Introduction

The use of hormone therapy by postmenopausal women has followed several pendulum-like swings in popularity over time. Initially, in the 1940s to 1970s, hormone therapy was very popular, as it was touted to sustain youth in women. Then it became popular for managing menopause-related symptoms. Later, in the 1980s and 1990s, it was popular because it was thought to reduce the risk for developing heart disease. In between these swings of high popularity, the pendulum swung the other way, and popularity was significantly diminished. This occurred when hormone therapy was associated with an increased risk for endometrial cancer. Popularity was low again when hormone therapy was first associated with breast cancer. Most recently, popularity has ebbed due to associations with coronary heart disease (CHD). Over the years, different subtypes of hormone therapy have been used. Table 1 lists the names and definitions for terms commonly used to denote hormone therapy.1–4

Multiple epidemiologic studies have suggested possible associations between the use of hormone therapy and various risks and benefits. Subsequent randomized controlled trials (RCTs) have tested these associations. As each new set of data emerges, more evidence has become available regarding potential benefits such as efficacy for managing menopause-related symptoms, reduced risk for colon cancer, and prevention of bone loss as well as potential risks such as CHD, stroke, and breast cancer. This article contains a brief review of the history of hormone therapy use in the United States. The current controversies in hormone therapy prescribing that have arisen following recent randomized controlled prevention trials are presented in depth. A discussion of the symptom-relieving and quality of life benefits related to hormone therapy use as demonstrated by observational studies and RCTs and a summary of current recommendations for use from several national and international organizations are presented.

The Early History of Hormone Therapy Use

The focus and purpose behind therapies used for postmenopausal women has shifted dramatically since diethylstilbestrol, the first synthetic estrogen, and Premarin, the first nonsynthetic estrogen manufactured from the urine of pregnant mares (the name Premarin was invented as a contraction of PREgnant MARes urINe), were released in 1938 and 1942, respectively. At first, treatment was focused on symptom control and attempts to keep women youthful by replacing estrogen deficiencies. In 1966, the gynecologist Robert Wilson released the book Feminine Forever, which sold 100,000 copies in the first 7 months alone. The book warned that, following menopause, women would become eunuchs, enduring a “living decay,”5(p 43) with withered breasts.5 Wilson identified estrogen as “one of the greatest biological revolutions in the history of civilization,”6(p 16) and between 1967 and 1975, the sales of Premarin tripled.1

Endometrial Cancer Risk Noted in Women Using Hormone Therapy

Premarin, which is conjugated equine estrogen (CEE), was the fifth most popular drug in the United States when researchers began to link it with an increased risk for endometrial cancer in 1975 through retrospective, case-controlled studies.6,7

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Following the publication of these studies, Premarin sales fell dramatically. In 1979, the National Institutes on Aging held a conference on postmenopausal estrogen use and concluded that estrogen replacement therapy was only effective for hot flashes and vaginal dryness. They further concluded that since estrogen replacement therapy (now called estrogen therapy) increased the risk for developing endometrial cancer “women using estrogens should take them only for the shortest possible time, in the lowest possible dose.”

In the 1980s, epidemiologic data indicated that adding a progestogen to estrogen therapy, called estrogen-progestogen therapy, significantly lowered the risk for developing endometrial cancer. During this decade, the biomedicinal model identified postmenopause as a deficiency state or endocrinopathy, which needed to be corrected. Once again, the pendulum swung in favor of hormone therapy, and its popularity soared. The focus of hormone therapy use had now shifted to menopause-related symptom management, especially for vaginal atrophy and vasomotor symptom control as well as correction of the underlying endocrinopathy.

### Hormone Therapy Terms, Abbreviations, and Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Hormone therapy</td>
<td>HT</td>
<td>Generic term that refers to any individual use of or combination of estrogen-only or estrogen-progestogen therapy via any route for menopause-related symptom management or prevention of low estrogen related health concerns.</td>
</tr>
<tr>
<td>Estrogen therapy</td>
<td>ET</td>
<td>Term that describes therapy when estrogen is taken alone. Estrogen may be taken via the oral, transdermal, or vaginal route.</td>
</tr>
<tr>
<td>Estrogen-progestogen therapy</td>
<td>EPT</td>
<td>Term that describes therapy when estrogen plus progestogen are taken together daily or as estrogen daily with progestogen taken intermittently. Estrogen may be taken by the oral, transdermal, or vaginal route. Progestogen is taken by the oral or transdermal (eg, combine estrogen-progestogen patch) route.</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>HRT</td>
<td>Term referring to use of hormone therapy for postmenopausal women. Older term that has been replaced by hormone therapy.</td>
</tr>
<tr>
<td>Menopause hormone therapy</td>
<td>MHT</td>
<td>Term used interchangeably with hormone therapy (see above).</td>
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### Hormone Therapy for Disease Prevention: Osteoporosis and Heart Disease

The protective effect of postmenopausal estrogen use against osteoporosis was also identified in the 1980s. Several observational studies demonstrated that hormone therapy had protective effects against CHD as well. These findings encouraged another shift in the focus for use of hormone therapy from menopause-related symptom management to disease prevention. Many clinicians began recommending hormone therapy to their postmenopausal patients for the prevention of CHD. Even the United States Preventive Services Task Force (USPSTF) recommended in 1996 that all postmenopausal women should be counseled about and consider using preventative hormone therapy. The USPSTF recommended considering hormone therapy; they did not actually say that every woman should take hormone therapy.

Around this same time, RCTs and observational studies published contradictory results, with some studies indicating reduced risks for breast cancer and others indicating increased risks. Still other RCTs and observational studies suggested beneficial effects for cognition, skin changes, and preventing colon cancer.

### FIRST LARGE RANDOMIZED CONTROLLED CORONARY HEART DISEASE PREVENTION TRIALS

Two major large RCTs were conducted in an effort to clearly determine the specific protective effects of estrogen on heart disease. These RCTs were requested by the Food and Drug Administration (FDA) and designed like the statin trials were designed to validate prior observational study data, which supported the use of estrogens for heart disease prevention. In the second study, breast cancer risk also was evaluated.

The Heart and Estrogen/Progestin Replacement Study (HERS) started in 1993. This study was designed to evaluate the effects of estrogen-progestogen therapy on postmenopausal women (N = 2763, average age 67 years) who had established CHD. Many clinicians were surprised that there were no significant differences in CHD events between the women in the treatment group (who received CEE 0.625 mg and medroxyprogesterone acetate [MPA] 2.5 mg in a single oral tablet) and the women in the control group (who received placebo) after 4 years of follow-up, despite lower lipid levels in the treatment group. In the first year of the study, women in the treatment group had more cardiac events than women in the placebo group. However, over the remaining 3 years, women in the treatment group had fewer events, which resulted in an overall null effect in the incidence of CHD events when the 2 groups were compared. In HERS II, which followed the HERS participants for 2.7 additional years, no additional beneficial effects of estrogen-progestogen therapy were identified, leading the researchers to advise against the use of estrogen-progestogen therapy for secondary prevention of CHD in women with established disease.
evaluate the efficacy of both estrogen-progestogen therapy and estrogen-only therapy on CHD prevention.22,25 The WHI is the first randomized primary prevention trial to evaluate the long-term risks of hormone therapy. Postmenopausal women aged 50 to 79 years (average age 63 years) participated. The estrogen-progestogen therapy arm included 16,608 women who had an intact uterus. They were randomized to receive CEE 0.625 mg plus MPA 2.5 mg in a single oral daily tablet or placebo. This arm of the study was stopped early in 2002 at an average of 5.2 years of follow-up because the overall risks of coronary events, pulmonary embolism, stroke, and breast cancer outweighed the benefits of treatment according to the global index, a preset statistical limit used in the WHI study to determine the risk-to-benefit ratio. Benefits included reduced risk for colorectal cancer and lower incidence of fracture (Table 2).22,26 There was no difference in mortality. These results were largely unchanged after an additional 3.2 years of observational follow-up of the estrogen-progestogen therapy arm participants.27

The WHI estrogen-only arm also was halted early in 2004 after an average of 6.8 years of follow-up. The estrogen-only arm included 10,739 women randomized to CEE 0.625 mg orally daily or placebo. The primary risk identified in this arm was stroke.25 The risk levels identified for breast cancer, CHD, pulmonary embolism, and colon cancer were not statistically significant, meaning there was no increase in risk and no decrease in risk for these 4 variables. The risk for hip fracture was statistically significantly reduced in women in the treatment arm and provided a potential benefit (Table 3).25

Following publication of the WHI results, many experts commented on problems with generalizing the results of this study.26,29 The mean age of the participants was 63 years, which is significantly higher than that of newly postmenopausal women, raising the question of how the results may differ in women who are newly postmenopausal. The hormone therapy preparation used was oral CEE 0.625 mg and MPA 2.5 mg or oral CEE 0.625 mg alone, raising questions about how the results might differ for other preparations, different routes of administration, or different doses. Additionally, women who had moderate to severe vasomotor symptoms were excluded from the trial because they would have been able to determine if they were receiving placebo or hormone therapy due to changes in their symptoms. This raises questions about how the effects of hormone therapy, and especially quality of life, might differ for women who are experiencing significant menopause-related symptoms.

The results of HERS/HERS II and WHI might differ if alternate formulations or routes of estrogen-only and estrogen-progestogen therapy were used. In the Papworth PHASE RCT, 255 postmenopausal women (average age 66.3 years in treatment group, 67 years in control group) with angiographically demonstrated ischemic heart disease were randomized to

### Table 2. Potential Risks and Benefits of Hormone Therapy as Identified in the Women’s Health Initiative Estrogen-Progestogen Therapy Arm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio, 95% Confidence Interval (Nominal, Locally Adjudicated)</th>
<th>Hazard Ratio, 95% Confidence Interval (Adjusted, Centrally Adjudicated)</th>
<th>Annualized Risk (Per 10,000 Women)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential risks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global index</td>
<td>1.15</td>
<td>1.03-1.28</td>
<td>29 vs 21</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41 (↑ 41%)</td>
<td>1.07-1.85</td>
<td>0.86-2.31 34 vs 16</td>
</tr>
<tr>
<td>Venous thromboembolic events</td>
<td>2.11 (↑ 111%)</td>
<td>1.58-2.82</td>
<td>1.26-3.55 34 vs 16</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1.29 (↑ 29%)</td>
<td>1.02-1.63</td>
<td>0.85-1.97 37 vs 30</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.26 (↑ 26%)</td>
<td>1.0-1.59</td>
<td>0.83-1.92 38 vs 30</td>
</tr>
<tr>
<td><strong>Potential benefits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.66 (↓ 34%)</td>
<td>0.45-0.98</td>
<td>0.33-1.33 10 vs 15</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.62 (↓ 38%)</td>
<td>0.43-0.92</td>
<td>0.32-1.34 10 vs 16</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.98</td>
<td>0.82-1.18</td>
<td></td>
</tr>
</tbody>
</table>


### Table 3. Potential Risks and Benefits of Estrogen-alone Therapy as Identified in the Women’s Health Initiative Estrogen-only Arm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio, 95% Confidence Interval</th>
<th>Hazard Ratio, 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.39 (↑ 39%)</td>
<td>1.10-1.77a</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0.77 (↓ 23%)</td>
<td>0.59-1.01</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1.08 (↑ 8%)</td>
<td>0.75-1.55</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>0.91 (↓ 9%)</td>
<td>0.75-1.12</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1.34 (↑ 34%)</td>
<td>0.87-2.06</td>
</tr>
<tr>
<td><strong>Potential benefits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.61 (↓ 39%)</td>
<td>0.41-0.91a</td>
</tr>
</tbody>
</table>

*Statistically significant.
Source: Anderson, Limacher, Assaf, et al.25

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receive either a 17β-estradiol 2.5 mg patch placed every 4 days (or a 17β-estradiol 3 mg patch with norethisterone 4 mg for the second half of each month) or placebo.30 After 2.5 years of follow-up, the event rate (hospitalization for unstable angina, myocardial infarction, or death) was higher among women in the treatment group than women in the placebo group (rate ratio 1.29; 95% confidence interval [CI], 0.84-1.95; \( P = .24 \)). Just as with HERS,21 the authors of the Papworth PHASE study concluded that transdermal hormone therapy should not be used for heart disease prevention in women with established CHD.30 Further research is needed to evaluate whether transdermal dosing or varied hormone therapy formulations will demonstrate different effects for CHD prevention in women without known CHD, for breast cancer, and how these results might differ if therapy were initiated close to the time of menopause.

In the immediate wake of the publication of the HERS and WHI results, several organizations (eg, the American College of Obstetricians and Gynecologists,7 the National Association of Nurse Practitioners in Women’s Health,38 the North American Menopause Society [NAMS]31), the USPSTF;32 and the FDA33 made recommendations for hormone therapy use. These entities agreed then that hormone therapy was appropriate for women with moderate to severe vasomotor symptoms or vaginal atrophy and should not be used solely for prevention of heart disease or bone loss. Additionally, hormone therapy was again recommended for use at the lowest effective dose and for the shortest duration possible.2,8,28,31,32 reminiscent of the use recommendations and efficacy identified by the National Institute on Aging in 1979.8

Following the release of the WHI results and the resultant media coverage about the early ending of the estrogen-progestogen therapy and later the estrogen-only arms, the use of oral estrogen-progestogen therapy declined by 45%, and the use of oral estrogen-only therapy declined by 22%.34 Of the women who discontinued hormone therapy, only about 16% overall reinitiated it later.35 Reinitiation was more likely among women who took estrogen-only therapy (24%) than it was among women who took estrogen-progestogen therapy (11%). The likelihood of reinitiating was lower among women with chronic conditions such as diabetes (relative risk [RR] 0.68; 95% CI, 0.61-0.76), hyperlipidemia (RR 0.83; 95% CI, 0.79-0.88), and cardiovascular disease (RR 0.87; 95% CI, 0.83-0.92).35

THE ROLE OF TIMING OF HORMONE THERAPY FOLLOWING ONSET OF MENOPAUSE

Subsequent to the WHI, Salpeter et al36 conducted a meta-analysis of data from 30 clinical trials that included a total of 26,708 women. The meta-analysis together with data on postmenopausal women from the Nurses’ Health Study37 (a prospective observation trial of 121,700 nurses aged 30-55 followed from 1976-2000) suggested that the time of initiation of hormone therapy plays an important role on its effects on CHD. Both the Salpeter meta-analysis and the Nurses’ Health Study data indicated that there is a reduction in CHD among women who initiate hormone therapy near to the time of menopause and no beneficial effects when hormone therapy is initiated in older women. Additionally, the WHI estrogen-only arm and estrogen-progestogen arm data have been reanalyzed to look at effects on CHD for women in various age cohorts.38,39 In these analyses, estrogen therapy provided some benefits against CHD among women in the 50 to 59 year age cohort, although not at a statistically significant level. No benefits were identified for women in the 60- to 69-year or 70- to 79-year age groups. A WHI substudy indicated that there was significantly less coronary artery calcification among women aged 50 to 59 who were treated with estrogen as compared with those treated with placebo.40 More recent research done in Italy with 134 postmenopausal women supports these WHI substudy results as well.41 The Italian study evaluated vascular endothelial function and found that beneficial effects of estrogen were reduced as time since menopause increased.

The relationship between cholesterol levels and CHD in postmenopausal women who use hormone therapy also has been evaluated. Bray et al42 studied WHI participants with normal lipid levels who were using estrogen-only or estrogen-progestogen therapy and found that they did not have increased risks for CHD or myocardial infarction. The women with a low density lipoprotein (LDL) to high density lipoprotein (HDL) ratio of less than 2.5 had no increased risks, while women whose LDL to HDL ratio was greater than or equal to 2.5 did.42 Higher LDL levels are associated with increased CHD risk (goal is for LDL to be lower than 100 mg/dL) while higher HDL levels are associated with reduced CHD risk (goal is for HDL to be greater than 50 mg/dL; if it is greater than 60 mg/dL, it is considered protective). Thus, if the LDL level is 2.5 times or more higher than the HDL, the LDL is too high, and the HDL is not high enough, and the risk for heart disease is increased.

One plausible explanation for the importance of time since menopause for initiating hormone therapy was recently identified.43 A molecule called 27-hydroxycholesterol (27HC), which is a byproduct of cholesterol metabolism, is an exogenous selective estrogen receptor modulator that competes with estrogen for receptor sites found in blood vessels. Prior to menopause, most women have low 27HC levels and circulating estrogen preferentially binds with the vascular receptor sites, which conveys a cardioprotective effect. Following menopause, 27HC levels rise and estrogen levels fall, creating an environment that favors 27HC binding to the vascular receptor sites, which blocks the beneficial effects of estrogen binding. The 27HC molecule also has been shown to exert partial agonist activity in breast cancer cells, suggesting that it may also negatively influence the pathology of breast cancer by promoting tumor growth.44 These hypotheses about the effects of 27HC were tested using mice models and need further validation among women. If borne out, these findings may provide important new data that may explain the effects of time since menopause on hormone therapy initiation as it relates to heart disease.

BREAST CANCER AND HORMONE THERAPY

Important implications regarding the potential risk for breast cancer also were uncovered in the WHI study.22,25 During the first 2 years of the estrogen-progestogen therapy arm, there was a lower incidence of breast cancer among women
receiving estrogen-progestogen therapy compared to those receiving placebo. Over the 5.6 years of the trial, the overall incidence of breast cancer increased among women receiving estrogen-progestogen therapy. The increased risk returned to baseline within 3 years of discontinuing therapy. However, the women in the estrogen-progestogen arm who were diagnosed with breast cancer during the trial were more likely to have node-positive disease (hazard ratio [HR] 1.78; 95% CI, 1.23–2.58) and had a trend toward a higher mortality rate in the 10.7 year follow-up analysis (HR 1.96; 95% CI, 1.00–4.04). Possible explanations for these seemingly contradictory findings have given rise to the question of whether progestogen may play a role in increasing the risk for breast cancer. The women in the estrogen-only arm initially had a nonsignificant decrease in breast cancer risk. After 10.7 years of follow-up, the incidence of breast cancer among women in the estrogen-only arm was lower than in those taking placebo (HR 0.77; 95% CI, 0.62–0.95), and reanalysis of the estrogen-only arm data indicated that the breast cancer risk did not increase among women who were at low risk for breast cancer at baseline. Possible explanation for the decrease in breast cancer seen with estrogen-only therapy is that exogenous estrogen alone may reduce breast cancer cell proliferation through apoptosis in the low estrogen environment of postmenopause.

Interestingly, recent epidemiologic data show declines in breast cancer rates that seemingly coincide with a reduced use of oral hormone therapy in the wake of the WHI results and mammography screening saturation. Epidemiologic data from the United States National Cancer Institute’s Surveillance, Epidemiology, and End Results registries indicated a decrease in breast cancer of 7% to 8% between 2002 and 2003. During this same time period, a 12% decrease in estrogen receptor (ER)-positive tumors was reported among women aged 50 to 59 years. A Kaiser analysis of data on breast cancer rates from 1980 through 2006 among women in the Portland, Oregon area showed declines in breast cancer rates from 2001 to 2004, with leveling off following 2004. In this same study, ER-positive tumor incidence followed the overall trend. Yet the incidence of ER-negative tumors, which are believed to be unaffected by hormone therapy, also inexplicably dropped from 2002 to 2006. The authors recognized that reduced hormone therapy use and changes in mammogram screening rates could have played a role in this noted decline; however, conclusions regarding any causal relationship cannot be made as the data are observational and do not specifically link hormone therapy use and the diagnosis of breast cancer.

Epidemiologic data on hormone therapy use and breast cancer incidence in Canada following the release of the WHI estrogen-progestogen therapy arm data were released. The increase in breast cancer incidence that occurred in Canada between 2004 to 2006 despite continued reductions in hormone therapy prescriptions and the leveling off of incident cases in the United States argues against a causal relationship between hormone therapy use and breast cancer. Instead, these data suggest that hormone therapy use may promote tumor growth of preexisting malignant breast tissue. This provides a possible explanation for why incident breast cancer rates are higher during years of extensive use, level off or fall when use declines, and then rise again after use has been low for a few years to reflect the natural disease trajectory as women age.

Even without these recent increases in breast cancer incidence, causation cannot be inferred from observational studies alone. Many factors other than hormone therapy that were not evaluated in these studies may affect breast cancer incidence, such as changes in the frequency of use of estrogen agonist/antagonists, smoking rates, alcohol consumption, family history, and physical activity.

Several sources indicate that mammography screening rates in the United States have had a small yet significant decline since 2000, which may in part explain the decreased incidence of breast cancer. The Canadian study indicated that mammography screening rates have remained stable since 2000, at a rate of about 72%. These data suggest that surveillance bias is not likely to result in underdiagnosing breast cancer. Clearly, more research is needed to determine linkages between specific risk factors and the incidence of breast cancer.

EMERGING HYPOTHESES ON WHEN TO INITIATE HORMONE THERAPY

Clearly, CHD and breast cancer risks may be affected by use of estrogen-only and estrogen-progestogen therapy. Reanalyses of the WHI data and the Salpeter meta-analysis suggest that heart disease risk may be altered or even alleviated if hormone therapy (oral estrogen-progestogen or estrogen-only) is initiated immediately after a woman becomes postmenopausal. These data have raised awareness that the exact timing of when hormone therapy is initiated may be important for CHD. Other research has suggested that the time of initiation also may be important for breast cancer risk. The data regarding potential effects on risk for CHD and breast cancer have given rise to 2 hypotheses: the timing hypothesis, concerning heart disease risk, and the gap hypothesis, concerning breast cancer risk.

The Timing Hypothesis: Hormone Therapy and Heart Disease Risk

Recent data suggest that starting estrogen-progestogen or estrogen-only therapy at the time of menopause or very soon after it occurs has some beneficial effects against CHD. Hsia et al reported on the WHI estrogen-only arm results by age-stratified groups. Their data demonstrated that women in the 50 to 59-year age strata had a trend toward a reduced risk for...
CHD (HR 0.63; 95% CI, 0.36-1.08). More recently, LaCroix et al reported on the 10-year follow-up of women in the WHI estrogen-only arm, and they found that the risk of stroke resolved and the risk for heart disease was lower among women who had been treated with estrogen-only therapy for an average of 5.9 years when compared to those who took placebo. The annualized rate was 0.64% and 0.67% in the estrogen-only and placebo groups, respectively (HR 0.97; 95% CI, 0.75-1.25). Among women in the 50 to 59-year age strata at baseline, there was a risk reduction of 40% to 50% for CHD endpoints among the women taking estrogen-only therapy. Of 10,000 women taking estrogen-only therapy, 12 fewer women would experience a myocardial infarction, 13 fewer would die, and 18 fewer would experience adverse events. In contrast, these risks were all increased among the women in the 70 to 79-year age strata who took estrogen-only therapy.

The Gap Hypothesis: Hormone Therapy and Breast Cancer Risk

In contrast, when breast cancer risk is considered, potential benefits have been identified when hormone therapy initiation is delayed for 5 years or more following menopause. In the prospective, observational Million Women study in Britain of more than 1.1 million women, the authors found that there was no or very little increase in the risk of breast cancer if hormone therapy (oral estrogen-only or oral estrogen-progestogen) was started 5 years after menopause had occurred (estrogen-only: RR 1.05; 95% CI, 0.89-1.24; estrogen-progestogen: RR 1.53; 95% CI, 1.38-1.70). However, there was a statistically significant increase in the risk for breast cancer among women who started hormone therapy before or less than 5 years since the onset of menopause (estrogen-only: RR 1.43; 95% CI, 1.35-1.51; estrogen-progestogen: RR 2.04; 95% CI, 1.95-2.14). Breast cancer incidence among women in the 50 to 59-year age cohort who had never used hormone therapy was 0.30% (95% CI, 0.29%-0.31%). Incidence among the women who initiated either estrogen-only or estrogen-progestogen therapy within 5 years of menopause was higher (estrogen-only: 0.43%; 95% CI, 0.42%-0.45%; estrogen-progestogen: 0.61%; 95% CI, 0.59%-0.64%). This pattern was consistent regardless of the type of hormone therapy used, the length of hormone therapy use, and weight differences among the women. These data support the gap hypothesis, which suggests that delaying initiation of hormone therapy for approximately 5 years after menopause may reduce the risk for developing breast cancer.

In teasing out the relationship between breast cancer and hormone therapy use, the age at which hormone therapy use is started also may play a role. Coombs et al conducted a risk-estimate analysis to evaluate the risk of breast cancer at varying ages in women using hormone therapy. This study estimated that the baseline risk of 6.1% among women starting hormone therapy at age 50 would increase to 6.3% with estrogen-only use and to 6.7% with estrogen-progestogen use. The increase was similar among older women; however, it was proportionally greater due to a lower baseline risk (1%-4%). The greatest increase in risk (2%-3%) was among women who used hormone therapy for 10 years or more. Risk returned rapidly to baseline with the cessation of hormone therapy use.

The length of time on therapy is also increasingly recognized as important. Use of estrogen-progestogen when initiated within 5 years of menopause onset was associated with a breast cancer HR of 2.75 (95% CI, 1.73-4.39) if used for more than 5 years and 1.85 (95% CI, 1.03-3.34) if used for 2 to 5 years. Similarly, WHI follow-up data of approximately 11 years indicated that the risk for breast cancer diagnosis and increased mortality occurred with estrogen-progestogen use of 4 to 5 years duration when therapy was initiated soon after menopause. When estrogen-progestogen therapy was initiated after a break in estrogen exposure, the risk was delayed. WHI participants treated with estrogen-only soon after menopause had no increase in breast cancer risk, and women who were treated after a break from estrogen exposure had a decreased risk. WHI participants treated with estrogen-only for a mean of 5.9 years had a statistically significantly decreased risk for breast cancer. The overall risk of breast cancer approximately 11 years after the WHI started among the women treated with estrogen-only therapy was 0.27%, while it was 0.35% among the women who took placebo (HR 0.77; 95% CI, 0.62-0.95). In a separate analysis, WHI participants treated with estrogen-only therapy for an average of 7.1 years had no increase in invasive breast cancer incidence (HR 0.80; 95% CI, 0.62-1.04; P = .09).

SYMPTOM-RELIEVING AND QUALITY OF LIFE BENEFITS OF HORMONE THERAPY

No discussion on hormone therapy use is complete without reflecting upon menopause-related symptom relief and quality of life. Balancing the possible risks and benefits of hormone therapy with the benefit of relieving menopause-related symptoms, which can have a significant negative toll on a woman’s quality of life, is important when considering use of this therapy for an individual woman. Menopause-related symptoms can interfere with work, personal life, and sleep. Sleep interruptions can foster difficulty with concentration, memory, and cognitive function and can increase irritability and moodiness. Vaginal dryness often renders sexual activity uncomfortable, and this can simultaneously cause physical distress as well as interfere with relationship stability and enjoyment. There is strong observational and RCT evidence that hormone therapy reduces menopause-related symptoms. Hormone therapy is well known to reduce both the frequency and intensity of vasomotor symptoms (estrogen-only oral or transdermal, estrogen-progestogen oral or transdermal, and systemic vaginal therapy) and improve vaginal dryness (oral, transdermal, or vaginal). Its beneficial effects on skin collagen and thickness help to reduce wrinkles. Hormone therapy (oral and transdermal) is known to reduce the risk for fractures. Additionally, evidence demonstrates that systemic hormone therapy (oral and transdermal) increases sleep quality, improves mood, and results in improved sexual function.

CURRENT RECOMMENDATIONS FOR HORMONE THERAPY USE

Clinicians and women must weigh and balance all of the data when considering hormone therapy as an option for managing menopause-related symptoms. Carefully deciphering both
the cause of the presenting symptoms and the various available management options is important. In most instances, there are multiple different approaches that a woman can select for menopause-symptom management.

First, it is important to consider a wide set of differential diagnoses that may be responsible for presenting symptoms. Some symptoms commonly associated with menopause also will occur with specific disease states (eg, endocrine disorders, especially thyroid disorders; depression; infections; heart disease; and depression or anxiety). Additionally, when some diseases are not well managed, menopause-related symptoms such as vasomotor symptoms and sleep disturbances can be exacerbated (eg, diabetes with hyperglycemia or hypoglycemia, hypertension with spikes in blood pressure, and depression or anxiety).

Once symptoms are determined to be menopause-related, a stepped approach to management similar to that described by Nachtigall et al is suggested by many of the national organizations. This approach recommends first using lifestyle changes such as regular aerobic exercise, maintaining core temperature with layers and fans and such, and avoiding triggers like alcohol and caffeine. Next, complementary therapies such as botanicals might be tried. If these methods prove unsatisfactory, hormone therapy or an alternative prescription option such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or gabapentin might be added. However, the alternative prescription options do not provide bone protection, so counseling and an active plan for maintaining and monitoring bone health to prevent osteoporosis is especially important.

If hormone therapy is being considered, screening for personal and family history of heart disease, breast cancer, clotting disorders, and diabetes and other endocrine disorders as well as personal history of sexually transmitted infections and HIV is important. If the risk for any of these disorders is low, most forms of systemic hormone therapy may be an option. When selecting between oral and transdermal systemic therapy options, it is important to remember that clotting risk, potential for gallbladder disease, and the effect on triglycerides may be lower with the transdermal route. If the patient’s lifestyle is less active or there is an unclear history regarding clotting disorders in her personal or family history, the transdermal route may be a better option. Additionally, all oral estrogens are metabolized in the liver into estrone, while transdermal estrogens largely avoid the first-pass effect through the liver. If a woman is taking other medications that compete for liver metabolism, has other systemic diseases that are well controlled (such as hypertension or history of gallbladder disease), or is at risk for elevated triglyceride levels (eg, metabolic syndrome, hyperlipidemia, diabetes), then the transdermal route may be a better option. However, exactly what the potential risks for heart disease and breast cancer are with non-oral routes of estrogens has not been established clearly.

All women with an intact uterus who are treated with systemic estrogens require progestogen therapy to reduce the risk for endometrial cancer. However, if the patient’s symptoms are predominantly related to vaginal atrophy, then systemic therapy likely is not necessary. In general, the use of local vaginal estrogen-only therapy is unlikely to increase risk for systemic disease (ie, heart disease, breast cancer), as the amount of systemically absorbed estrogen is minimal. If low doses of vaginal estrogen-only therapy are used, the risk for endometrial cancer is lower, and progestogen use may not be needed in women with an intact uterus.

Several national and international organizations as well as the FDA have published recommendations or guidelines to guide hormone therapy use. Some of these recommendations are the same as those that were originally published in the immediate wake of the HERS and WHI results publications, and others have been updated to reflect more recent data. These recommendations or guidelines are summarized in Table 4. The general consensus is to individualize use for a woman after considering her unique personal and family health and risk profile and to use the lowest dose that is effective for the shortest period of time. The NAMS recognized in their 2012 hormone therapy position statement the differences in risk for breast cancer as opposed to CHD, venous thromboembolic events, stroke, and mortality when hormone therapy is initiated close to the time of menopause. They note that the risks for hormone therapy use among women aged 50 to 59 years are low overall and support initiating therapy around the time of menopause to manage symptoms and reduce bone loss. Additionally, the overall mortality risk for heart disease among women is much higher than the overall risk for breast cancer in general. The International Menopause Society and a recent review paper by Harman et al suggest that limiting the length of time for hormone therapy use is not necessary. However, the NAMS state that safety data limit the use of estrogen-progestogen therapy to 3 to 5 years. They note that duration of use of estrogen-only therapy is more flexible, given the more favorable risk profile seen after an average of 7 years of use. Further evidence, which will most likely be obtained from observational data as well as ongoing RCTs, will be needed to validate safety for longer use over time.

CONCLUSION

The evidence for hormone therapy use and its relationship to CHD and breast cancer continues to evolve. Currently, the evidence suggests conflicting information regarding when it may be best to initiate hormone therapy. The risk for CHD appears to be reduced when hormone therapy is started at the time of menopause or very soon after. Conversely, the risk for developing breast cancer appears to be increased if hormone therapy is started at or within the first 5 years of menopause and reduced when therapy is initiated 5 years after menopause. The duration of hormone therapy also is emerging as an important factor in relation to breast cancer risk. Breast cancer risks appear to be lower when the length of estrogen-progestogen therapy use is shorter, such as 3 to 5 years. The data suggest that any increased risk for breast cancer returns to baseline within a few years after therapy is discontinued.

The current recommendations regarding purpose and use of hormone therapy following the WHI data release have largely shifted back to mirror those identified by the National Institute on Aging in 1979. The 1979 recommendations stated that hormone therapy should be used for managing menopause-related symptoms such as vasomotor...
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<th>Organization</th>
<th>Recommendations/Guidelines</th>
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| American Association of Clinical Endocrinologists | - Hormone therapy may be appropriate for treating severe menopause-related symptoms in select women based on risk-benefit profile.  
- Follow FDA guidelines for lowest dose over shortest period of time.  
- A progestogen should be used for women with an intact uterus.  
- Consider use of transdermal or vaginal route. |
| American College/Congress of Obstetricians and Gynecologists (ACOG) | - Hormone therapy is the most effective treatment for menopausal vasomotor symptoms.  
- Use of hormone therapy for alleviation of vasomotor symptoms should be reassessed annually.  
- The lowest effective dose should be used for the shortest possible time. |
| American Society of Reproductive Medicine (ASRM) | - Hormone therapy (estrogen-only, estrogen-progestogen) is effective for menopause-related symptom relief (vasomotor, vaginal atrophy, sleeplessness, depressed mood, lethargy).  
- Goals of therapy are symptom relief and minimizing complications and side effects.  
- Use of hormone therapy is individualized considering quality of life, risks, and preferences.  
- Breast cancer risk is higher with estrogen-progestogen than with estrogen-only therapy, and risk returns to baseline 5 years after discontinuing therapy.  
- Hormone therapy is not indicated for heart disease prevention (primary or secondary).  
- Route of therapy may affect clotting risk.  
- A progestogen should be used for women with an intact uterus. |
| Endocrine Society | - Standard doses of estrogen-only or estrogen-progestogen therapy are highly effective for treatment of vasomotor symptoms, prevent bone loss and fractures, increase risk for thromboembolic events, and improve quality of life; lower doses are effective for many women.  
- Estrogen-progestogen therapy reduces the risk for colon cancer.  
- Estrogen-only therapy increases the risk for endometrial cancer; adding progestogen mediates this risk.  
- Vaginal estrogen is highly effective for vaginal atrophy, overactive bladder, and urinary tract infection.  
- Estrogens increase the risk of breast cancer after more than 5 years of use, estrogen-progestogen therapy increases risk after 3 to 5 years of use; breast cancer risk returns to baseline within 3 to 5 years of discontinuation.  
- Benefits of hormone therapy outweigh risks for many postmenopausal women under the age of 60, especially for symptom management. |
| Food and Drug Administration | - Hormone therapy should be used at the lowest doses for the shortest duration to reach treatment goals.  
- The precise dose that confers the lowest risk or least serious side effects is not known with certainty.  
- When these products are being prescribed solely for the treatment of symptoms of vulvovaginal atrophy, topical vaginal products should be considered. |
| International Menopause Society | - Use of hormone therapy should be individualized for each woman and reevaluated annually.  
- Hormone therapy should be recommended only when there is a clear reason for use (ie, physical effects of low estrogen, significant symptoms).  
- A progestogen should be used for women with an intact uterus.  
- Hormone therapy may reduce risks for osteoporosis, heart disease, affective disorders, and dementia in women with early menopause and is advised until at least the normal age of menopause is reached. |
### Table 4. Summary of Organization Recommendations for Use of Hormone Therapy to Relieve Menopause-related Symptoms

<table>
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<th>Organization</th>
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<td>North American Menopause Society (NAMS)</td>
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| • Use the lowest dose that is effective.  
| • No reason for a specific limit on duration of hormone therapy use.  
| • Safety is affected by user age; women 60 years or less have low risk.  
| • Treatment of moderate to severe vasomotor symptoms remains the primary indication for systemic hormone therapy.  
| • A progestogen should be used for women with an intact uterus.  
| • Use of hormone therapy needs to be individualized and based on the individual woman’s priorities and personal risk factors.  
| • There is growing observational study data suggesting that transdermal estrogen therapy may have a lower risk for stroke, myocardial infarction, and deep vein thrombosis.  
| • Comprehensive pretreatment evaluation and regular reevaluation is needed.  
| • Use of hormone therapy for women who experience menopause at an early age at least up to the median age for usual menopause is considered safe and logical.  
| • Duration of estrogen-progestogen therapy use is limited due to increased risks for breast cancer after 3 to 5 years of use.  
| • Duration of use of estrogen-only therapy is more flexible due to the more favorable risk profile seen after an average of 7 years of use.  
| • Data support starting hormone therapy close to the time of menopause to manage symptoms and prevent bone loss.  
| • Safety data is lacking to support use of estrogen therapy in breast cancer survivors. |
| National Association of Nurse Practitioners in Women’s Health |  
| • Hormone therapy remains the only FDA-approved therapy for the relief of moderate to severe vasomotor symptoms.  
| • For many women the benefits of short-term, low-dose hormone therapy outweigh potential risks.  
| • Hormone therapy should be initiated only in women with menopausal symptoms (usually women in their 40s or early 50s) and reassessed frequently.  
| • Health care professionals and women must consider each individual woman’s beliefs and values, personal and family history, and emotional and physical needs when considering therapeutic options. |

Symptoms and vaginal dryness. They further stated that the lowest doses of hormone therapy that mediate symptoms should be used and for the shortest period of time. As noted in Table 4, most national and international organizations support these recommendations today. Similarly, the 2012 USP-STF draft statement on hormone therapy use for prevention of chronic conditions recommends against the use of estrogen-only or estrogen-progestogen for prevention of chronic disease. They note that these recommendations do not apply to women aged under 50 years who are surgically postmenopausal or for women who are using hormone therapy for the purpose of managing menopause-related symptoms.

The perception of menopause as a disease is being challenged by women and their clinicians alike. MacPherson’s charge to deconstruct the biomedical paradigm is finally being heeded, at least with regard to menopause. Women are adopting this stance and have begun to embrace the transition to postmenopause as a normal life event that can be managed in a myriad of ways and not necessarily requiring medica-

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### CONFLICT OF INTEREST

The author has served as consultant or speaker for Amgen, Pfizer, and Depomed within the past 12 months.
REFERENCES


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