JE, et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: The women's health initiative randomized trials. JAMA. 2017; 318(10):927–938. [PubMed: 28898378]
8. Wood CE, Clarkson TB, Chen H, et al. Comparative effects of oral conjugated equine estrogens and micronized 17beta-estradiol on breast proliferation: a retrospective analysis. Menopause. 2008; 15(5):890–898. [PubMed: 18520696]
9. Wong T, Shah NR. Breast cancer from oral and transdermal estradiol: a cohort study of Finnish women. Women's Health. 2007; 3(3):321–324.
10. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017; 24(7):728–753. [PubMed: 28650869]
11. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials. 1998; 19(1):61–109. [PubMed: 9492970]
12. Breast cancer and hormone-replacement therapy in the Million Women Study. The Lancet. 2003; 362(9382):419–427.
13. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Research and Treatment. 2008; 107(1):103–111. [PubMed: 17333341]
14. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen-only therapy. Obstet Gynecol. 2006; 108(6):1354–1360. [PubMed: 17138766]
15. [Accessed August 21, 2017] How to Read Hormone Receptor Test Results. 2017. http://www.breastcancer.org/symptoms/diagnosis/hormone_status/read_results
16. Col NF, Hirota LK, Orr RK, Erban JK, Wong JB, Lau J. Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. J Clin Oncol. 2001; 19
17. Col NF, Kim JA, Chlebowski RT. Menopausal hormone therapy after breast cancer: a meta-analysis and critical appraisal of the evidence. Breast Cancer Research. 2005; 7(4):R535. [PubMed: 15987460]
18. Holmberg L, Iversen O-E, Rudenstam CM, et al. Increased Risk of Recurrence After Hormone Replacement Therapy in Breast Cancer Survivors. JNCI: Journal of the National Cancer Institute. 2008; 100(7):475–782. [PubMed: 18364505]

19. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. Journal of Clinical Oncology. 2016; 34(6): 611–635. [PubMed: 26644543]

20. Haddow A, Watkinson JM, Paterson E, Koller PC. Influence of Synthetic Oestrogens on Advanced Malignant Disease. British medical journal. 1944; 2(4368):393–398. [PubMed: 20785660]

21. Obiorah I, Jordan VC. 2012 Nams/Pfizer- Wulf H. Utian Endowed Lecture The scientific rationale for a delay after menopause in the use of conjugated equine estrogens in postmenopausal women that causes a reduction in breast cancer incidence and mortality. Menopause (New York, NY). 2013; 20(4):372–382.

22. Lewis JS, Meeke K, Osipo C, et al. Intrinsic Mechanism of Estradiol-Induced Apoptosis in Breast Cancer Cells Resistant to Estrogen Deprivation. JNCI: Journal of the National Cancer Institute. 2005; 97(23):1746–1759. [PubMed: 16333030]

23. Lacut K, Oger E, Le Gal G, et al. Differential effects of oral and transdermal postmenopausal estrogen replacement therapies on C-reactive protein. Thromb Haemost. 2003; 90(1):124–131. [PubMed: 12876635]

24. Powers MS, Schenkel L, Darley PE, Good WR, Balestra JC, Place VA. Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17 beta-estradiol: comparison with conventional oral estrogens used for hormone replacement. Am J Obstet Gynecol. 1985; 152(8): 1099–1106. [PubMed: 2992279]

25. Žegura B, Gužic-Salobir B, Šebeštjen M, Keber I. The effect of various menopausal hormone therapies on markers of inflammation, coagulation, fibrinolysis, lipids, and lipoproteins in healthy postmenopausal women. Menopause. 2006; 13(4):643–650. 610.1097/1001.gme.0000198485.0000170703.0000198487a. [PubMed: 16837886]

26. Shufelt CL, Merz CNB, Prentice RL, et al. Hormone Therapy Dose, Formulation, Route of Delivery, and Risk of Cardiovascular Events in Women: Findings from the WHI Observational Study. Menopause (New York, NY). 2014; 21(3):260–266.

Table 1

Demographic Characteristics by Hormone Therapy Dose and Formulation among Women with a hysterectomy at baseline (N=26,525)

	Former (n=3,908)	Oral low dose CEE (n=846)	Oral conventional dose CEE (n=9,903)	Oral high dose CEE (n=2,004)	Oral Estradiol (n=1,226)	Transdermal Estradiol (n=1,134)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age at screening, mean (SD)	66.19 (7.05)	66.81 (6.96)	63.94 (6.91)	61.71 (7.01)	61.27 (7.23)	60.56 (6.76)
Age at menopause, mean (SD)	43.70 (7.19)	45.80 (7.40)	45.56 (6.92)	43.14 (6.92)	46.02 (6.74)	45.92 (6.68)
Race/ethnicity						
White	3183 (81.4)	753 (89.0)	8444 (85.3)	1755 (87.6)	1038 (84.7)	976 (86.1)
Black	414 (10.6)	32 (3.8)	635 (6.4)	124 (6.2)	83 (6.8)	93 (8.2)
Hispanic	119 (3.0)	18 (2.1)	338 (3.4)	76 (3.8)	47 (3.8)	38 (3.4)
American Indian	22 (0.6)	5 (0.6)	36 (0.4)	10 (0.5)	9 (0.7)	4 (0.4)
Asian/Pacific Islander	97 (2.5)	28 (3.3)	333 (3.4)	21 (1.0)	37 (3.0)	11 (1.0)
Unknown	73 (1.9)	10 (1.2)	117 (1.2)	18 (0.9)	12 (1.0)	12 (1.1)
Education						
0–8 years	60 (1.5)	5 (0.6)	113 (1.1)	13 (0.7)	9 (0.7)	4 (0.4)
Some high school	193 (5.0)	22 (2.6)	288 (2.9)	55 (2.8)	36 (3.0)	29 (2.6)
High school diploma/GED	764 (19.7)	136 (16.1)	1669 (17.0)	364 (18.3)	212 (17.4)	147 (13.0)
School after high school	1575 (40.5)	346 (41.0)	3809 (38.7)	879 (44.1)	464 (38.1)	495 (43.8)
College degree or higher	1294 (33.3)	334 (39.6)	3959 (40.2)	683 (34.3)	497 (40.8)	454 (40.2)
Household income						
< $10,000	172 (4.8)	11 (1.4)	277 (3.0)	54 (2.9)	22 (1.9)	27 (2.5)
$10,000 – $19,999	563 (15.6)	90 (11.4)	893 (9.6)	161 (8.6)	94 (8.2)	62 (5.8)
$20,000 – $34,999	1040 (28.9)	208 (26.3)	2147 (23.1)	423 (22.5)	240 (20.9)	226 (21.2)
$35,000 – $49,999	706 (19.6)	186 (23.5)	2018 (21.7)	445 (23.6)	248 (21.6)	217 (20.4)
$50,000 – $74,999	605 (16.8)	151 (19.1)	2033 (21.9)	401 (21.3)	270 (23.5)	241 (22.7)
≥ $75,000	515 (14.3)	146 (18.4)	1920 (20.7)	398 (21.1)	276 (24.0)	291 (27.3)
Body-mass index (kg/m^2)		+				
Mean (SD)	28.16 (6.05)	26.55 (4.73)	27.00 (5.36)	27.35 (5.64)	27.22 (5.28)	27.37 (5.45)

Menopause. Author manuscript; available in PMC 2019 September 01.

	Former (n=3,908)	Oral low dose CEE (n=846)	Oral conventional dose CEE (n=9,903)	Oral high dose CEE (n=2,004)	Oral Estradiol (n=1,226)	Transdermal Estradiol (n=1,134)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
< 25	1300 (33.7)	353 (41.9)	4028 (41.1)	784 (39.4)	482 (39.7)	413 (36.8)
25 – < 30	1410 (36.6)	336 (39.9)	3526 (36.0)	668 (33.6)	420 (34.6)	426 (38.0)
≥ 30	1145 (29.7)	153 (18.2)	2253 (23.0)	536 (27.0)	313 (25.8)	282 (25.2)
Smoking status						
Never	1969 (51.2)	437 (52.5)	5085 (51.9)	985 (49.6)	640 (52.8)	554 (49.8)
Past	1661 (43.2)	370 (44.4)	4237 (43.3)	858 (43.2)	490 (40.5)	496 (44.6)
Current	216 (5.6)	26 (3.1)	470 (4.8)	144 (7.2)	81 (6.7)	63 (5.7)
Total recreational physical activity (MET-hrs/wk) quartiles						
0 – 3.0	1073 (27.7)	175 (21.0)	2350 (23.9)	590 (29.7)	301 (24.8)	283 (25.1)
3.04 – 9.96	996 (25.7)	218 (26.2)	2443 (24.9)	492 (24.8)	289 (23.8)	300 (26.6)
10.0 – 19.75	965 (24.9)	234 (28.1)	2574 (26.2)	499 (25.1)	324 (26.7)	271 (24.0)
≥ 19.80	835 (21.6)	206 (24.7)	2446 (24.9)	406 (20.4)	301 (24.8)	273 (24.2)
Treated diabetes ever	222 (5.7)	29 (3.4)	333 (3.4)	69 (3.4)	28 (2.3)	47 (4.1)
Oophorectomy						
None	1167 (31.5)	292 (35.5)	3476 (36.3)	592 (30.6)	440 (36.9)	378 (33.8)
Partial	490 (13.2)	100 (12.2)	1157 (12.1)	245 (12.7)	147 (12.3)	132 (11.8)
Bilateral	2050 (55.3)	430 (52.3)	4955 (51.7)	1096 (56.7)	607 (50.8)	607 (54.3)
Alcohol consumption						
Non-drinker	501 (12.9)	87 (10.4)	1040 (10.6)	237 (11.9)	149 (12.2)	109 (9.6)
Past drinker	904 (23.3)	163 (19.4)	1782 (18.1)	388 (19.5)	213 (17.5)	211 (18.7)
<1 drink per month	446 (11.5)	87 (10.4)	1117 (11.3)	260 (13.1)	149 (12.2)	146 (12.9)
<1 drink per week	777 (20.0)	166 (19.8)	2004 (20.3)	413 (20.7)	260 (21.4)	223 (19.7)
1 – <7 drinks per week	823 (21.2)	223 (26.5)	2667 (27.1)	461 (23.1)	299 (24.6)	298 (26.4)
≥ 7 drinks per week	429 (11.1)	114 (13.6)	1238 (12.6)	233 (11.7)	147 (12.1)	143 (12.7)
Family history of breast cancer in mother or sister	683 (19.2)	146 (18.9)	1418 (15.7)	253 (14.0)	157 (14.0)	141 (13.6)
Gail 5 year risk, mean(SD)	1.96 (1.19)	2.08 (1.19)	1.83 (1.00)	1.68 (0.93)	1.68 (0.89)	1.64 (0.94)
Age at first period						

Menopause. Author manuscript; available in PMC 2019 September 01.

	Former (n=3,908)	Oral low dose CEE (n=846)	Oral conventional dose CEE (n=9,903)	Oral high dose CEE (n=2,004)	Oral Estradiol (n=1,226)	Transdermal Estradiol (n=1,134)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
≤ 9	54 (1.4)	7 (0.8)	122 (1.2)	31 (1.6)	27 (2.2)	19 (1.7)
10	211 (5.4)	40 (4.7)	539 (5.5)	133 (6.7)	73 (6.0)	65 (5.7)
11	665 (17.1)	127 (15.1)	1547 (15.7)	343 (17.2)	208 (17.0)	171 (15.1)
12	1024 (26.3)	234 (27.8)	2670 (27.1)	534 (26.7)	312 (25.5)	318 (28.1)
13	1073 (27.5)	241 (28.6)	2894 (29.3)	568 (28.4)	341 (27.9)	324 (28.6)
14	489 (12.6)	116 (13.8)	1198 (12.1)	221 (11.1)	166 (13.6)	126 (11.1)
15	220 (5.6)	44 (5.2)	530 (5.4)	107 (5.4)	56 (4.6)	68 (6.0)
16	122 (3.1)	26 (3.1)	277 (2.8)	42 (2.1)	31 (2.5)	33 (2.9)
≥ 17	37 (0.9)	8 (0.9)	90 (0.9)	21 (1.1)	10 (0.8)	7 (0.6)
Age at first birth, y						
Never pregnant/No term pregnancies	460 (13.1)	98 (12.8)	1032 (11.4)	207 (11.0)	140 (12.4)	112 (10.8)
< 20	540 (15.4)	100 (13.1)	1289 (14.3)	374 (20.0)	150 (13.3)	165 (15.9)
20 – 29	2263 (64.6)	505 (66.0)	6138 (68.0)	1210 (64.6)	774 (68.5)	694 (66.7)
≥ 30	239 (6.8)	62 (8.1)	568 (6.3)	83 (4.4)	66 (5.8)	69 (6.6)
Number of pregnancies						
Never pregnant	359 (9.2)	82 (9.7)	819 (8.3)	161 (8.1)	104 (8.5)	85 (7.5)
1	291 (7.5)	63 (7.5)	659 (6.7)	154 (7.7)	91 (7.4)	75 (6.6)
2	775 (19.9)	183 (21.7)	2026 (20.6)	429 (21.5)	307 (25.1)	264 (23.4)
3	863 (22.2)	182 (21.6)	2396 (24.3)	473 (23.7)	270 (22.1)	280 (24.8)
4	693 (17.8)	138 (16.4)	1736 (17.6)	357 (17.9)	195 (16.0)	163 (14.4)
≥ 5	907 (23.3)	194 (23.0)	2209 (22.4)	421 (21.1)	255 (20.9)	263 (23.3)
Number of term pregnancies						
Never pregnant	359 (9.2)	82 (9.7)	819 (8.3)	161 (8.1)	104 (8.5)	85 (7.5)
No term pregnancies	101 (2.6)	16 (1.9)	213 (2.2)	46 (2.3)	36 (3.0)	27 (2.4)
1	353 (9.1)	73 (8.7)	842 (8.6)	215 (10.8)	103 (8.4)	100 (8.9)
2	986 (25.4)	234 (27.8)	2578 (26.2)	560 (28.1)	396 (32.5)	349 (30.9)
3	972 (25.0)	205 (24.3)	2580 (26.2)	499 (25.0)	287 (23.5)	293 (26.0)

	Former (n=3,908)	Oral low dose CEE (n=846)	Oral conventional dose CEE (n=9,903)	Oral high dose CEE (n=2,004)	Oral Estradiol (n=1,226)	Transdermal Estradiol (n=1,134)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
4	570 (14.7)	123 (14.6)	1535 (15.6)	291 (14.6)	169 (13.9)	142 (12.6)
≥ 5	547 (14.1)	110 (13.0)	1270 (12.9)	221 (11.1)	125 (10.2)	133 (11.8)
Prior HT use	3908 (100.0)	215 (25.4)	1951 (19.7)	341 (17.0)	295 (24.1)	314 (27.7)

CEE denotes conjugated equine estrogens.

* Low-dose CEE is defined as <0.625 mg/d. +Conventioanl-dose CEE is defined as 0.625 mg/d. #High-dose CEE is defined as >0.625 mg

Table 2

Direct Comparison of Transdermal HT and Oral Conventional Dose CEE in women with a hysterectomy

	Transdermal HT vs. Oral Conventional-dose CEE			
Total Invasive Breast Cancer Incidence	**# cases by baseline HT**		**HR (95% CI)**	
	Transdermal	**Conv. dose CEE**		
With Hysterectomy				
Total Cohort	35	343	0.75	(0.47, 1.19)
<10 yrs since menopause	8	73	0.71	(0.30, 1.67)
≥10 yrs since menopause	27	270	0.75	(0.44, 1.30)

Low-dose CEE is defined as <0.625 mg/d. Conventional-dose CEE is defined as 0.625 mg/d.

All HR are from a Cox proportional hazard model stratified by baseline 5-year age intervals, and adjusted for age (linear), race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, Other), smoking (never, former, current), quartiles of total recreational physical activity, BMI categories (<25, 25–<30, ≥30), BMI (linear), treated diabetes (no,yes), oophorectomy (no, partial, bilateral), education and household income, alcohol consumption, parity, cumulative frequency of mammography, Gail score for breast cancer (this takes into account family history, menarche, and age at 1st birth), prior HT use.

Table 3

Direct Comparison of Oral High-Dose CEE and Oral Low-Dose CEE versus Conventional Dose CEE in women with a hysterectomy

	Oral High dose (>0.625mg) vs. Oral Conventional-dose CEE (0.625mg)				Oral Low dose (<0.625mg) vs. Oral Conventional-dose CEE (0.625mg)			
Total Invasive Breast Cancer Incidence	**# cases by baseline HT**		**HR (95% CI)**		**# cases by baseline HT**		**HR (95% CI)**	
	High dose CEE	**Conv. dose CEE**			**Low dose CEE**	**Conv. dose CEE**		
With Hysterectomy								
Total Cohort	64	343	0.87	(0.61, 1.25)	30	343	0.99	(0.65, 1.48)
<10 yrs since menopause	10	73	0.92	(0.41, 2.05)	1	73	1.05	(0.38, 2.94)
≥10 yrs since menopause	54	270	0.86	(0.57, 1.29)	29	270	0.99	(0.63, 1.55)

Low-dose CEE is defined as <0.625 mg/d. Conventional-dose CEE is defined as 0.625 mg/d.

All HR are from a Cox proportional hazard model stratified by baseline 5-year age intervals, and adjusted for age (linear), race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, Other), smoking (never, former, current), quartiles of total recreational physical activity, BMI categories (<25, 25–<30, ≥30), BMI (linear), treated diabetes (no,yes), oophorectomy (no, partial, bilateral), education and household income, alcohol consumption, parity, cumulative frequency of mammography, Gail score for breast cancer (this takes into account family history, menarche, and age at 1st birth), prior HT use.

Table 4

Direct Comparison of Oral Estradiol and Conventional Dose CEE in women with a hysterectomy

	Oral Estradiol vs. Oral Conventional-dose CEE			
Total Invasive Breast Cancer Incidence	**# cases by baseline HT**		**HR (95% CI)**	
	Oral Estradiol	**Conv. dose CEE**		
With Hysterectomy				
Total Cohort	51	343	1.20	(0.84, 1.39)
<10 yrs since menopause	18	73	1.46	(0.78, 2.73)
≥10 yrs since menopause	33	270	1.05	(0.67, 1.66)

Conventional-dose CEE is defined as 0.625 mg/d.

All HR are from a Cox proportional hazard model stratified by baseline 5-year age intervals, and adjusted for age (linear), race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, Other), smoking (never, former, current), quartiles of total recreational physical activity, BMI categories (<25, 25–<30, ≥30), BMI (linear), treated diabetes (no,yes), oophorectomy (no, partial, bilateral), education and household income, alcohol consumption, parity, cumulative frequency of mammography, Gail score for breast cancer (this takes into account family history, menarche, and age at 1st birth), prior HT use