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# Update in Hormone Therapy Use in Menopause

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The original report from the Women's Health Initiative (WHI) changed our understanding of the benefits and risks of hormone therapy. Since that time, reanalysis of the WHI and additional data from other studies have further refined these concepts. Here we provide an update on recent advances in the field. Menopausal hormone therapy continues to have a clinical role in the management of vasomotor symptoms. However, our understanding of the role of hormones in cardiovascular disease and breast cancer continues to evolve. Further analyses of the effect of age and proximity to menopause at the time of initiation of therapy, duration of treatment, dose, route of administration, and the persistence of risks and benefits after stopping hormone therapy are described. In addition, recent data have emerged suggesting that there may be a link between hormone therapy and cancers of the lung and ovary. Finally, we discuss new advances in hormone therapy that will likely lead to a more favorable benefit-to-risk ratio, enabling safer effective menopausal symptom relief. (***J Clin Endocrinol Metab*** **96: 255–264, 2011)**

Over the past several decades, a large number of observational studies suggested that the use of hormone therapy in menopause not only relieved vasomotor symptoms, but also reduced the risk of several chronic medical conditions such as osteoporosis and cardiovascular disease. However, in 2002, the results of a prospective randomized trial, the Women's Health Initiative (WHI), demonstrated that many of the benefits identified in observational studies were not present in a population randomized to treatment; some hypothesized that the previously purported benefits may have been due not to the therapy but rather to confounding and selection biases, as well as other methodological limitations. In response to the findings of the WHI and other randomized trials, menopausal hormone therapy (MHT) use declined dramatically. The WHI confirmed a decreased risk of osteoporosis and fractures in menopausal women assigned to hormone therapy; it also confirmed an increased risk of breast cancer previously identified in women who use combination estrogen plus progestin (E + P) hormone therapy. However, the WHI trial also revealed that women assigned to MHT had an increase in coronary disease, stroke, and venous thromboembolic events. In the past few years, there has been renewed interest in the risks of MHT, especially that of breast cancer as well as the apparent elevation, rather than reduction, in the risk of coronary events. Since the original publication of the WHI results in 2002, a large number of subsequent studies have looked at these concepts in detail. In addition, recent data have emerged suggesting that there may be a link between hormone therapy and cancers of the lung and ovary. Further analyses of the effect of age and proximity to menopause at the time of initiation of therapy, duration of treatment, dose, route of administration, and the persistence of risks and benefits after stopping hormone therapy have all recently been described. Here we provide an overview of recent developments in this field, including the central role of timing of initiation.

## Coronary Heart Disease (CHD)

The original report from the WHI demonstrated that women randomized to conjugated equine estrogens (CEEs) combined with medroxyprogesterone acetate

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Abbreviations: BMI, Body mass index; CEE, conjugated equine estrogen; CHD, coronary heart disease; CI, confidence interval; E + P, estrogen plus progestin; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate; TSEC, tissue-selective estrogen complex.

(MPA) experienced a small increased risk of CHD events relative to women receiving placebo [hazard ratio (HR), 1.24; 95% confidence interval (CI), 0.97–1.60] (1). Although this increased risk did not reach statistical significance in adjusted analysis, it refuted the idea that hormone therapy could reduce CHD in most women. Moreover, women randomized to CCE alone had approximately the same risk of coronary events as did women receiving placebo.

In the observational studies and in animal models that suggested beneficial cardiovascular effects of hormone therapy, the subjects generally initiated therapy at the time of menopause (often for management of vasomotor symptoms), or in animal studies, treatment began immediately after ovariectomy. This contrast with the WHI, where treatment was initiated more than a decade after menopause in most study participants, led to development of the "timing hypothesis." This theory proposed that initiation of MHT at or shortly after menopause is cardioprotective, whereas starting treatment at a time remote from menopause may be harmful. Indeed, in the WHI, the trend toward lower rates of CHD events was noted in women who were within 10 yr of menopause or who were 50–59 yr old at the time of entry into the trial (1, 2). In the E + P arm, women within 10 yr of the menopausal transition had an HR of CHD events of 0.89, compared with 1.71 in those more than 20 yr from menopausal transition. In the CEE-alone arm, those aged 50–59 yr had an HR of 0.56, compared with older women where the HR approached 1.0. Additionally, women enrolled in the CEE trial and aged 50–59 at baseline had coronary calcium measured by computed tomography; women who received CEE had significantly lower scores at trial completion than those who received placebo (3). In this young population, the incidence of coronary events was low, and the absolute risk of clinical CHD events was small. In a more recent analysis, the results were examined after pooling the data from the WHI estrogen-alone and E + P trials (4). Women enrolled within 10 yr from the onset of menopause had an HR for CHD of 0.76 (CI, 0.50–1.16). The HR continued to rise with years from menopause. Initiating therapy from 10 to 19 yr after menopause gave an HR of 1.10 (CI, 0.84–1.45), and when initiated after 20 or more years, the HR was 1.28 (CI, 1.03–1.58). The *P* value for trend was 0.02, supporting the timing hypothesis, which predicts that protection from atherosclerosis is evident only when hormone therapy is initiated proximal to the onset of menopause and before the development of advanced atherosclerotic plaques.

The timing hypothesis is further supported by several recent studies. A Bayesian meta-analysis of hormone therapy mortality in younger postmenopausal women (mean age, 55 yr) presented the combined results of 19 randomized clinical trials that enrolled 16,000 women at a mean age of 55 yr, totaling 83,000 patient-years. This study showed a relative risk of mortality of 0.73, with a 95% CI of 0.52–0.96 (5). The analysis also demonstrated a cardiovascular benefit when MHT was initiated early, supporting the timing hypothesis. Current ongoing prospective randomized trials will formally test this hypothesis. Two ongoing trials, the Kronos Early Estrogen Prevention Study (KEEPS) and the Early *vs.* Late Intervention Trial with Estradiol (ELITE), will test the timing hypothesis by measuring the effect of early intervention with hormone therapy on development and progression of atherosclerosis (6).

A recent publication suggests that a woman's baseline cardiovascular risk may modulate her CHD outcome on hormone therapy (7). A nested case control study was performed in the WHI Hormone Trials. Baseline lipids were obtained from 271 patients with CHD and 707 controls. Favorable lipid status at baseline tended to predict better CHD outcomes with the use of either CEE or combined MHT. Women with a low-density lipoprotein (LDL)/high-density lipoprotein (HDL) cholesterol ratio of less than 2.5 showed no increased risk and a trend toward reduction in CHD when using hormones (odds ratio, 0.60; CI, 0.34–1.06). In contrast, women with an elevated LDL/HDL ratio of at least 2.5 had an increased risk of CHD. The odds ratio was 1.73, with a 95% CI of 1.18–2.53 (*P* for interaction = 0.02). The ability to stratify patients into groups who will most benefit or be at greatest risk in terms of cardiovascular effects of hormone therapy is an area of significant interest and has potential to inform clinical decision-making.

Another recently identified predictor of response to hormone therapy is the presence of hot flushes (8). Women who complained of significant hot flushes had vascular function assessed by pulse wave analysis and endothelial function with nitroglycerin and salbutamol challenges. Women with severe hot flushes were susceptible to unfavorable vascular effects of oral estrogen treatment and demonstrated less compliant vasculature after treatment. In the WHI, women who were remote from menopause and had persistent vasomotor symptoms tended to have elevated CVD risk on hormone therapy (4). It is still unclear whether vasomotor symptoms early in menopause predict adverse CVD outcomes on hormone therapy. This important issue requires further study because women with vasomotor symptoms are the ones most likely to seek treatment.

These more recent analyses indicate that the effects of hormone therapy are likely influenced by the timing of initiation and perhaps other identifiable risk factors during the menopausal transition and the years beyond. Greater distance from menopause, adverse lipid profiles, and other cardiovascular disease risk may well increase the risks

of CHD in response to MHT. In contrast, those close to the onset of menopause and with healthy endothelium may even derive benefit. The ability to identify those most likely to receive benefit as well as those most likely to have adverse vascular effects will be further defined in the KEEPS, ELITE, and WHI trials (9). Another recently addressed question is the degree of persistence of benefits and risks after MHT has been stopped. During the 2.4 yr after termination of the WHI CEE + MPA trial, risks of CHD, stroke, and venous thromboembolism among women in the active intervention arm returned toward baseline and were not significantly different from the risks in the placebo group (10).

## Thromboembolism

A recent large meta-analysis examined the risk of venous thromboembolism in women using hormone therapy (11). The odds ratio of first time venous thromboembolism in current users of oral estrogen therapy was significantly elevated, with a relative risk of 2.5 and CI of 1.9–3.4. The thromboembolism risk was also elevated in current users of transdermal estrogen preparations; however, the risk did not reach statistical significance in this group (relative risk, 1.2; CI, 0.9–1.7). In this study, the risk of venous thromboembolism was similar between unopposed oral estrogen and oral MHT. Former users of oral estrogen had a similar risk of venous thromboembolism to never-users, suggesting that this effect is due to increased production of clotting factors rather than vascular damage. The post-stopping findings of the WHI also showed a return to baseline risk during the 2.4-yr postintervention period (10).

Although numerous studies have suggested that venous thromboembolic risk is lower with transdermal hormone preparation, none of these studies have been randomized trials, nor have they fully taken into account the differences in dosing regimens. The effect of oral *vs.* transdermal therapy needs to be tested in a randomized clinical trial before reaching conclusions of superiority. Oral regimens provide superior benefits on lipids, showing greater reductions in total cholesterol and LDL and increases in HDL than do transdermal preparations. However, clotting factors and triglycerides are raised to a greater degree by the use of oral preparations. Trials such as KEEPS will help to determine whether these changes in lipids and coagulation factors contribute to atherosclerosis in newly menopausal women. Appropriately powered randomized clinical trials are needed to determine whether changes in risk factors and biomarkers will translate into changes in cardiovascular outcomes over time. The immediate adverse effect on coagulation needs to be balanced against the potential long-term benefits of oral therapy on atherosclerosis.

## Cancer

### Breast cancer

The effects of MHT on cancers, in particular breast cancer, has caused concern among patients considering MHT; this risk is the most commonly cited reason for women avoiding or discontinuing MHT during the menopausal transition. Well before the release of the results of the WHI, an increased risk of breast cancer had been attributed to the use of hormone therapy, especially combination E + P; however, the absolute risk was small and was thought to be outweighed by the tremendous benefit incorrectly ascribed to hormone therapy in reducing cardiovascular disease. The WHI confirmed the effect of combination MHT on breast cancer. However, surprisingly, the WHI also showed no significant increase in the risk of breast cancer among women using CEE alone for an average of 7 yr (relative risk, 0.80; CI, 0.62–1.04) (12). Subsequent subgroup analysis demonstrated that women who were compliant with study medication (CEE) had a significant reduction in invasive breast cancer (13). This effect may be due to the time between onset of menopause and the start of therapy. Starting estrogen more than 5 yr from the onset of menopause was associated with a significant reduction in risks of breast cancer (relative risk, 0.58; CI, 0.36–0.93), whereas starting immediately provided no advantageous effect (13). Prior users of estrogen therapy, who tended to start estrogen closer to the onset of menopause, did not experience a reduction of breast cancer, whereas those who had not used estrogen before entry in the trial saw a reduction in breast cancer. The effect of this so-called "gap time" may explain these unexpected findings, although this concept remains controversial and should certainly not serve as an indication for hormone therapy use.

Evidence for the gap time hypothesis remains limited, but a recent observational study from France similarly demonstrated that the risk of breast cancer varied with gap time (14). Between 1992 and 2005, a total of 1,726 invasive breast cancers were identified among 53,310 postmenopausal women during an average of 8.1 yr of follow-up. The risk of breast cancer varied according to the timing of treatment initiation. Within the first 2 yr after MHT initiation, the HR for detection of breast cancer was 1.54 (CI, 1.28–1.86) when treatment was initiated within 3 yr from the onset of menopause, whereas it was not elevated (HR, 1.00; CI, 0.68–1.47) when treatment was initiated after a greater than 3-yr absence from sex steroid exposure.

The gap time hypothesis is further supported by studies using estrogen to treat breast cancer. In postmenopausal women, breast tumors that express estrogen receptor respond to treatment with high-dose estrogen therapy (using

far greater doses than are used in MHT); however, similar tumors in premenopausal women do not respond to estrogen. The decline in estrogen levels associated with menopause may sensitize breast cancer cells to the pro-apoptotic effects of estrogen. Estrogen deprivation using aromatase inhibitors also sensitizes hormone receptor-positive breast cancers to later treatment with estrogen. Recent clinical trials have shown that high doses of estrogen therapy can be used to treat postmenopausal breast cancers and that estrogen treatment also resensitizes them to the beneficial effects of estrogen deprivation when subsequently treated with aromatase inhibitors (15). Similarly, estrogen deprivation before the initiation of menopausal estrogen therapy may sensitize nascent breast cancer to estrogen, explaining the dichotomy in breast cancer risk between those women initiating estrogen near the onset of menopause and those receiving treatment after a substantial delay. In summary, rapid and dramatic changes in estrogen exposure appear to alter breast cancer growth. Estrogen may induce apoptosis and treat breast cancer after estrogen deprivation, whereas withholding estrogen is known to be an effective treatment for estrogen receptor-positive breast cancers. This paradoxical response to addition or loss of estrogen may explain both the short-term decrease in breast tumors reported after initiating menopausal estrogen treatment and the decrease in breast cancer reported after stopping estrogen.

The gap time hypothesis suggests potentially lower breast cancer risk when estrogen is started remotely from menopause. Obviously this would not be an indication for hormone therapy use and would be of little benefit to women seeking relief of menopausal symptoms at the menopausal transition. Furthermore, the gap time hypothesis suggests that the optimal time of estrogen initiation in regard to breast cancer is far different than for CHD. The timing hypothesis and the gap time hypothesis do not allow for simultaneous optimization of breast and CHD risk reduction.

Short-term suspension of hormone therapy has been suggested as a way to improve the reliability of mammographic screening. Whereas withholding MHT does reduce breast density, it does not reduce the number of women who required second mammograms or the number of interventions due to abnormal mammograms (16). Withholding MHT before mammography is therefore not warranted.

The mechanism by which estradiol and progestins influence breast tissue and breast cancer growth in women is still an open question. Does breast tissue proliferation lead to an increase in diagnosis of occult and previously undiagnosed breast cancer? The majority of invasive breast cancers develop slowly over many years. The diagnosis of breast cancer in less than 5 yr from the onset of treatment in clinical trials such as the WHI suggests that these tumors arose from preexisting undetected cancers before entry into the trials. Therefore, it is likely that E + P exerts a promotional effect on existing occult tumors rather than causing initiation of new tumors. Consistent with this theory are a large number of observational studies that have shown that women diagnosed with breast cancer while using hormone therapy may have a better prognosis than those who are not on hormone therapy. A recent report supports this relationship (17). Over 1000 women who had undergone therapy for breast cancer were followed from 1994–2002. Those who used MHT before diagnosis more often had tumors that were less than 1 cm, node negative, grade 1, and overall they had a decreased risk of death. These data are consistent with MHT promoting the growth of less aggressive estrogen-responsive tumors to the point of diagnosis rather than the development of new tumors. In fact, tumor prognostic factors appear better and survival rates higher for hormone users of any duration; however, this remains controversial. These data are not confirmed by results of the WHI where tumors were similar or even more advanced in women assigned to E + P compared with placebo. In another recent study reporting long-term follow-up of almost 300 women treated for postmenopausal breast cancer, use of hormone therapy for greater than 10 yr correlated with improved prognosis and survival; however, interpretation of these data must be evaluated in light of the results of randomized trials (18).

Rapid changes in breast cancer were demonstrated as an effect of cessation of MHT in the WHI (19). The combined results of the postintervention phase of both the estrogen-alone and E + P WHI trials were examined. The elevated risk decreased rapidly after stopping medication despite similar frequency of mammographic screening in all groups. The differences were no longer apparent within 2 yr, which, given the long-term nature of breast cancer development, is more consistent with an alteration of growth of the existing cancers than cessation of new tumor initiation. If hormone therapy were initiating new tumors, these neoplasms would still be detected for many years after cessation of hormone therapy because they become mammographically detectable only after 5–10 yr. A second recent study examined a cohort of 67,000 postmenopausal women in the United States (20). Approximately 2300 cases of invasive breast cancer were diagnosed during 13 yr of follow-up. As expected, current use of E + P was associated with an increased risk of breast cancer, with a relative risk of 1.75. There was no increased risk with the use of estrogen alone. The risk increased within the first 2–3 yr of use and attenuated within 2 yr of ces-

sation. Again, these growth parameters were consistent with an effect of E + P on tumor growth rather than on initiation (21).

Efforts to minimize breast cancer risk during the use of E + P have also considered the differences between sequential and continuous progestin treatment. A recent study showed that sequential progestin use resulted in a trend toward a smaller increase in relative risk of breast cancer compared with continuous progestin use (22). In this study, oral and transdermal E + P therapies were both associated with comparable risk elevations in breast cancer. The use of norethisterone acetate was accompanied by a higher risk than that of MPA. These data suggest that sequential or cyclic therapy may have a less adverse effect on cancer risk, whereas the route of administration of the progestin did not matter.

## Endometrial cancer

Endometrial cancer is common, being diagnosed in approximately 40,000 women annually. The majority of these are diagnosed after the age of 50. Endometrioid (type I) endometrial cancer is by far the most common variant and is usually well differentiated and hormonally responsive. Papillary serous and clear cell endometrial cancers are poorly differentiated, are usually diagnosed late, are not hormonally responsive, and may arise in the untreated postmenopausal women; in contrast, endometrioid endometrial cancers are almost never seen without estrogen exposure and are induced by unopposed estrogen at a high rate. As a result of unopposed estrogen use, endometrial hyperplasia or cancer will occur in nearly half of women within 3 yr. Although either continuous or sequential progestin administration largely negates the increased risk as demonstrated in numerous trials including the WHI (23), long-term variations between progestin regimens have been recently described (24). Data from nearly 250,000 MHT users in Finland were extracted from a national registry. The use of continuous daily progestin therapy for 3 yr or more was associated with a significant reduction in the risk of type I endometrial cancer. All approved progestins appear to be similarly effective. The use of continuous E + P therapy was associated with a 76% reduced risk of endometrial cancer (CI, 6–60%). This effect was first observed after 3 to 5 yr of use and persisted after 10 yr. In contrast, sequential therapies did not produce the same decrease in risk; surprisingly, long-term use (more than 5 yr) was associated with an increased risk compared with those who never used MHT. Moreover, the use of sequential progestin every third month demonstrated a further increase in risk of nearly 300%. Although these cancers are estrogen sensitive and cure rates after treatment are quite high, the use of continuous regimen will largely prevent any increased risk. However, the decrease in endometrial cancer risk must be balanced with the data presented above that demonstrate a less adverse effect of sequential progestin regimens compared with continuous administration in relation to breast cancer risk.

## Ovarian cancer

Several recent studies have shown a small but significantly increased risk of epithelial ovarian cancer in current and recent users of estrogen therapy (25). A population-based study was conducted involving a prospective cohort of all Danish women aged 50–79 who used hormone therapy and were followed from 1995 through 2005; nearly 1 million women were assessed for ovarian cancer (26). Over 3000 incident ovarian cancers were detected, of which 2681 were epithelial cancers. Compared with women who never took hormone therapy, users of MHT had an increased relative risk of 1.38 (95% CI, 1.26–1.51) for all ovarian cancers and 1.44 (95% CI, 1.30–1.58) for epithelial ovarian cancer. The risk declined after cessation of therapy. The risk was no longer statistically significant by 2 yr after discontinuation; the CI reached 1.0 by 2–4 yr and was actually significantly decreased after 6 yr. Although the relative risk of ovarian cancer was increased with the use of MHT, the absolute risk was quite small. There was approximately one extra ovarian cancer for every 8300 women taking hormone therapy per year. These effects were seen regardless of the duration or formulation of hormone administration. Similarly, the WHI also noted an increase in ovarian cancer risk, although it did not reach statistical significance. Twenty cases of ovarian cancer were diagnosed in women receiving E + P, whereas only 12 were diagnosed in women receiving placebo (23). Because ovarian cancer is not usually thought of as an estrogen-responsive tumor, the biological basis of this effect will be an interesting focus of future investigations. However, due to the small excess risk, the elevated risk of ovarian cancer will be unlikely to influence prescribing habits.

## Colon cancer

Observational studies have previously found a reduction in the risk of colon cancer associated with hormone use, especially among women who used E + P-based regimens. Although overall diagnoses were decreased, a larger proportion of poor prognosis tumors were detected in WHI among the E + P users (28). In the estrogen-alone arm of the WHI, there was no reduction in the risk of colorectal cancer (29). Tumor size, stage, and grade were comparable, as was mortality. In a postintervention phase of the WHI, with a mean follow-up of 2.4 yr, the incidence

of colorectal cancer was no longer decreased (10). Therefore, the potential decrease in colorectal cancer risk with active therapy will not persist beyond current use. This purported benefit is fleeting and is also unlikely to alter patterns of hormone therapy use.

### Lung cancer

The WHI demonstrated a trend toward an increase in lung cancer in women receiving E + P compared with those receiving placebo. However, when mortality was examined, more women died from non-small cell lung cancer in the E +P group compared with placebo. Furthermore, in the postintervention period of the WHI trial, women assigned to the E +P arm of the study continued to have an increased mortality from lung cancer (30). After a mean of 5.6 yr of treatment and 2.4 yr of additional follow-up, the HR for lung cancer diagnosis was 1.23, with a CI of 0.92–1.63. More women died from lung cancer in the combined hormone therapy group than the placebo group (73 *vs.* 40 deaths, respectively; HR, 1.71; CI, 1.16–2.52). Although treatment with E +P does not significantly increase the incidence of lung cancer, it does increase death from lung cancer, and the risk continues after cessation of therapy. This should be of concern to hormone therapy users who are smokers or who have other risk factors for lung cancer.

## Stroke

The incidence of stroke is clearly age dependent. When a prospective observational study was performed on the women enrolled in the Nurses Health Study, both MHT and estrogen therapies were associated with an increased risk of stroke similar to the findings of the WHI (31). The increased risk was evaluated both in women initiating hormone therapy at a young age, near the menopausal transition, and at more than 10 yr from menopause. A similar relative increase was found in those initiating MHT near the menopausal transition as was found in those starting at a later age; however, the absolute incidence of stroke was relatively low in young women. Furthermore, in the Nurses' Health Study, women within 4 yr of menopause onset and taking lower than traditional doses of MHT did not have an elevation in stroke risk. Whether timing of initiation is associated with an increased risk of carotid atherosclerosis will also be tested in studies such as KEEPS and ELITE, which examine carotid artery intima-media thickness. Vascular changes noted in these studies may be predictors of not only CHD but also cerebral vascular disease and stroke.

## Cognitive Function

Beneficial effects of estrogen on cognitive function have been frequently reported. Complaints of memory loss are common at the time of the menopausal transition. Dementia, including Alzheimer's disease, climbs steeply with age. The incidence varies with gender, and more women are diagnosed with Alzheimer's disease than men. Although some of this difference may be due to the greater longevity of women compared with men, a direct effect of estrogen has been proposed. Dementia has been examined as an endpoint in the WHIMS (WHI Memory Study) Trial, a substudy of the WHI that included women older than 65 yr at the time of randomization. The risk of dementia was shown to be increased by MHT in WHIMS. The effect of CEE + MPA on cognitive function in the same population was examined in the WHI Study of Cognitive Aging (WHISCA) (32). The results varied by cognitive domain examined in these older women, suggesting beneficial and detrimental actions of ovarian hormones on cognitive ability in women remote from menopause. It has been speculated that the timing hypothesis may also apply to dementia, similar to the role of timing in coronary disease as discussed above. Younger women exposed to estrogen may have different outcomes compared with those who initiated exposure at 65 yr or older, as was the case in WHIMS. A recent study supports the application of the timing hypothesis to central nervous system disease (33). Women 65 yr of age and older were recruited in a French study. These women were administered a battery of cognitive tests. In the examination of over 3000 naturally postmenopausal women, current hormone therapy users performed significantly better than never-users, with a more beneficial effect seen with longer duration of therapy. However, in contradistinction to the timing hypothesis, initiation of MHT close to the menopause was not associated with improved cognition, and MHT did not significantly reduce dementia risk over the course of this study.

Almost 900 postmenopausal women with prior hysterectomy and a mean age of 64, who were free of dementia and were enrolled in the WHI and also the WHIMS CEE trial were assessed for changes in cognitive function. Compared with placebo, unopposed CEE use was associated with lower spatial rotational ability; however, CEE use did not influence any other cognitive function examined. These women were also followed for 2.7 yr after stopping hormone therapy. In the postintervention trial, CEE did not appear to have enduring effect on cognitive function in older women. In another study, magnetic resonance imaging was performed on over 1400 women 1–4 yr after they had participated in the WHI randomized placebo-

controlled trials of CEE (34). Women included in this study were ages 65–80 and free of dementia or other cognitive impairment at baseline. The 53 women who developed cognitive impairment or dementia had relatively smaller hippocampal and total brain volumes. In older women who developed cognitive impairment or dementia, it would be interesting to determine whether increased brain atrophy could predict which women would respond in a negative way to hormone therapy or whether the therapy contributed to the observed effect. Currently, the KEEPS trial is examining the effect of MHT on cognitive function in newly menopausal women.

## Menopausal Symptoms

There is little doubt that hormone therapy affects quality of life in symptomatic women by decreasing the number of hot flushes, improving associated vasomotor symptoms, and improving sleep. A recent prospective randomized trial conducted in the United Kingdom assessed health-related quality of life after combined hormone replacement therapy (35). A total of 3721 women with a uterus were randomized to combined E + P or placebo. When compared with placebo, women assigned to combined MHT had decreased severity of vasomotor symptoms, improved sexual functioning, and diminished sleep problems. Fewer women in the MHT group reported hot flushes, night sweats, aching joints and muscles, insomnia, or vaginal dryness. No significant differences in other menopausal symptoms or in depression were observed. Although these changes affect only quality of life, menopausal symptoms are experienced by the vast majority of hormone therapy users. The number of women receiving this benefit would be large in comparison to those affected by the risks previously discussed.

Large numbers of women currently seek relief of vasomotor symptoms during the menopausal transition. Because these symptoms primarily affect quality of life, one must weigh the clear benefits of MHT on symptoms against the risk of CHD, stroke, thromboembolism, and cancer. Also to be considered is the duration of effect, especially in light of the postintervention WHI data showing that many of the benefits dissipate after completion of therapy (10). Although thromboembolism risk decreases, as does the cardiovascular risk, the risk of breast cancer remains elevated. The decreased risk of fracture also dissipates rapidly after cessation of hormone therapy. The benefit on colorectal cancer disappears. Overall, there is an increased risk of diagnosis of all cancers in women in the postintervention phase of the WHI. As a result, it is clear that MHT, although appropriate for symptom management, is not an appropriate intervention for the primary or secondary prevention of chronic disease.

## Alternate MHT Regimens

There has been considerable debate over the use of alternative formulations and different dosing regimens. Low-dose, cyclic, and transdermal formulations have been suggested as potentially favorable alternatives. Unfortunately, no large, prospective, randomized trials exist that carefully compare these alternative regimens. In the KEEPS trial, a transdermal regimen is being directly compared with an oral regimen to determine whether both have an equivalent effect on the progression of atherosclerosis.

When deciding on the appropriate dose of estradiol, one should also take into account the effect of body mass index (BMI). Although age is not associated with serum estradiol concentration in postmenopausal women using hormone therapy, increased BMI does correlate with higher serum estradiol levels in overweight and obese women; when using estrogen therapy, these women achieved greater serum concentrations of estradiol compared with women with a normal BMI (36). Lower estrogen doses may be effective in obtaining therapeutic symptom relief in obese women. However, the therapeutic range of any estrogen has yet to be well defined for most clinical endpoints.

Alternative therapies include phytoestrogen supplements and isoflavones that have been reported to protect against osteoporosis in the menopause; however, multiple studies show little benefit. These include a recently published study that compared four commercial sources of isoflavones to MHT or a bisphosphonate (37). Treatment with most phytoestrogens failed to decrease net bone reabsorption. Dietary supplements were far inferior to either bisphosphonates or MHT. Also, soy provided little benefit in reducing vasomotor or other menopausal symptoms. Similarly, several studies addressed the effect of soy-based phytoestrogens and soy consumption on breast cancer risk. Recently, the Shanghai Women's Health Study correlated soy consumption in over 73,000 women to the development of breast cancer (38). Those who consumed the greatest amount of soy had a significantly reduced premenopausal breast cancer risk (relative risk, 0.41; CI, 0.25–0.70). However, the effect was isolated to premenopausal soy consumption; there was no significant association of soy with postmenopausal breast cancer in this large, population-based, prospective cohort study.

The use of bioidentical hormones has gained popularity in recent years. Bioidentical hormones contain estradiol or progesterone either from a pharmaceutical formulation or compounded locally in pharmacies. Food and Drug Ad-

ministration-approved bioidentical products are limited to micronized estradiol or progesterone. There is no evidence to support any benefit of combining estradiol with estrone or estriol, both weak estrogens. There is also no evidence demonstrating superiority of estradiol administered in a compounded fashion to standard pharmaceutical regimens. Many compounded regimens are delivered by the transdermal route, and although that route of delivery may have advantages, well-designed prospective trials are needed to compare outcomes. The addition of progesterone in bioidentical preparations is variable and inconsistent; women with a uterus should always be administered a progestin to prevent endometrial cancer.

Similarly, there is no evidence that individualizing the dosing of estrogens provides superior outcome to standard dosing. There is evidence to support the fact that thrombotic phenomena are dose related. Given the wide range of dosing options available, starting with low-dose therapy is generally recommended. Currently, CEEs are available in doses as low as 0.3 mg, and estradiol 0.5 mg. Transdermal regimens that deliver daily doses as low as 14 $\mu$g are also available.

## Future Developments in MHT

Whereas there is a real need to treat vasomotor symptoms and sleep disturbance in the menopausal transition, the long-term risks of hormone therapy preclude extended duration of use for the prevention of chronic disease. Although current studies are under way to determine whether CHD risk will be impacted by the timing of initiation, the cancer risks are present at all ages, and some seem to persist after stopping hormone therapy. The reduction in hip and vertebral fracture dissipates after stopping hormone therapy, whereas the long-term risk of breast cancer and possibly lung and ovarian cancers continues. Alternative therapies for menopausal symptoms that would not increase the risk of cancer are sorely needed. Because breast cancer seems significantly impacted by the use of progestin, ways to oppose estrogen's effect on the uterus without the use of a progestin are currently under development. The combination of low-dose CEE with a selective estrogen receptor modulator provides a new entity called a tissue-selective estrogen complex (TSEC). Early clinical trials suggests that some TSECs are effective in reducing menopausal symptoms, increasing bone density, providing favorable lipid effects, while not increasing breast cancer risk and providing endometrial protection without a progestin (39–41). Specifically, CEE and bazedoxifene are effective at reducing menopausal symptoms, have a favorable safety profile, improve bone density, and have limited unfavorable side effects (27, 42, 43). Animal models and *in vitro* studies using human breast cancer cell lines suggest minimal breast stimulation. Estrogen remains the most effective therapy for relief of vasomotor and other menopausal symptoms. The TSEC combination promises to be a significant improvement in the relief of vasomotor symptoms with potentially lower risks than traditional MHT.

## Therapeutic Implications

Recent progress in menopausal therapy research reinforces current guidelines for hormone use. Hormone therapy is appropriate for relief of vasomotor symptoms but should not be used for chronic disease prevention. Hormone therapy should be used for limited duration. Fracture prevention is an important benefit of hormone therapy, but this benefit is rapidly lost after cessation of hormone therapy. A transition to a selective estrogen receptor modulator or bisphosphonate will provide continued benefit after cessation of MHT for those in need of osteoporosis prevention or treatment. Because of the potential harms of long-term use of MHT, including the long-term rising risk of breast and potentially lung and ovarian cancer, therapy should be discontinued after treatment of vasomotor symptoms or other menopause-related symptoms is no longer required. Although reduction in CHD risk may be seen after long-term therapy in newly menopausal women, prevention of CHD is not an indication for therapy. We await the results of the KEEPS and ELITE trials for additional insights. However, any potential cardiovascular benefits in young women may be offset by the increasing risk of breast cancer as discussed above, especially with combination E + P therapy. Perhaps with the development of new hormone therapies that do not stimulate breast proliferation, such as the TSECs, longer term therapy may become appropriate for some women.

In summary, MHT continues to have a clinical role in the management of vasomotor symptoms. The evidence for the use of MHT in young menopausal women for chronic disease prevention is still under evaluation, and women should not be prescribed MHT for this purpose at the present time. Hormone therapy remains an appropriate strategy for management of menopausal symptoms in women during the menopausal transition. Although there is an increased risk of certain cardiovascular outcomes and cancer, the absolute risk for these events is low, especially in the age group most in need of symptom relief. Symptomatic women will receive quality of life benefit from the use of hormone therapy with minimal risk over the short term. Initiation of hormone therapy is not appropriate for women more than 10 yr from their last menstrual period or for those at high baseline risk of cardiovascular disease

or breast cancer. Alternative therapies are available for chronic disease prevention in high-risk groups.

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## References

1. **Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M** 2003 Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 349:523–534
2. **Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S** 2004 Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 291:1701–1712
3. **Manson JE, Allison MA, Rossouw JE, Carr JJ, Langer RD, Hsia J, Kuller LH, Cochrane BB, Hunt JR, Ludlam SE, Pettinger MB, Gass M, Margolis KL, Nathan L, Ockene JK, Prentice RL, Robbins J, Stefanick ML** 2007 WHI and WHI-CACS Investigators. Estrogen therapy and coronary-artery calcification. N Engl J Med 356:2591–2602
4. **Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, Ko M, LaCroix AZ, Margolis KL, Stefanick ML** 2007 Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 297:1465–1477
5. **Salpeter SR, Cheng J, Thabane L, Buckley NS, Salpeter EE** 2009 Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. Am J Med 122:1016–1022.e1
6. **Harman SM, Brinton EA, Cedars M, Lobo R, Manson JE, Merriam GR, Miller VM, Naftolin F, Santoro N** 2005 KEEPS: The Kronos Early Estrogen Prevention Study. Climacteric 8:3–12
7. **Bray PF, Larson JC, Lacroix AZ, Manson J, Limacher MC, Rossouw JE, Lasser NL, Lawson WE, Stefanick ML, Langer RD, Margolis KL** 2008 Women's Health Initiative Investigators. Usefulness of baseline lipids and C-reactive protein in women receiving menopausal hormone therapy as predictors of treatment-related coronary events. Am J Cardiol 101:1599–1605
8. **Tuomikoski P, Ebert P, Groop PH, Haapalahti P, Hautamäki H, Rönnback M, Ylikorkala O, Mikkola TS** 2009 Effect of hot flushes on vascular function: a randomized controlled trial. Obstet Gynecol 114:777–785
9. **Miller VM, Black DM, Brinton EA, Budoff MJ, Cedars MI, Hodis HN, Lobo RA, Manson JE, Merriam GR, Naftolin F, Santoro N, Taylor HS, Harman SM** 2009 Using basic science to design a clinical trial: baseline characteristics of women enrolled in the Kronos Early Estrogen Prevention Study (KEEPS). J Cardiovasc Transl Res 2:228–239
10. **Heiss G, Wallace R, Anderson GL, Aragaki A, Beresford SA, Brzyski R, Chlebowski RT, Gass M, LaCroix A, Manson JE, Prentice RL, Rossouw J, Stefanick ML** 2008 WHI Investigators. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA 299:1036–1045
11. **Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY** 2008 Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ 336:1227–1231
12. **Prentice RL, Chlebowski RT, Stefanick ML, Manson JE, Langer RD, Pettinger M, Hendrix SL, Hubbell FA, Kooperberg C, Kuller LH, Lane DS, McTiernan A, O'Sullivan MJ, Rossouw JE, Anderson GL** 2008 Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative clinical trial and observational study. Am J Epidemiol 167:1407–1415
13. **Stefanick ML, Anderson GL, Margolis KL, Hendrix SL, Rodabough RJ, Paskett ED, Lane DS, Hubbell FA, Assaf AR, Sarto GE, Schenken RS, Yasmeen S, Lessin L, Chlebowski RT** 2006 WHI Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA 295:1647–1657
14. **Fournier A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F** 2009 Estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? J Clin Oncol 27:5138–5143
15. **Ellis MJ, Gao F, Dehdashti F, Jeffe DB, Marcom PK, Carey LA, Dickler MN, Silverman P, Fleming GF, Kommareddy A, Jamalabadi-Majidi S, Crowder R, Siegel BA** 2009 Lower-dose vs high-dose oral estradiol therapy of hormone receptor-positive, aromatase inhibitor-resistant advanced breast cancer: a phase 2 randomized study. JAMA 302:774–780
16. **Buist DS, Anderson ML, Reed SD, Aiello Bowles EJ, Fitzgibbons ED, Gandara JC, Seger D, Newton KM** 2009 Short-term hormone therapy suspension and mammography recall: a randomized trial. Ann Intern Med 150:752–765
17. **Sener SF, Winchester DJ, Winchester DP, Du H, Barrera E, Bilimoria M, Krantz S, Rabbitt S** 2009 The effects of hormone replacement therapy on postmenopausal breast cancer biology and survival. Am J Surg 197:403–407
18. **Christante D, Pommier S, Garreau J, Muller P, LaFleur B, Pommier R** 2008 Improved breast cancer survival among hormone replacement therapy users is durable after 5 years of additional follow-up. Am J Surg 196:505–511
19. **Chlebowski RT, Kuller LH, Prentice RL, Stefanick ML, Manson JE, Gass M, Aragaki AK, Ockene JK, Lane DS, Sarto GE, Rajkovic A, Schenken R, Hendrix SL, Ravdin PM, Rohan TE, Yasmeen S, Anderson G** 2009 WHI Investigators. Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med 360:573–587
20. **Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, Feuer EJ, Edwards BK, Berry DA** 2007 The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med 356:1670–1674
21. **Calle EE, Feigelson HS, Hildebrand JS, Teras LR, Thun MJ, Rodriguez C** 2009 Postmenopausal hormone use and breast cancer associations differ by hormone regimen and histologic subtype. Cancer 115:936–945
22. **Lyytinen H, Pukkala E, Ylikorkala O** 2009 Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. Obstet Gynecol 113:65–73
23. **Anderson GL, Judd HL, Kaunitz AM, Barad DH, Beresford SA, Pettinger M, Liu J, McNeeley SG, Lopez AM** 2003 Women's Health Initiative Investigators. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA 290:1739–1748
24. **Jaakkola S, Lyytinen H, Pukkala E, Ylikorkala O** 2009 Endometrial cancer in postmenopausal women using estradiol-progestin therapy. Obstet Gynecol 114:1197–1204

25. **Rossing MA, Cushing-Haugen KL, Wicklund KG, Doherty JA, Weiss NS** 2007 Menopausal hormone therapy and risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev 16:2548–2556
26. **Mørch LS, Løkkegaard E, Andreasen AH, Krüger-Kjaer S, Lidegaard O** 2009 Hormone therapy and ovarian cancer. JAMA 302: 298–305
27. **Peano BJ, Crabtree JS, Komm BS, Winneker RC, Harris HA** 2009 Effects of various selective estrogen receptor modulators with or without conjugated estrogens on mouse mammary gland. Endocrinology 150:1897–1903
28. **Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, Hubbell FA, Ascensao J, Rodabough RJ, Rosenberg CA, Taylor VM, Harris R, Chen C, Adams-Campbell LL, White E** 2004 Women's Health Initiative Investigators. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 350:991–1004
29. **Ritenbaugh C, Stanford JL, Wu L, Shikany JM, Schoen RE, Stefanick ML, Taylor V, Garland C, Frank G, Lane D, Mason E, McNeeley SG, Ascensao J, Chlebowski RT** 2008 Women's Health Initiative Investigators. Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. Cancer Epidemiol Biomarkers Prev 17:2609–2618
30. **Chlebowski RT, Schwartz AG, Wakelee H, Anderson GL, Stefanick ML, Manson JE, Rodabough RJ, Chien JW, Wactawski-Wende J, Gass M, Kotchen JM, Johnson KC, O'Sullivan MJ, Ockene JK, Chen C, Hubbell FA** 2009 Women's Health Initiative Investigators. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. Lancet 374:1243–1251
31. **Grodstein F, Manson JE, Stampfer MJ, Rexrode K** 2008 Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. Arch Intern Med 168: 861–866
32. **Resnick SM, Maki PM, Rapp SR, Espeland MA, Brunner R, Coker LH, Granek IA, Hogan P, Ockene JK, Shumaker SA** 2006 Women's Health Initiative Study of Cognitive Aging Investigators. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. J Clin Endocrinol Metab 91:1802–1810
33. **Ryan J, Carrière I, Scali J, Dartigues JF, Tzourio C, Poncet M, Ritchie K, Ancelin ML** 2009 Characteristics of hormone therapy, cognitive function, and dementia: the prospective 3C Study. Neurology 73:1729–1737
34. **Espeland MA, Tindle HA, Bushnell CA, Jaramillo SA, Kuller LH, Margolis KL, Mysiw WJ, Maldjian JA, Melhem ER, Resnick SM** 2009 Women's Health Initiative Memory Study. Brain volumes, cognitive impairment, and conjugated equine estrogens. J Gerontol A Biol Sci Med Sci 64:1243–1250
35. **Welton AJ, Vickers MR, Kim J, Ford D, Lawton BA, MacLennan AH, Meredith SK, Martin J, Meade TW** 2008 WISDOM team. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. BMJ 337:a1190
36. **Karim R, Mack WJ, Hodis HN, Roy S, Stanczyk FZ** 2009 Influence of age and obesity on serum estradiol, estrone, and sex hormone binding globulin concentrations following oral estrogen administration in postmenopausal women. J Clin Endocrinol Metab 94: 4136–4143
37. **Weaver CM, Martin BR, Jackson GS, McCabe GP, Nolan JR, McCabe LD, Barnes S, Reinwald S, Boris ME, Peacock M** 2009 Antiresorptive effects of phytoestrogen supplements compared with estradiol or risedronate in postmenopausal women using (41)Ca methodology. J Clin Endocrinol Metab 94:3798–3805
38. **Lee SA, Shu XO, Li H, Yang G, Cai H, Wen W, Ji BT, Gao J, Gao YT, Zheng W** 2009 Adolescent and adult soy food intake and breast cancer risk: results from the Shanghai Women's Health Study. Am J Clin Nutr 89:1920–1926
39. **Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G** 2009 Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. Fertil Steril 92:1045–1052
40. **Archer DF, Lewis V, Carr BR, Olivier S, Pickar JH** 2009 Bazedoxifene/conjugated estrogens (BZA/CE): incidence of uterine bleeding in postmenopausal women. Fertil Steril 92:1039–1044
41. **Lobo RA, Pinkerton JV, Gass ML, Dorin MH, Ronkin S, Pickar JH, Constantine G** 2009 Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. Fertil Steril 92:1025–1038
42. **Komm BS** 2008 A new approach to menopausal therapy: the tissue selective estrogen complex. Reprod Sci 15:984–992
43. **Kharode Y, Bodine PV, Miller CP, Lyttle CR, Komm BS** 2008 The pairing of a selective estrogen receptor modulator, bazedoxifene, with conjugated estrogens as a new paradigm for the treatment of menopausal symptoms and osteoporosis prevention. Endocrinology 149:6084–6091