

## POSITION STATEMENT

# The 2012 Hormone Therapy Position Statement of The North American Menopause Society

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### Abstract

**Objective:** This position statement aimed to update the evidence-based position statement published by The North American Menopause Society (NAMS) in 2010 regarding recommendations for hormone therapy (HT) for postmenopausal women. This updated position statement further distinguishes the emerging differences in the therapeutic benefit-risk ratio between estrogen therapy (ET) and combined estrogen-progestogen therapy (EPT) at various ages and time intervals since menopause onset.

**Methods:** An Advisory Panel of expert clinicians and researchers in the field of women's health was enlisted to review the 2010 NAMS position statement, evaluate new evidence, and reach consensus on recommendations. The Panel's recommendations were reviewed and approved by the NAMS Board of Trustees as an official NAMS position statement.

**Results:** Current evidence supports the use of HT for perimenopausal and postmenopausal women when the balance of potential benefits and risks is favorable for the individual woman. This position statement reviews the effects of ET and EPT on many aspects of women's health and recognizes the greater safety profile associated with ET.

**Conclusions:** Recent data support the initiation of HT around the time of menopause to treat menopause-related symptoms and to prevent osteoporosis in women at high risk of fracture. The more favorable benefit-risk ratio for ET allows more flexibility in extending the duration of use compared with EPT, where the earlier appearance of increased breast cancer risk precludes a recommendation for use beyond 3 to 5 years.

**Key Words:** Bioidentical hormones – Breast cancer – Cardiovascular disease – Cognitive decline – Coronary heart disease – Dementia – Depression – Diabetes mellitus – Endometrial cancer – Estrogen – Estrogen-progestogen therapy – Estrogen therapy – Hormone therapy – Menopause – Mood – The North American Menopause Society – Osteoporosis – Ovarian cancer – Perimenopause – Postmenopause – Premature menopause – Premature ovarian insufficiency – Progestogen – Sexual function – Stroke – Total mortality – Urinary health – Quality of life – Vaginal atrophy – Vaginal health – Vasomotor symptoms – Venous thromboembolism – Women's Health Initiative.

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The intent of The North American Menopause Society (NAMS) 2012 Hormone Therapy Position Statement is to clarify the benefit-risk ratio of estrogen therapy (ET) versus estrogen-progestogen therapy (EPT) for both treatment of menopause-related symptoms and disease prevention at various time intervals since menopause. The availability of long-term data related to the effects of hormone therapy (HT) both during and after use of HT prompted the

NAMS Board of Trustees to update its position statement. NAMS convened a seventh Advisory Panel to provide recommendations. The Panel's recommendations were reviewed and approved by the 2011-2012 NAMS Board of Trustees.

The term HT is used to encompass both ET and EPT when outcomes are not specific to one or the other treatment.

These statements do not represent codified practice standards as defined by regulating bodies and insurance agencies.

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This position statement was developed by The North American Menopause Society (NAMS) 2012 Hormone Therapy Position Statement Advisory Panel consisting of representatives of the NAMS Board of Trustees and other experts in women's health: Margery L.S. Gass, MD, NCMP (Co-Chair); JoAnn E. Manson, MD, DrPH, NCMP (Co-Chair); Felicia Cosman, MD; Francine Grodstein, ScD; V. Craig Jordan, OBE, PhD, DSc, FMedSci; Richard H. Karas, MD, PhD; Andrew M. Kaunitz, MD; Pauline M. Maki, PhD; Peter J. Schmidt, MD; Jan L. Shifren, MD, NCMP; Cynthia A. Stuenkel, MD, NCMP; and Wulf H. Utian, MD, PhD, DSc(Med), NCMP. The Board of Trustees approved the position statement on January 15, 2012.

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### METHODS

An Advisory Panel of clinicians and researchers expert in the field of women's health was enlisted to review the previous position statement of July 2010 (available at <http://www.menopause.org/PSHT10.pdf>), evaluate the literature published subsequently, and conduct an evidence-based analysis with the goal of reaching consensus on recommendations.

NAMS acknowledges that no single trial data can be extrapolated to all women. However, because the Women's Health Initiative (WHI) is, for some outcomes, the only large long-term randomized controlled trial (RCT) of postmenopausal women using HT, these findings were given prominent

consideration among all the studies reviewed in the development of this position statement. Nonetheless, the WHI hormone trials had several characteristics that limit generalizing the findings to all postmenopausal women. These include the use of only one route of administration (oral), only one formulation of estrogen (conjugated estrogens [CEs]), and only one progestogen (medroxyprogesterone acetate). Unlike most HT studies that focused on symptomatic, recently postmenopausal women, the WHI enrolled generally healthy postmenopausal women aged 50 to 79 years in a prevention trial. These parameters should be taken into consideration when applying the WHI findings to clinical practice as should be the findings from observational studies with their known limitations. In general, the panel gave more weight to RCTs.

## BENEFITS AND RISKS OF HORMONE THERAPY

### Vasomotor symptoms

ET with or without a progestogen is the most effective treatment of menopause-related vasomotor symptoms and their potential consequences, such as diminished sleep quality, irritability, difficulty concentrating, and subsequently reduced quality of life (QOL).<sup>1,2</sup> Treatment of moderate to severe vasomotor symptoms remains the primary indication for HT. Almost all systemic HT products except for the ultralow-dose estradiol transdermal patch (approved for the prevention of osteoporosis) have government approval for this indication.<sup>3</sup> Progestogen alone also reduces vasomotor symptoms but not as effectively as estrogen does.<sup>4</sup>

### Vaginal symptoms

ET is the most effective treatment of moderate to severe symptoms of vulvar and vaginal atrophy (eg, vaginal dryness, dyspareunia, and atrophic vaginitis).<sup>5</sup> Many systemic HT products and all local vaginal ET products have government approval for treating symptomatic vaginal atrophy. Some low-dose systemic regimens may be inadequate for the relief of vaginal symptoms and may require the addition of low-dose local ET to achieve the desired results. When ET is considered solely for treatment of vaginal atrophy, local vaginal ET is advised. Lower doses of vaginal ET than previously used, with less frequent administration, often yield satisfactory results.<sup>6</sup>

A progestogen is generally not indicated when ET at the recommended low doses is administered locally for vaginal atrophy, although clinical trial data supporting endometrial safety beyond 1 year are lacking.<sup>7</sup> Because endometrial hyperplasia increases with increasing dose and duration of estrogen exposure, thorough evaluation of any uterine bleeding in women using low-dose local ET is advised.

### Sexual function

A significant effect of ET on sexual interest, arousal, and orgasmic response independent from its role in treating menopausal symptoms is not supported by current evidence.<sup>8</sup> Low-dose local ET may improve sexual satisfaction by improving lubrication and increasing blood flow and sensa-

tion in vaginal tissues. In an analysis of the persistence of sexual activity in the WHI, HT was not correlated with longer persistence of sexual activity.<sup>9</sup> HT is not recommended as the sole treatment of other problems of sexual function, including diminished libido.<sup>10</sup>

### Urinary tract health

Local ET may benefit some women with overactive bladder.<sup>11</sup> One RCT found that an estradiol ring had a clinical benefit equivalent to that of oxybutynin among women with overactive bladder.<sup>12</sup> Systemic HT may worsen or provoke stress incontinence.<sup>13-15</sup> Ultralow-dose transdermal estradiol therapy neither increased nor decreased incontinence.<sup>16</sup> A large RCT reported an increased risk of kidney stones with HT.<sup>17</sup>

Two studies reported a decreased risk of recurrent urinary tract infection through the use of intravaginal estrogen.<sup>18,19</sup> Only ET administered by the vaginal route has been shown to be effective for this purpose. No HT product has government approval for any urinary health indication.

### Quality of life

Although no HT product has government approval for enhancing QOL, use of HT can result in an improvement in health-related QOL (HQOL) in symptomatic women through the alleviation of symptoms.<sup>1,2,20</sup> There is no clear evidence that HT improves HQOL in asymptomatic women.<sup>20-23</sup> With regard to physical functioning as a measure of HQOL, data from the WHI found no benefit of HT in women 65 years or older when measured for grip strength, chair standing, and walking.<sup>24</sup>

### Osteoporosis

There is RCT evidence that standard-dose HT reduces postmenopausal osteoporotic fractures, including hip, spine, and all nonspine fractures, even in women without osteoporosis.<sup>25,26</sup> Low doses are effective in maintaining or improving bone mineral density. No HT product currently has government approval for the treatment of osteoporosis. Many systemic HT products, however, have government approval for the prevention of postmenopausal osteoporosis.

When alternate osteoporosis therapies are not appropriate or cause adverse effects, the extended use of HT is an option for women who are at high risk of osteoporotic fracture. There is no evidence that HT stops working with long-term treatment; however, the benefits of HT on bone mass and fracture reduction dissipate quickly after the discontinuation of treatment,<sup>27,28</sup> necessitating a transition to a different osteoporosis treatment (or prevention strategy) to preserve bone mass. Within a few years of the discontinuation of ET in the WHI, the cumulative incidence of hip fracture was the same in the ET and placebo groups.<sup>28</sup>

Unless there is a contraindication, women experiencing an early menopause who require prevention of bone loss are probably best served by the administration of HT or oral contraceptives, rather than other bone-specific treatments, until they reach the normal age of menopause at which time treatment may be reassessed. The presumed increased risk of fracture in

older women who had an early menopause, however, was not substantiated in a recent report from the Study of Osteoporotic Fractures.<sup>29</sup> Women older than 65 years with a history of early menopause and no HT use did not sustain more fractures than did the group who had menopause at the average age. Removal of both ovaries at the time of hysterectomy compared with ovarian conservation was similarly found not to increase the subsequent rate of hip fracture.<sup>30</sup>

### Cardiovascular effects

The cardiovascular effects discussed are coronary heart disease (CHD), carotid intima media thickness, coronary artery calcium, stroke, and venous thromboembolism (VTE).

#### Coronary heart disease

Most observational studies (primarily composed of women who began HT around the time of menopause) support the potential benefits of systemic HT in reducing the risk of CHD.<sup>31</sup> Most RCTs do not.<sup>31,32</sup> However, it is understood that the characteristics of women participating in observational studies are markedly different from those of many women enrolled in RCTs designed to evaluate the cardiovascular effects of HT.<sup>33-35</sup> These demographic and biologic differences can influence baseline cardiovascular risks and may modify the overall observed effects of HT on cardiovascular risk. In the WHI clinical trials, overall CHD risk was estimated to be increased by eight cases per 10,000 women per year in the EPT arm; in the ET arm, overall CHD risk was estimated to be decreased by three cases per 10,000 women per year<sup>36</sup> (see "Dose and route of administration").

*Timing of initiation.* Secondary analyses of the WHI data indicate that the disparity in findings between observational studies and RCTs is related partly to the timing of initiation of HT in relation to age and proximity to menopause.<sup>36,37</sup> Most participants in the observational studies of CHD risk were younger than 55 years at the time HT was initiated and within 2 to 3 years of menopause. On the other hand, women enrolled, to date in RCTs with clinical cardiovascular endpoints have an age of 63 to 64 years and are more than 10 years beyond menopause. When analyzed by age and time since menopause at initiation of HT, the ET arm of the WHI<sup>38</sup> is in general agreement with observational studies<sup>39</sup> suggesting that ET may reduce CHD risk (coronary revascularization and composite outcomes including myocardial infarction [MI] and coronary death) when initiated in younger and more recently postmenopausal women without a uterus.<sup>36</sup> These findings for ET were even stronger with extended follow-up of the cohort and inclusion of 4 years after stopping. For women ages 50 to 59 years, the hazard ratio (HR) for CHD was 0.59 (95% CI, 0.38-0.90); for total MI, it was 0.54 (95% CI, 0.34-0.85; *P* for interaction by age = 0.05 and 0.007, respectively).<sup>28</sup>

Combined data incorporating both the ET and EPT trials of the WHI show a statistical trend of an HT effect relative to placebo on CHD by time since menopause, indicating that the women who initiate HT more than 10 years beyond menopause are at increased risk for CHD, and those women who initiate HT

within 10 years of menopause tend to have a lower risk of CHD.<sup>36</sup> However, statistical modeling of the combined WHI data, including data from the WHI observational studies, did not find that CHD risks varied by the timing of HT initiation.<sup>36,40</sup>

*Coronary artery calcium.* Some observational studies,<sup>41,42</sup> but not all,<sup>43</sup> suggest that long-term HT is associated with less accumulation of coronary artery calcium, which is strongly correlated with atheromatous plaque burden and future risk of clinical CHD events. In an ancillary substudy of younger women (<60 y) in the WHI ET trial, after an average of 7 years of treatment, women who had been randomized to ET had lower levels of coronary artery calcium than did those randomized to placebo.<sup>44</sup> Although the effect in older women was not evaluated, these findings suggest that ET initiated by recently postmenopausal women may slow the development of calcified atherosclerotic plaque.

*Carotid intima media thickness.* Observational studies<sup>45-47</sup> demonstrate less accumulation of carotid plaque as measured through ultrasound in women taking HT. Two RCTs reported contradictory findings with regard to carotid plaque.<sup>48,49</sup>

#### Stroke

The WHI EPT and ET trials demonstrated an increased risk of ischemic stroke and no effect on the risk of hemorrhagic stroke.<sup>50,51</sup> In these trials, when the entire cohort was analyzed, there were eight additional strokes per 10,000 women per year of EPT and 11 additional strokes per 10,000 women per year of ET. In recent analyses that combined results from the WHI EPT and ET trials, HT in younger women (ages 50-59 y) at study entry had no significant effect on risk of stroke (relative risk [RR], 1.13; 95% CI, 0.73-1.76).<sup>36,40</sup>

Although stroke was not increased in the group ages 50 to 59 years in the combined analysis of the WHI, it was almost doubled in the ET group less than 10 years since menopause. This apparent contradiction in the data is hard to explain but may be caused by relatively few events and the difficulty in accurately timing the onset of menopause in the ET group. In both the ET and EPT trials, excess stroke risk dissipated rapidly after discontinuation of HT.<sup>27,28</sup>

In women randomized in the WHI within 5 years of menopause, there were three additional strokes per 10,000 women per year of EPT, which is not statistically significant.<sup>36</sup> The excess risk of stroke in this age group observed in the WHI studies would fall into the rare-risk category. Stroke risk was not significantly increased in the Heart and Estrogen/Progestin Replacement Study<sup>52</sup> and the Women's Estrogen for Stroke Trial secondary prevention trials.<sup>53</sup> The Women's International Study of long Duration Oestrogen after Menopause RCT found no excess risk of stroke in EPT users compared with women on placebo in 1 year.<sup>54</sup>

The results of observational studies on the risk of stroke with HT have been inconsistent. Several studies (including the Nurses' Health Study [NHS], the largest and longest prospective cohort study of women's health) indicated an increased risk of ischemic stroke consistent with the findings from the WHI,<sup>55</sup> whereas other studies showed no effect on

stroke risk.<sup>56-58</sup> In the NHS, among women ages 50 to 59 years, the RR of stroke for current EPT users was not significantly elevated (RR, 1.34; 95% CI, 0.84-2.13), but it was significantly increased for current users of ET among women ages 50 to 59 years (RR, 1.58; 95% CI, 1.06-2.37).<sup>55</sup> The lowest dose of estrogen (eg, 0.3 mg CE) was not associated with an increased risk in the NHS, although this was based on the relatively few women who were taking that dose (see “Dose and route of administration”).

### **Venous thromboembolism**

Data from both observational studies and RCTs consistently demonstrate an increased risk of VTE with oral HT.<sup>59,60</sup> In the WHI trials, when the entire cohort was analyzed, there were 18 additional VTEs per 10,000 women per year of EPT<sup>60</sup> and 7 additional VTEs per 10,000 women per year of ET.<sup>61</sup> VTE risk in RCTs emerges soon after HT initiation (ie, during the first 1-2 y), and the magnitude of the excess risk seems to decrease somewhat in time. In the WHI trials, the absolute excess VTE risk associated with either EPT or ET was lower in women who started HT before age 60 years than in older women who initiated HT after age 60 years. In women ages 50 to 59 years who were randomized to HT,<sup>61</sup> there were 11 additional VTEs per 10,000 women per year of EPT and 4 additional VTEs per 10,000 women per year of ET. These risks fall into the rare-risk category. The baseline risk of VTE also increased relative to body mass index (BMI). For obese women (BMI, >30 kg/m<sup>2</sup>), the baseline risk was almost threefold greater. At any BMI, the risk of VTE doubled with HT and returned to baseline soon after HT discontinuation.<sup>27,28</sup>

Women with a previous history of VTE, obese women, or women who possess a factor V Leiden mutation are at increased risk of VTE with HT use.<sup>60,62,63</sup> There are limited observational data suggesting lower risks of VTE with transdermal than with oral ET,<sup>64-66</sup> but there are no comparative RCT data on this subject. Lower doses of oral ET may also confer less VTE risk than higher doses, but no comparative RCT data are available to confirm this assumption. Studies that have evaluated the contribution of various progestogens to clotting suggest that norepregnanes may be more thrombogenic.<sup>67,68</sup>

HT is currently not recommended for coronary protection in women of any age. Initiation of HT by women ages 50 to 59 years or by those within 10 years of menopause to treat typical menopausal symptoms does not seem to increase the risk of CHD events. There is emerging evidence that the initiation of ET in early postmenopause may reduce coronary artery disease and CHD risk. Two ongoing studies of early HT intervention may provide further information on this topic: the Early versus Late Intervention Trial with Estradiol and the Kronos Early Estrogen Prevention Study.

### **Diabetes mellitus**

Large RCTs demonstrate that HT reduces the diagnosis of new onset type 2 diabetes mellitus (T2DM), although no HT product has government approval to prevent T2DM. Women who received active treatment in the WHI EPT arm had a

statistically significant 21% reduction (HR, 0.79; 95% CI, 0.67-0.93) in the incidence of T2DM requiring treatment, which indicates 15 fewer cases per 10,000 women per year of therapy.<sup>69</sup> A similar statistically significant risk reduction was also noted in the Heart and Estrogen/Progestin Replacement Study trial (HR, 0.65; 95% CI, 0.48-0.89).<sup>70</sup> In the WHI ET trial, there was a 12% reduction (HR, 0.88; 95% CI, 0.77-1.01) in incident T2DM or 14 fewer cases per 10,000 women per year of ET.<sup>71</sup> Unfortunately, none of these trials included an oral glucose tolerance test to evaluate postchallenge glucose levels. In the Postmenopausal Estrogen and Progestin Intervention trial, fasting glucose levels were reduced in women assigned to HT; however, 2-hour postchallenge glucose levels, which may be associated with CHD risk, were elevated.<sup>72</sup> There is inadequate evidence to recommend HT for the sole or primary indication of the prevention of T2DM in perimenopausal or postmenopausal women.

### **Endometrial cancer**

Unopposed systemic ET in postmenopausal women with an intact uterus is associated with increased endometrial cancer risk related to the ET dose and duration of use. A meta-analysis reported a summary RR of 2.3 (95% CI, 2.1-2.5) overall and an RR of 9.5 if used for more than 10 years.<sup>73</sup> This increased risk persisted for several years after ET discontinuation. To negate this increased risk, adequate concomitant progestogen is recommended for women with an intact uterus when using systemic ET (see “Progestogen indication”). In general, HT is not recommended in women with a history of endometrial cancer. Progestogen alone could be considered for the management of vasomotor symptoms but no long-term data are available.

### **Breast cancer**

#### ***Estrogen-progestogen therapy***

Diagnosis of breast cancer increases with EPT use beyond 3 to 5 years.<sup>74</sup> In the WHI overall, this increased risk, in absolute terms, was eight additional breast cancers per 10,000 women using EPT for 5 or more years. Studies have not clarified whether the risk differs between continuous and sequential use of progestogen, with observational studies suggesting that risk may be greater with continuous use of progestogen. It is also not clear whether there is a class effect with progestogens or whether the specific agent used influences the degree of breast cancer risk. Data from a large observational study suggest that EPT with micronized progesterone carries a low risk of breast cancer with short-term use but carries an increased risk of breast cancer with all EPT formulations with long-term use.<sup>75</sup>

EPT and, to a lesser extent, ET increase breast cell proliferation, breast pain, and mammographic density, and EPT may impede the diagnostic interpretation of mammograms, therein delaying the diagnosis of breast cancer.<sup>74,76</sup> Evolving but not conclusive evidence suggests that the increased risk of breast cancer with EPT may be a result of the promotion of

preexisting cancers that are too small to be diagnosed by imaging studies or clinical examination. Some of these small cancers may never progress without the stimulation of HT. Long-term follow-up found that the risk of new diagnosis of breast cancer dissipated in the 3 years after cessation of EPT.<sup>77</sup> However, the follow-up also revealed that breast cancer mortality was increased in EPT users in the WHI who were followed for 11 years after study initiation. The breast cancer death rates with EPT were two additional deaths per 10,000 women per year attributed to breast cancer and two additional deaths per 10,000 women per year attributed to all-cause mortality.<sup>78</sup>

In the WHI, the initial reports suggested that the increase in breast cancer risk was limited to those who had used EPT before enrollment.<sup>79</sup> Because most women initiate EPT shortly after menopause, a reanalysis of the data examined the effect of a “gap time” (duration of time between onset of menopause and start of EPT) on breast cancer risk. In a combined analysis of the WHI observational study and the EPT clinical trial, those starting EPT shortly after menopause had an HR of 2.75 for breast cancer with more than 5 years of use, whereas those with a gap time of greater than 5 years did not.<sup>80</sup> A detailed secondary analysis reported that women who experienced a hiatus in their exposure to hormones before randomization to EPT were found to have a delayed increase in breast cancer compared with previous EPT users.<sup>81</sup> The French E3N (a prospective cohort study of French women that examined the potential relationship between premenopausal and postmenopausal breast cancer occurrence) also reported a greater risk of breast cancer in those women with a short (<3 y) as opposed to those with a long gap time.<sup>75</sup> The Million Women Study (MWS) investigators reported an increased risk in women initiating HT shortly after menopause.<sup>82</sup>

These data on breast cancer (potentially more harm with early postmenopausal HT use) are in contrast with the findings on CHD, stroke, VTE, and all-cause mortality that suggest greater safety in younger women closer to menopause. For all outcomes, the absolute risk of events in younger women is lower than that for older women.

### **Estrogen therapy**

Women in the ET arm of the WHI demonstrated no increase in risk of breast cancer after an average of 7.1 years of use, with six fewer cases of invasive breast cancer per 10,000 women per year of ET use, which is not statistically significant.<sup>76</sup> The decrease in risk was observed in all three age groups studied (ages 50-59, 60-69, and 70-79 y). Other findings in the ET group included a reduction in ductal carcinomas (HR, 0.71; 95% CI, 0.52-0.99).<sup>76</sup> In analyses based on extended follow-up of the WHI ET trial, including after stopping, the HR for breast cancer was 0.77 (95% CI, 0.62-0.95).<sup>28</sup> However, in women assigned to CE who developed invasive breast cancer, fewer breast cancers presented with localized disease (HR, 0.69; 95% CI, 0.51-0.95), and tumors were larger and more likely to be node positive compared with those in women assigned to placebo.<sup>76</sup>

The hypothesis for the decreased incidence of breast cancer with use of CE in the WHI is the apoptotic effect that estrogen has on breast cancer cells in a low-estrogen environment. Although the use of CE in the WHI did not show an age-related difference in the reduction of breast cancer, all laboratory evidence suggests that the longer breast cancer cells are estrogen-deprived, the more probable that physiologic estrogen will have a tumoricidal effect.<sup>83</sup>

The decreased risk of breast cancer as seen in the ET arm of the WHI was not observed in the MWS.<sup>82</sup> The RR for breast cancer in the MWS was increased in women who started ET within 5 years after menopause, with an absolute increased risk of 13 cases per 10,000 women per year.<sup>82</sup> Whether the difference between these findings and the WHI ET arm reflects differences in the timing of ET initiation, the types of ET, study populations, increased mammographic surveillance of women using HT, or other factors not controlled for in an observational study has not been determined.

When ET was extended beyond 15 years in the NHS, breast cancer risk increased.<sup>84-86</sup> A large meta-analysis of 67,370 women in observational studies found no increased risk with less than 5 years of ET use and RRs of 1.31 for 5 to 9 years of use, 1.24 for 10 to 14 years of use, and 1.56 for more than 15 years of use.<sup>87</sup> The possibility of differences in mammographic surveillance for breast cancer in users and nonusers of HT in observational studies cannot be excluded.

### **HT after breast cancer**

Controversy surrounds the use of HT in survivors of breast cancer. Some observational studies suggest that HT use may not increase the risk of recurrent breast cancer.<sup>88-94</sup> These reports have been questioned because of the potential bias from the selection of women at lower risk of recurrence for HT use. An RCT of HT use in women with a history of breast cancer and bothersome vasomotor symptoms was terminated early, after 2 years of follow-up, when significantly more new breast cancer events were diagnosed in women randomized to HT.<sup>95</sup> These data would indicate that HT use in breast cancer survivors may be associated with an increased risk of recurrence.

### **Ovarian cancer**

Published data on the role of HT and risk of ovarian cancer are conflicting. Some studies did not find an association.<sup>96,97</sup> There is a relatively large volume of observational trial data that points to an association between HT and increased ovarian cancer risk, particularly with long-term use.<sup>98-109</sup> In the National Institutes of Health American Association of Retired Persons Diet and Health Cohort, no elevated risk of ovarian cancer was seen with less than 10 years of ET use, but a significantly increased risk was seen after 10 years.<sup>107</sup> One meta-analysis reported an increase in annual ovarian cancer risk for EPT of 1.11-fold (95% CI, 1.02-1.21), and a 1.28-fold (95% CI, 1.18-1.40) increase was reported for ET.<sup>110</sup> A second meta-analysis reported RRs of 1.24 (95% CI, 1.15-1.34) for cohort studies and 1.19 (95% CI, 1.02-1.40) for case-control studies with use of any HT.<sup>111</sup> The use of HT for less than

5 years was associated with a significant RR of 1.03, whereas use for more than 10 years was associated with an RR of 1.21 ( $P < 0.05$  for both RRs). ET was associated with a higher risk of ovarian cancer than EPT.

In the WHI, the only RCT to date to study ovarian cancer, EPT was not associated with a statistically significant increase in ovarian cancer after a mean of 5.6 years of use.<sup>112</sup> There were 4.2 cases per 10,000 for HT users and 2.7 cases per 10,000 per year for the placebo group.

The association between ovarian cancer and EPT use beyond 5 years would fall into the rare- or very rare-risk category. Women at increased risk of ovarian cancer (eg, those with a family history or a *BRCA* mutation) should be counseled about this potential association.

### Lung cancer

In a post hoc analysis of the EPT arm of the WHI that included data from a mean of 7.1 years of intervention plus approximately 1 year of postintervention follow-up (total mean years of data, 7.9), the incidence of non-small-cell lung cancer (which accounts for about 80% of lung cancer) was not significantly increased (HR, 1.28; 95% CI, 0.94-1.73;  $P = 0.12$ ), but the number of lung cancer deaths (from non-small-cell lung cancer) increased (HR, 1.87; 95% CI, 1.22-2.88;  $P = 0.004$ ), and the number of poorly differentiated and metastatic tumors increased in the treatment group (HR 1.87; 95% CI, 1.22-2.88;  $P = 0.004$ ).<sup>77</sup> The cases were essentially limited to past and current smokers and to women older than 60 years. The absolute rates of death from non-small-cell lung cancer were small: nine per 10,000 per year on EPT and five per 10,000 on placebo. Because the WHI was not designed to assess lung cancer and chest imaging was not part of the study protocol, the findings are preliminary and require validation in further studies.

In the WHI ET trial, no increase in lung cancer incidence or mortality was observed in the treatment compared with the placebo group.<sup>113</sup> There was no significant treatment effect related to age. Mortality from lung cancer was increased in current smokers in both treatment and placebo groups compared with nonsmokers and former smokers.

Reports from observational trials are mixed.<sup>114-122</sup> One large observational study reported an increase in incident lung cancer associated with increasing duration of EPT use (50% increase after 10 y of therapy); there was no association with duration of ET use.<sup>123</sup> One meta-analysis reported an increased risk of adenocarcinoma of the lung.<sup>124</sup> Another meta-analysis reported a possible protective effect against lung cancer for users of HT with the exception of current smokers.<sup>125</sup>

These findings underscore the need to encourage the cessation of smoking and possibly to increase surveillance in older smokers who are current or past users of EPT.

### Mood and depression

For postmenopausal women without clinical depression, evidence is mixed concerning the effects of HT on mood.

Several small short-term trials among middle-aged women with vasomotor symptoms suggested that HT improves mood, whereas other trial results showed no change. Progestogens in EPT may worsen mood in some women, possibly in those with a history of premenstrual syndrome, premenstrual depressive disorder, or clinical depression.

Only a few RCTs have examined the effects of HT in middle-aged or older women who have depression. One small RCT involving depressed perimenopausal and postmenopausal women found no short-term benefit from ET, but post hoc analyses revealed that higher estradiol levels were associated with decreased depressive symptoms in perimenopausal women but not postmenopausal women.<sup>126</sup> Two small RCTs support the antidepressant efficacy of short-term ET in depressed perimenopausal women,<sup>127,128</sup> whereas one RCT failed to demonstrate the antidepressant efficacy of ET in depressed women who were 5 to 10 years into postmenopause.<sup>129</sup> It is controversial whether ET might, in some circumstances, augment the antidepressant effects of selective serotonin reuptake inhibitors.<sup>130,131</sup>

Although HT might have a positive effect on mood and behavior, HT is not an antidepressant and should not be considered as such. Evidence is insufficient to support HT use in the treatment of depression.

### Cognitive aging and dementia

Very small clinical trials support the use of ET for cognitive benefits when initiated immediately after surgical menopause.<sup>132,133</sup> To date, clinical trials of ET have demonstrated no substantial effect on episodic memory or executive function at the time of menopause.<sup>134</sup> Reports from the longitudinal Study of Women's Health Across the Nation suggest that natural menopause has a significant but small effect on some aspects of cognitive function that may be time limited. This effect is not explained by menopausal symptoms.<sup>135,136</sup> Recent literature suggests a transient negative effect of the menopausal transition on cognition, but it is a negligible long-term effect.<sup>134,135</sup>

The NHS found no benefit on cognitive function from long-term use of HT among women who had started HT in early menopause; rather, there was a suggestion of a more rapid cognitive decline among HT users.<sup>137</sup> Conversely, in the Study of Women's Health Across the Nation, women who initiated hormones (oral contraceptives or HT) after enrollment but before their final menstrual period and then discontinued the hormones had a beneficial cognitive effect, whereas women who initiated hormones after the final menstrual period had a detrimental effect on cognitive performance.<sup>135</sup>

For postmenopausal women older than 65 years, findings from several large well-designed clinical trials indicate that HT does not improve memory or other cognitive abilities and that EPT is harmful for memory.<sup>138-140</sup> The WHI Memory Study of women aged 65 to 79 years reported an increase in dementia incidence with HT use.<sup>141</sup> The estimate of dementia cases attributed to HT was 12 per 10,000 persons per year of ET use and 23 per 10,000 persons per year of EPT use. The

effect was not statistically significant for ET but was for EPT and the combined ET and EPT groups.<sup>141</sup>

Evidence from the WHI Study of Cognitive Aging, an ancillary study of WHI and WHI Memory Study that enrolled women aged 66 years or older, indicated a worsening of verbal memory but a trend toward a positive effect on figural memory among women using EPT compared with those using placebo.<sup>140</sup> There are currently no placebo-controlled trial data comparing the effects of different progestogens on memory or dementia in younger or older postmenopausal women. Overall, the RCTs of ET demonstrate no adverse impact on memory. The WHI Study of Cognitive Aging found neither benefit nor persistent negative impact of HT on memory during a 2.7-year interval.<sup>142</sup>

A number of observational studies have reported associations between HT and reduced risk of developing Alzheimer disease (AD).<sup>143</sup> HT exposure in observational studies is more likely to involve ET use by younger women closer to menopause, suggesting an early window during which HT use might reduce AD risk. However, recall bias and the healthy-user bias may account for protective associations in the observational studies. Similarly, an increased risk of dementia observed with early oophorectomy, countered by use of estrogen until age 50 years,<sup>144</sup> may be at least partially caused by demographic differences between groups.<sup>145</sup> HT exposure in observational studies is also more likely to involve women on ET rather than EPT. For women with AD, limited clinical results suggest that ET has no substantial effect.

In summary, available data do not adequately address whether HT used soon after menopause increases or decreases the rate of cognitive decline or later dementia risk. In the absence of more definitive findings, HT cannot be recommended at any age for preventing or treating cognitive aging or dementia.

#### **Premature menopause and primary ovarian insufficiency**

Women experiencing premature menopause (age  $\leq 40$  y) or primary ovarian insufficiency (POI) are medically a distinctly different group from women who reach menopause at the median age of 51.3 years. Premature menopause and POI are associated with a lower risk of breast cancer and earlier onset of estrogen-related bone loss. Other conditions that have been associated with premature menopause, such as CHD and Parkinson disease, may be the result of other factors responsible for both premature menopause and the specific condition. For example, mutations found in the gene encoding mitochondrial DNA polymerase gamma have been reported to be associated with both premature menopause and Parkinson disease.<sup>146</sup>

Some observational reports suggest an increased risk of CHD with early natural or surgical menopause in the absence of HT and a reduced risk when HT is administered.<sup>147</sup> Analysis of the Framingham data revealed that women who had an earlier menopause also had more CHD risk factors.<sup>148</sup> The authors concluded that CHD risk factors may cause earlier menopause and not the converse. Both a history of heart disease and smoking have been associated with earlier meno-

pause.<sup>149</sup> Another extensive analysis of three birth cohorts from three different countries concluded that there is no change in the rate of increase in CHD mortality at menopause. The rate of increase is constant during a woman's lifetime.<sup>150</sup>

The existing data regarding HT in women experiencing menopause at the median age should not be extrapolated to women experiencing premature menopause and initiating HT at that time. The well-documented safety of supraphysiologic doses of HT in the form of oral contraceptives in young women suggests that physiologic dosing of HT for women with POI or premature menopause would convey minimal risk. Given the potential harmful effects of estrogen deficiency on bone mass in young women who may still be building their peak bone mass and the severity of vasomotor symptoms in younger women, the benefits of HT are potentially greater in this age group (see "Osteoporosis").

The lack of clinical trials on this topic necessitates clinical judgment. In the absence of contraindications, NAMS recommends the use of HT or oral contraceptives until the median age of natural menopause, with periodic reassessment.

#### **Total mortality**

The WHI trials are consistent with observational studies and meta-analyses<sup>151</sup> indicating that HT may reduce total mortality when initiated soon after menopause. The WHI suggests that both ET and EPT nonsignificantly reduce total mortality by 30% when initiated in women younger than 60 years and that when data from the ET and EPT arms were combined, that reduction was statistically significant.<sup>36</sup> There were 10 fewer deaths per 10,000 women aged 50 to 59 years, compared with 16 additional deaths among those aged 70 to 79 years.<sup>36</sup> The mortality advantage for younger women did not remain significant when evaluated by years since menopause.<sup>36</sup>

### **PRACTICAL THERAPEUTIC ISSUES**

#### **Class versus specific product effect**

All estrogens have some common features and effects as well as potentially different properties. The same is true of all progestogens. However, in the absence of RCTs designed to compare clinical outcomes of various estrogens and progestogens, clinicians will be required to generalize the clinical trial results, tempered by emerging reports from observational studies (as addressed in individual sections of this report), for one agent to all agents within the same hormonal family. On a theoretical basis, however, there are likely to be differences within each family based on factors such as relative potency of the compound, androgenicity, glucocorticoid effects, bio-availability, and route of administration.

#### **Progestogen indication**

The primary menopause-related indication for progestogen use is to negate the increased risk of endometrial cancer from systemic ET use. All women with an intact uterus who use systemic ET should also be prescribed adequate progestogen. With occasional exceptions (eg, history of extensive endometriosis), postmenopausal women without a uterus should not be prescribed a progestogen with systemic ET.<sup>152-154</sup>

A progestogen is generally not indicated when ET is administered locally in a low dose for vaginal atrophy, although trials to date have been limited to only 1 year.<sup>155</sup> Although one 2-year study of the ultralow-dose estradiol patch found no statistically significant increase in endometrial hyperplasia,<sup>156</sup> intermittent progestogen probably should be used with long-term use of any systemic ET, including the ultralow-dose patch, which carries that recommendation in the product information sheet (see “Dose and route of administration”).

Concomitant progestogen may improve the efficacy of low-dose ET in treating vasomotor symptoms. Some women who use EPT may experience dysphoria from the progestogen component. A combination of estrogen with an estrogen agonist/antagonist is currently under investigation and may become an alternate option to progestogen.

### Dose and route of administration

The lowest effective dose of estrogen consistent with treatment goals, benefits, and risks for the individual woman should be the therapeutic goal, with an appropriate dose of progestogen added to counter the adverse effects of systemic ET on the uterus. Among the lower doses typically used when initiating systemic ET are 0.3 mg to 0.45 mg oral CE, 0.5 mg oral micronized 17 $\beta$ -estradiol, and 0.014 mg to 0.0375 mg transdermal 17 $\beta$ -estradiol patch. Low-dose formulations of estradiol are available in approved topical gels, creams, and sprays. Estrogen doses less than those traditionally prescribed (<0.625 mg CE) often require longer duration of treatment upon initiation to achieve maximal efficacy in reducing vasomotor symptoms.<sup>157,158</sup> Tailoring the dose to a woman’s individual needs represents an appropriate strategy in HT management.

Lower HT doses generally have fewer adverse effects, such as breast tenderness and uterine bleeding, and may have a more favorable benefit-risk ratio than standard doses. In a nested case-control study from the UK General Practice Research database, the risk of stroke was not increased with low-dose transdermal estrogen ( $\leq 0.05$  mg) but did increase with oral therapies and with higher transdermal doses.<sup>159</sup> Lower doses of HT have not been tested in long-term trials with clinical outcomes to support an assumed more favorable benefit-risk ratio.

All routes of administration of ET can effectively treat menopausal symptoms. Nonoral routes of administration including transdermal, vaginal, and intrauterine systems may offer both advantages and disadvantages compared with the oral route, but the long-term benefit-risk ratio has not been demonstrated in RCTs with clinical outcomes. There are differences related to the role of the first-pass hepatic effect, the hormone concentrations in the blood achieved by a given route, and the biologic activity of ingredients. With transdermal therapy, there is no significant increase in triglycerides, C-reactive protein, or sex hormone-binding globulin and little effect on blood pressure. With cutaneous therapies, caution should be exercised to avoid inadvertent transfer to children and animals.<sup>160</sup>

There is growing observational evidence that transdermal ET may be associated with a lower risk of deep vein thrombosis, stroke, and MI.<sup>64,65,68,161</sup>

There are multiple progestogen dosing-regimen options for endometrial safety. The dose varies based on the progestogen used and the estrogen dose, typically starting at the lowest effective doses of 1.5 mg medroxyprogesterone acetate, 0.1 mg norethindrone acetate, 0.5 mg drospirenone, or 100 mg micronized progesterone. Different doses may have different health outcomes. A long-term Finnish observational study reported that continuous use of EPT reduced the risk of endometrial neoplasia compared to no use of HT, and sequential progestogen therapy with ET increased the risk, particularly with long-cycle progestogen.<sup>162</sup> In this study, all progestogens performed similarly within a given regimen.

Oral progestogens, combined with systemic estrogen, and combined progestogen-estrogen matrix patches have demonstrated endometrial protection and are government approved. A progestin-containing intrauterine system and a vaginal progesterone cream are government approved for use in premenopausal women; however, neither has been approved for use in postmenopausal women. A small study reported that when used with systemic ET in perimenopausal and postmenopausal women, the progestin-containing intrauterine system was found to provide endometrial protection equivalent to protection provided by systemic progestogen administered continuously and superior protection compared with progestogen given sequentially.<sup>163</sup>

### Bioidentical hormones

The term bioidentical hormones is most often used to describe custom-made HT formulations (called bioidentical hormone therapy [BHT]) that are compounded for an individual according to a healthcare provider’s prescription. The term is used by proponents of BHT to convey that the hormones they use are identical to the hormones made by the ovaries. In that regard, the term can also be used to refer to many well-tested, government-approved, brand-name HT products containing hormones chemically identical to those produced by women (primarily in the ovaries), such as 17 $\beta$ -estradiol and progesterone.

Custom-compounding of HT may combine several hormones (eg, estradiol, estrone, and estriol) and use nonstandard routes of administration (eg, subdermal implants). Some of the hormones are not government approved (estriol) or monitored and some of the compounded therapies contain non-hormonal ingredients (eg, dyes, preservatives) that some women cannot tolerate. Use of BHT has escalated in recent years, along with the use of salivary hormone testing, which has been proven to be inaccurate and unreliable. There may be increased risks to the women using these products. Custom-compounded formulations, including BHT, have not been tested for efficacy or safety; product information is not consistently provided to women along with their prescription, as is required with commercially available HT; and batch standardization and purity may be uncertain. The dosing of compounded progesterone is particularly difficult to assess because the levels in serum, saliva, and tissue are markedly different.<sup>164</sup> Custom-compounded drug formulations are not government approved.



The US Food and Drug Administration has ruled that some compounding pharmacies have made claims about the safety and effectiveness of BHT unsupported by clinical trial data and considered to be false and misleading.<sup>165</sup> Pharmacies have been instructed not to use estriol without an investigational new drug authorization. The Food and Drug Administration also states that there is no scientific basis for using saliva testing to adjust hormone levels.

NAMS recommends that BHT products include a patient package insert identical to that required for products that have government approval. In the absence of efficacy and safety data for BHT, the generalized benefit-risk ratio data of commercially available HT products should apply equally to BHT. For most women, government-approved HT will provide appropriate therapy without the risks of custom preparations. Therefore, NAMS does not generally recommend compounded EPT or ET unless necessary because of allergies to ingredients contained in government-approved products.

## TREATMENT ISSUES

### Duration of use

One of the most challenging issues regarding HT is the duration of use. Long-term follow-up data from the WHI have clarified the increased risk of breast cancer and breast cancer mortality with 4 to 5 years of EPT used at the time of menopause and a slightly later onset of breast cancer if used after a hiatus in estrogen exposure.<sup>74,78</sup> Regarding ET, there was no increase in risk of breast cancer with early postmenopausal use in the WHI or NHS, and there was decrease in breast cancer incidence when used after a hiatus in estrogen exposure in the WHI.<sup>76,85</sup> Long-term use of ET (15-20 y in the NHS) can be expected to increase breast cancer, but to a lesser degree than EPT.<sup>85</sup>

Potential coronary artery disease and CHD benefits were also seen with early use of ET. In the WHI ET trial, women ages 50 to 59 years had a significantly lower risk of combined endpoints including CHD and total MI and no elevation in breast cancer risk.<sup>28</sup> Observational studies suggest that longer duration of HT use is associated with a reduced risk of CHD and related mortality.<sup>166</sup> The WHI RCTs and observational study suggest a pattern of lower risk of CHD among women who used HT for 5 or more years,<sup>40</sup> but this is not conclusive and should be considered in light of other factors altered by duration of therapy, such as breast cancer. In contrast, both ET and EPT are associated with an initial increase in CHD risk among women who are more distant from menopause at the time of HT initiation.<sup>38,167,168</sup>

These findings allow for longer duration of use with ET based on a woman's symptoms, preferences, and current benefit-risk profile.

Provided that the woman is well aware of the potential benefits and risks and has clinical supervision, extending EPT use with the lowest effective dose is acceptable under some circumstances, including (1) for the woman who has determined that the benefits of menopause symptom relief outweigh risks, notably after failing an attempt to stop EPT, and (2) for the

woman at high risk of fracture for whom alternate therapies are not appropriate or cause unacceptable adverse effects.

### Discontinuation of HT

Data from long-term follow-up of women who discontinued ET and EPT have increased our understanding of the sequelae of discontinuing HT. In the WHI, women in the EPT group who had stopped HT for 3 years had a rate of cardiovascular events, fractures, and colon cancers equivalent to that of women who had been assigned to placebo.<sup>27</sup> The only statistical difference was an increase in the rates of all cancer in women who had been assigned to EPT, with an excess of 30 cancers per 10,000 women per year of EPT, including a number of fatal lung cancers.<sup>27,77</sup> For women without a uterus, when followed for 3 years after stopping ET, there was no overall increased or decreased risk of CHD, deep-vein thrombosis, stroke, hip fracture, colorectal cancer, or total mortality. A statistically significant decreased risk of invasive breast cancer persisted (8 fewer cases/10,000 women).<sup>28</sup> Discontinuance of HT will lead to a transient increased incidence of fracture, including hip fracture.<sup>169</sup> After 4 years of follow-up in the ET arm of the WHI, cumulative fracture rates were similar for both ET and placebo groups.<sup>28</sup>

HRs for all-cause mortality, reflecting the balance of all of the above and other outcomes, tended to be neutral in both the EPT and ET arms of the WHI (HR, 0.98 and 1.04, respectively). During the 3-year postintervention phase of the EPT trial, mortality rates were borderline elevated (HR, 1.15; 95% CI, 0.95-1.39) primarily because of the aforementioned increase in cancer. During the entire EPT follow-up period (active treatment plus poststopping phases), the HR for all-cause mortality in the EPT arm was 1.04 (95% CI, 0.91-1.18)<sup>27</sup> and 1.02 (95% CI, 0.91-1.15) in the ET arm.<sup>28</sup>

Regarding other outcomes after discontinuance of EPT, an initial analysis of data from the National Cancer Institute's Surveillance, Epidemiology, and End Results registries showed that the age-adjusted incidence rate of breast cancer in women in the United States fell sharply (by 6.7%) in 2003, as compared with the rate in 2002.<sup>170</sup> The decrease was evident only in women who were 50 years or older and was more evident in cancers that were estrogen receptor positive, which represent most breast cancers. It was theorized that the drop could be related to the large number of women discontinuing HT after the termination of the EPT arm of the WHI.

Vasomotor symptoms have an approximately 50% chance of recurring when HT is discontinued, independent of age and duration of use.<sup>171,172</sup> In one RCT, tapering the dose of HT for 1 month and abruptly discontinuing HT had a similar impact on vasomotor symptoms.<sup>173</sup> The decision to continue HT should be individualized based on the severity of symptoms and current benefit-risk ratio considerations.

## CONCLUSIONS AND RECOMMENDATIONS

- Individualization is of key importance in the decision to use HT and should incorporate the woman's health and

quality of life priorities as well as her personal risk factors, such as risk of venous thrombosis, CHD, stroke, and breast cancer.

- The recommendation for duration of therapy differs for EPT and ET. For EPT, duration is limited by the increased risk of breast cancer and breast cancer mortality associated with 3 to 5 years of use; for ET, a more favorable benefit-risk profile was observed during a mean of 7 years of use and 4 years of follow-up, a finding that allows more flexibility in duration of use.
- ET is the most effective treatment of symptoms of vulvar and vaginal atrophy; low-dose, local vaginal ET is advised when only vaginal symptoms are present.
- Women with premature or early menopause who are otherwise appropriate candidates for HT can use HT at least until the median age of natural menopause (age 51 y). Longer duration of treatment can be considered if needed for symptom management.
- Although ET did not increase breast cancer risk in the WHI, there is a lack of safety data supporting the use of ET in breast cancer survivors, and one RCT reported a higher increase in breast cancer recurrence rates.
- Both transdermal and low-dose oral estrogen have been associated with lower risks of VTE and stroke than standard doses of oral estrogen, but RCT evidence is not yet available.

### SUMMARY

In the decade since the first publication of results from the WHI EPT study, much has been learned. There is a growing body of evidence that HT formulation, route of administration, and the timing of therapy produce different effects. Constructing an individual benefit-risk profile is essential for every woman considering any HT regimen. A woman's interest in using HT will vary depending on her individual situation, particularly the severity of her menopausal symptoms and their effect on her QOL. The absolute risks known to date for use of HT in healthy women ages 50 to 59 years are low. In contrast, long-term HT or HT initiation in older women is associated with greater risks.

Recommendations for duration of use differ between ET and EPT. Given the more favorable safety profile of ET, it could be considered for longer duration of therapy in the absence of adverse effects and risk factors. Women experiencing premature menopause are at increased risk of osteoporosis and, possibly, cardiovascular disease, and they often experience more intense symptoms than do women reaching menopause at the median age. Therefore, HT generally is advised for these young women until the median age of menopause when treatment should be reassessed.

Additional research is needed to understand the different effects of ET and EPT and how they apply to individual women. Further research is also needed to more clearly delineate the role of aging versus menopause and the effects of genetics,

lifestyle, and individual clinical characteristics on midlife women's health.

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