Estrogen and progestogen therapy in postmenopausal women

Practice Committee of the American Society for Reproductive Medicine

The American Society for Reproductive Medicine, Birmingham, Alabama

This Educational Bulletin discusses the effectiveness of hormone therapy (HT) for relieving vasomotor and urogenital symptoms and the side effects associated with such treatment; considers the evidence concerning the effects of HT on the risk of osteoporosis and related fractures and on the risks of coronary artery disease, dementia, and colorectal cancer; and considers the longer term effects of HT on the risks of stroke, venous thromboembolism, and cancer of the breast, endometrium, and ovary. (Fertil Steril® 2008;90:S88–102. ©2008 by American Society for Reproductive Medicine.)

Hormone therapy (HT) can be used to manage problems associated with the decline in ovarian estrogen production after menopause. Menopause occurs naturally when the ovarian follicular pool is functionally exhausted or can be induced by surgical removal of both ovaries. The resulting hypoestrogenic state may affect estrogen target tissues adversely, including the brain, skeleton, and skin as well as the cardiovascular and genitourinary systems. Differences in genetics, body mass index, and body habitus also may influence the levels of endogenous estrogen and androgen in postmenopausal women. The frequency and severity of menopausal symptoms, the reaction of target tissues to estrogen deficiency, and the response to HT vary significantly among women.

GOALS OF THERAPY

There are two broad categories of menopausal HT: estrogen-alone therapy (ET) and estrogen combined with progestogen therapy (E/PT). For the purposes of this document, the term progestogen refers to natural progesterone as well as synthetic congeners of progesterone (progestins).

The goals of menopausal HT are to [1] reduce symptoms resulting from estrogen depletion, including hot flushes, sleeplessness, lethargy, and depressed mood; [2] treat urogenital atrophy and vaginal dryness; and [3] minimize the risk of side effects and complications relating to HT. (See Table 1 for panel of risk and rate definitions.) Although ET and E/PT may improve a woman’s quality of life, each woman has a unique risk profile that might lead to more, or less, benefit from HT. Patient preferences as well as evidence from medical research influence management decisions. As a result, a standard treatment applied to all menopausal women will not necessarily meet the needs of many individual women. Health-care providers should therefore consider the relative balance between the benefits and risks of treatment for the individual patient and the likelihood of adherence to the prescribed regimen before drawing conclusions or recommending HT (Tables 2 and 3). Ongoing care should involve periodic reassessments of any associated side effects and newly published research findings.

This Educational Bulletin focuses first on the effectiveness of HT for relieving vasomotor and urogenital symptoms and on the side effects associated with such treatment. Next, it considers the evidence concerning the effects of HT on the risk of osteoporosis and related fractures and on the risks of coronary artery disease, dementia, and colorectal cancer. Finally, it considers the long-term effects of HT on the risks of stroke, venous thromboembolism, and cancer of the breast, endometrium, and ovary.

TREATMENT OF ESTROGEN-DEFICIENCY SYMPTOMS

Neurovascular Symptoms

The principal symptom of the early menopausal years is the vasomotor (hot) flush. Hot flushes and night sweats are experienced by 50% to 85% of postmenopausal women and cause significant distress for approximately 25%. Sleep disturbances caused by nocturnal hot flushes and sweating can lead to lethargy and depressed mood, although depression is equally common in premenopausal and postmenopausal women. Vasomotor symptoms are more common and more severe after surgical menopause. The frequency of hot flushes decreases with time. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, the percentage of women taking placebo who experienced vasomotor symptoms declined from 56% at baseline to 30% in year 3 (1). Only a small percentage of women continue to suffer from vasomotor flushes 10 years after menopause. Fifteen years after menopause, approximately 3% of women report very frequent hot flushes, and 12% report moderate to severe hot flushes (2, 3).

Hormone therapy is the most effective treatment for hot flushes and also decreases sleep disturbances, directly or indirectly, thereby improving quality of life. The value of such treatment has been demonstrated in numerous randomized controlled trials (RCTs). A systematic review of 24 RCTs involving 3329 women who had moderate to severe hot flushes found that HT reduced the frequency of hot flushes by 50% to 60%

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flushes by about 18 per week or by about 75% (95% confidence interval [CI], 64.3–82.3%) compared with placebo. The severity of vasomotor symptoms also was reduced significantly (odds ratio [OR] 0.13, 95% CI, 0.07–0.23) (4). One of the trials, the 3-year PEPI trial, involved 875 menopausal women (mean age: 56 years) who were randomly allocated to one of five treatments: placebo, estrogen alone (conjugated equine estrogens [CEE]), estrogen plus cyclic progestogen (either medroxyprogesterone acetate [MPA] or micronized progesterone), and estrogen plus continuous progestin (MPA). All hormone treatments were more effective than placebo in reducing hot flushes. There were no statistically significant differences among the treatments, and the size of the treatment effect became smaller after the first year. For instance, the likelihood of having severe vasomotor symptoms was approximately 78% lower in the four active treatment groups than in the placebo group during the first year of treatment (summary relative rate [RR] 0.22; 95% CI, 0.17–0.30) and approximately 60% lower during the third year of treatment (summary RR 0.40; 95% CI, 0.30–0.53). The estimated number needed to treat for the first year effect was approximately two: for every two patients treated during the first year, one would report fewer severe vasomotor symptoms. During the third year, because the placebo group was experiencing fewer symptoms, the number needed to treat rose to six patients. In the Heart and Estrogen/progestin Replacement Study (HERS), HT reduced hot flashes, trouble sleeping, and vaginal dryness more than placebo among women who were on average 18 years postmenopausal (mean age: 67 years). The benefit was greatest for younger women who were symptomatic at study entry (2).

The existing evidence regarding the effects of HT on vasomotor symptoms is as follows: HT reduces the number of hot flushes by about 18 per week more than placebo (4); there are no significant differences among the effects of different types of estrogen or routes of administration (5, 6); and any influence on symptoms from progestogen treatment, in continuous or cyclic forms, cannot be determined from the trial evidence (5, 6).

With respect to secondary benefits, estrogen increased feelings of well-being in several trials (7–10). However, in the PEPI trial, cognitive–affective symptoms such as
Forgetfulness (present in 34% of women at baseline), feeling easily distracted (25%), and difficulty concentrating (24%) were not changed by ET or E/PT compared with placebo after 1 year or 3 years of treatment (1). Symptoms of anxiety were present in only 5% at baseline and were unchanged over 3 years in each arm of the PEPI trial. In the HERS secondary prevention trial that compared E/PT with placebo, HT improved health-related quality-of-life measures only in those women who had menopausal symptoms at baseline (2).

The Women’s Health Initiative (WHI) primary prevention trial of continuous combined E/PT involved women who were mainly symptom-free and was not designed to assess the effects of treatment on menopausal symptoms. Nevertheless, quality-of-life measures were collected at baseline and at 1 year in all women and at 3 years in a subgroup of 1511 of the 16,608 women randomized to receive placebo or E/PT. After 1 year, E/PT had no significant effect on general health, vitality, mental health, depressive symptoms, or sexual satisfaction; however, there were small but significant improvements in sleep disturbance, physical functioning, and bodily pain. At 3 years, there were no significant benefits observed in any quality-of-life outcomes. Among women aged 50 to 54 years with moderate-to-severe vasomotor symptoms at baseline, E/PT improved vasomotor symptoms and sleep disturbance but did not affect other quality-of-life outcomes (3).

### Urogenital Symptoms

Estrogen is an effective treatment for symptoms of urogenital atrophy such as vaginal dryness and sexual discomfort. A meta-analysis of 10 randomized placebo-controlled trials found

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**TABLE 2**

<table>
<thead>
<tr>
<th>Title</th>
<th>Acronym</th>
<th>Study</th>
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<tbody>
<tr>
<td><strong>Randomized controlled trials</strong></td>
<td></td>
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<tr>
<td>Postmenopausal Estrogen/Progestin Interventions Trial</td>
<td>PEPI</td>
<td>Greendale et al., 1998 (1)</td>
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<td>Heart and Estrogen/progestin Replacement Study</td>
<td>HERS</td>
<td>Hulley et al, 1998 (24)</td>
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<td>Women’s Health Initiative Hormone Trials</td>
<td>WHI-HT</td>
<td>E/PT: Writing Group, 2002 (26); ET: The WHI Steering Committee, 2004 (27); Rossouw et al., 2007 (49)</td>
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<td><strong>Observational studies</strong></td>
<td></td>
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<td>NHS</td>
<td>Grodstein et al., 2000 (40)</td>
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<td>The Million Women Study</td>
<td>MWS</td>
<td>Beral et al., 2003 (96)</td>
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<td>Women’s Health Initiative Observational Study</td>
<td>WHI-OS</td>
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**TABLE 3**

<table>
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<tr>
<th>Outcome</th>
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<th>HERS</th>
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<td>RH</td>
<td>95% CI</td>
<td>RH</td>
</tr>
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<td>CHD</td>
<td>1.2</td>
<td>0.97–1.60</td>
<td>0.99</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.4</td>
<td>0.86–2.31</td>
<td>1.23</td>
</tr>
<tr>
<td>VTE</td>
<td>2.1</td>
<td>1.26–3.55</td>
<td>2.79</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.2</td>
<td>0.97–1.59</td>
<td>1.30</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>0.6</td>
<td>0.32–1.24</td>
<td>0.69</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.6</td>
<td>0.33–1.33</td>
<td>1.09</td>
</tr>
</tbody>
</table>

CHD: coronary heart disease; CI: confidence interval; HERS: Heart and Estrogen/progestin Replacement Study (24); RH: adjusted relative hazards; VTE: venous thromboembolism; WHI: Women’s Health Initiative (26, 27, 48, 49, 87).
significant improvement in all outcomes evaluated: dyspareunia, related symptoms, and the physician’s assessment (11). The vaginal route of administration resulted in more symptomatic relief than the oral, transdermal, or parenteral routes of administration. Few of the studies included in the analysis evaluated whether treatment benefits extended beyond 6 months.

Estrogen also has been recommended for the treatment of urinary incontinence, a problem that affects 5% to 14% of women 60 years of age or older. The presence of estrogen receptors in urethral mucosa and smooth muscle suggests that estrogen could improve symptoms of urinary incontinence. In a meta-analysis including five RCTs involving a total of 117 women, subjective improvement in symptoms of urinary incontinence was significantly greater in women who received ET than in those who received placebo (12). However, HERS reported contrasting results from a considerably larger trial involving 2763 postmenopausal women; among the 1525 participants who reported at least one episode of urinary incontinence per week, E/PT was associated with a worsening of incontinence symptoms compared with the placebo group (13). After an average follow-up period of 4.1 years, incontinence had worsened in 38.4% of the HT group and 28.4% of the placebo group. In the WHI trials, for the one third of women who were continent at baseline, estrogen alone and E/PT increased the incidence of urinary incontinence of all types. Stress incontinence developed in 16% to 17% of the HT groups and 9% of the placebo groups. Although the biological mechanisms for increased urinary incontinence with estrogen or estrogen plus progestogen remain obscure, HT also worsened urinary incontinence in women who were incontinent at baseline in the WHI trials (14).

**Side Effects Associated with Treatment of Symptoms**

Irregular or withdrawal bleeding during HT is a frequent reason for early discontinuation of treatment (15). Factors that favor continuation of treatment are those associated with less likelihood of bleeding: hysterectomy, an older age when initiating treatment, age greater than 60 years, use of continuous combined rather than sequential E/PT, and a sufficient dose of progestin in continuous combined E/PT (16–18). In a multicenter RCT involving 1724 postmenopausal women, bleeding was reported in 15% of estrogen-only cycles, 18% of continuous combined E/PT cycles, and 74% of the sequential E/PT cycles (17). In one trial, 208 out of 373 women who had not had hysterectomies had vaginal bleeding during treatment with estradiol valerate (19). In five RCTs involving continuous combined treatment regimens, bleeding rates were approximately 35% at cycle 2 or 3, 24% at cycle 6, and 16.5% (95% CI, 14.5–18.9) at cycle 12.

In the WHI E/PT study, 33% of women in the HT group required evaluation with endometrial biopsy for bleeding compared with 6% of women in the placebo group (P<.001) (20). In the HERS trial, uterine bleeding occurred in 31% of the HT group and spotting in another 33% during the first year of the study. Those frequencies decreased to 11% and 20%, respectively, during the fourth year. By comparison, uterine bleeding and spotting occurred in 2% and 13% of placebo-treated women during year 1 and in 2.5% and 6% during year 4 (2).

In the subgroup of women in the WHI E/PT trial who had no breast tenderness at baseline, the group receiving E/PT developed breast tenderness more often than the placebo group (9.3% vs. 2.4%) (21). Breast pain was present at baseline in 4% of women in the PEPI trial. Compared with placebo treatment, breast symptoms were not worse with unopposed estrogen, but were approximately two-fold more likely with each of the three progestin formulations. For every 21 (95% CI, 12–90) patients treated with progestin formulations for 3 years, there would be one more with worse breast symptoms than in 21 placebo-treated women (1).

Musculoskeletal symptoms were commonly reported by women before treatment in the PEPI trial, including aches and pains (48%), joint pain (44%), muscle stiffness (42%), and skull and neck aches (34%) (1). Musculoskeletal symptoms were significantly improved in women receiving treatment with conjugated estrogens and cyclic or continuous MPA. The frequency of headache was not significantly changed during treatment. In the PEPI trial, 32% of women reported concerns about perceived weight gain during HT at baseline. However, the proportion reporting perceived weight gain was decreased in the HT groups at 12 and 36 months, and the reduction was significant in those who received treatment with CEE and continuous MPA (OR 0.61; 95% CI, 0.41–0.91) (1). In the HERS trial there was no difference between the HT and placebo groups in reported weight gain (2).

**HORMONE USE TO PREVENT DISEASE**

**Osteoporosis and Fractures**

Osteoporosis is common in white postmenopausal women and causes 1.5 million fractures per year in the United States (22). Hip fracture is the most severe consequence of osteoporosis, and its incidence in women rises exponentially from approximately 100 to 1000 per 100,000 women per year from age 60 to age 80 years (22). Osteoporosis is an important risk factor for fracture, but numerous other factors determine fracture incidence. Randomized controlled trials involving the surrogate outcome of bone mineral density uniformly indicate that HT maintains or improves bone mineral density in the spine, proximal femur, and radius (23). Four RCTs have evaluated the effectiveness of HT for prevention of clinical fractures (24–27) (Table 4).

The HERS trial involved 2763 American women with established heart disease (average age: 66.7 years) in which fracture incidence was a secondary outcome. The interventions were 0.625 mg of CEE plus 2.5 mg of MPA daily (continuous E/PT) or placebo. After a mean 4.1-year of follow-up period, E/PT did not alter significantly the likelihood of hip
randomized controlled trials and hip fracture with estrogen and progestin or unopposed estrogen.

<table>
<thead>
<tr>
<th>Study</th>
<th>Exposure</th>
<th>Relative rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hulley et al., 2002 (24)</td>
<td>Estrogen–progestin</td>
<td>1.09</td>
<td>0.48–2.46</td>
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<tr>
<td>Komulainen et al., 1998 (25)</td>
<td>All hormones</td>
<td>0.43</td>
<td>0.20–0.91</td>
</tr>
<tr>
<td>WHI 2002 (26)</td>
<td>Estrogen–progestin</td>
<td>0.66</td>
<td>0.33–1.33</td>
</tr>
<tr>
<td>WHI 2004 (27)</td>
<td>Estrogen</td>
<td>0.61</td>
<td>0.33–1.11</td>
</tr>
<tr>
<td>Summary</td>
<td></td>
<td>0.64</td>
<td>0.45–0.92</td>
</tr>
</tbody>
</table>


fracture (RR 1.09; 95 % CI, 0.48–2.46) or other type of fracture (RR 0.93; 95 % CI, 0.73–1.20) (24).

A Finnish RCT with fracture incidence as the primary outcome measure involved 464 postmenopausal women (average age: 52.7 years) who were randomly allocated to one of four groups: E/PT alone (estradiol and cyproterone), vitamin D alone, E/PT plus vitamin D, or placebo. After a mean 4.3-year follow-up period, and after adjusting for baseline bone density and fracture history, the two HT groups had significantly fewer nonvertebral fractures than the two groups not receiving HT (RR 0.43; 95 % CI, 0.20–0.91) (25). However, the trial is vulnerable to small sample errors because there were only three hip fracture events, all occurring in the non-HT groups.

In the WHI trial of E/PT versus placebo, the mean age of the 16,608 women in the study was 63.3 years (26). Ten and 15 hip fractures per 10,000 woman-years were observed in the E/PT and placebo groups, respectively, yielding a relative hazard of 0.66 (adjusted 95 % CI, 0.33–1.33). Because hip fracture was a secondary outcome, the 95 % CI for that outcome has been adjusted for the number of statistical comparisons that were made.

In the WHI trial of ET versus placebo, the mean age of the 10,739 women was 63.6 years (27). Eleven and 17 hip fractures per 10,000 woman-years were observed in the ET and placebo groups, respectively, yielding a relative hazard of 0.61 (adjusted 95 % CI, 0.33–1.11). For the four RCTs combined, which involved a total of 29,323 women, HT reduced the overall relative likelihood of hip fracture by approximately one third (RR 0.64; 95 % CI 0.45–0.92) (see Table 4) (24–27).

The WHI trials were the first to show a significant overall reduction in fractures among women who were not known to be at high risk for osteoporotic fracture. Although the majority of postmenopausal fractures are osteoporotic, hip, and vertebral fractures accounted for only 14% of all osteoporotic fractures in the WHI E/PT trial. Even with adjusted 95 % CIs, the hazard ratio (HR) for any fracture in the E/PT group was significantly reduced (HR 0.76; 95 % CI, 0.63–0.92) (26). In the WHI ET trial, total fractures were 30% less likely in those receiving ET (HR 0.70; adjusted 95 % CI, 0.59–0.83) (27).

The absolute effect of E/PT and ET on hip fracture incidence in women who were not at high risk was small, involving only five and six fewer hip fractures per 10,000 women per year, respectively. The reduction in fracture risk with HT was no longer evident 2.5 years after discontinuation of hormone use (28). Therefore, HT is not warranted solely for the prevention of hip fractures. Although osteopenia and osteoporosis may be prevented with HT, alternative treatments may have a better risk–benefit ratio. Further trials are needed to compare other prevention strategies with those that include HT.

**Senile Dementia and Cognitive Impairment**

More than 33% of women 65 years or older will develop dementia during their lifetime (29). In a meta-analysis that included two cohort studies and 10 case-control studies, HT was associated with a 34% reduction in the risk of dementia (summary OR 0.66; 95 % CI, 0.53–0.82) (30). There was insufficient information in the studies to assess the effect of estrogen or progestogen with regard to formulation, dosage, duration, or time since last use. Results of three subsequent epidemiologic studies are conflicting but do not change the overall estimate of risk reduction in a meaningful way (31–33).

Memory loss is the first discernible symptom of Alzheimer disease, but it has been difficult to demonstrate an effect of HT on memory, either in normal women or in women with early dementia. A meta-analysis including nine RCTs and eight cohort studies that employed a variety of cognitive tests in women free of dementia found that HT was associated with improved verbal memory, vigilance to task, reasoning, and motor speed; generally, benefits were limited to symptomatic women and were unlikely to be detected in asymptomatic women (30). Not included in the meta-analysis was a report on cognitive function among healthy older women in the Nurses’ Health Study cohort (34); HT users scored higher in only one of four cognitive tests. The estimated risk of hormone users having a poor score on the test of verbal fluency was 30% lower (RR = 0.70; 95 % CI, 0.45–1.09); results were similar for ET and E/PT. In a trial involving 180 healthy postmenopausal women aged 45 to 55 years who were randomly assigned to receive E/PT or placebo for an interval of 4 months, modest adverse effects on short-term and long-term verbal memory were observed (P<.10) (34, 35).

Mild cognitive impairment (MCI) is a stage between normal cognitive functioning and dementia. In the Women’s
Health Initiative Memory Study (WHIMS), neither ET nor E/PT prevented MCI (36–38). In the ET trial, 76 participants were diagnosed with MCI in the CEE group compared with 58 in the placebo group (HR 1.34; 95% CI, 0.95–1.89) (38). In the E/PT trial, 63 participants were diagnosed with MCI in the E/PT group versus 59 in the placebo group (HR 1.07; 95% CI, 0.74–1.55) (36). When data from both trials were pooled as planned in the original WHIMS protocol, the combined HR was 1.25 (95% CI, 0.97–1.60). Annual assessments of global cognitive function in the WHIMS E/PT trial showed no difference between groups (37).

In the WHI ET trial, probable dementia was diagnosed more frequently in those participants assigned to CEE (n = 28) than in those taking placebo (n = 119) (HR 1.49; 95% CI, 0.83–2.66) (37). In the E/PT study, the HR for probable dementia was 2.05 (95% CI, 1.21–3.48) in women who received E/PT compared with those who received placebo. There were 45 and 22 cases of probable dementia per 10,000 woman-years in the E/PT and placebo groups, respectively. Approximately 50% of cases were classified as Alzheimer disease in each group. Approximately 12.5% of cases in the E/PT group were classified as vascular dementia compared with 5% in the placebo group (36). Incidence rates for probable dementia in the ET trial were statistically similar to those observed in the E/PT trial (P = .11). For both WHIMS trials, the pooled likelihood of probable dementia was 1.76 (95% CI, 1.19–2.60; P = .005) in the HT groups compared with the placebo groups (38). In the WHIMS E/PT study, cases of probable dementia appeared in the first year of treatment in both the E/PT and placebo groups, suggesting that some of the women had cognitive decline at baseline.

Available level I evidence does not support a role for ET or E/PT in the prevention of cognitive impairment or dementia and suggests that HT is unlikely to slow the progression of symptoms.

Coronary Heart Disease
Cardiovascular disease is the leading cause of death in postmenopausal women. Coronary heart disease (CHD) rates are lower in premenopausal women than in men of comparable age, but the incidence rises after the menopause to approximately 3 to 5 cases per 1000 per year in low-risk women (26, 27). The association of an increasing risk with postmenopausal estrogen deficiency motivated trials of HT treatment as a preventive measure. The potential effectiveness of HT in preventing CHD has been evaluated in three types of studies: epidemiologic studies (the most common); RCTs evaluating intermediate outcomes; and, finally, the highest level of evidence, RCTs that evaluated primary or secondary prevention of CHD using definitive outcomes such as nonfatal myocardial infarction (MI) and CHD death.

Epidemiologic studies A summary of epidemiologic studies that appeared in a 1996 World Health Organization Technical Report suggested that HT use reduced the risk of nonfatal MI or CHD death by 44% (summary RR 0.56; 95% CI, 0.51–0.61) compared with no use (39). In a subsequent analysis from the Nurses’ Health Study, the relative risk of a major coronary event (nonfatal MI or CHD mortality) was lower among current users of HT compared with never-users. After adjustment for cardiovascular risk factors, the relative risk was 0.61 (95% CI, 0.52–0.71) (40). Among women taking oral conjugated estrogens, the reduction in risk for 0.3-mg and 0.625-mg daily dosages and for conjugated estrogens plus progestin was similar. In the epidemiologic studies, ET was the dominant treatment, and progestogen diminished some of the intermediate effects of ET on lipids and other heart disease risk factors. In five epidemiologic studies which provided information about ET and E/PT exposure, the average risk reduction was 39% (95% CI, 27%–49%) with ET and 31% (95% CI, 13%–45%) with E/PT (41).

Intermediate outcome RCTs The results of RCTs that have evaluated intermediate outcomes are less consistent than those observed in epidemiologic studies, but many studies recorded favorable effects of HT on lipid profiles, including lipoprotein (a) (23, 42–45). However, HT does not slow the progression of coronary artery atherosclerosis, as estimated by angiographic measurements of coronary artery diameter. In the Estrogen Replacement and Atherosclerosis Trial (42), angiographic end points were used to determine the effect of ET and E/PT on the progression of atherosclerosis in 309 postmenopausal women with documented CHD who were followed for an average of 3.2 years. Neither conjugated estrogens alone (0.625 mg/day) nor continuous combined HT (0.625 mg of conjugated estrogens plus 2.5 mg of MPA per day) affected the progression of coronary atherosclerosis when compared with placebo treatment, even though lipoprotein profiles were improved in both HT groups (42). Corresponding results were found in the Women’s Estrogen-progesterin Lipid Lowering Hormone Atherosclerosis Regression Trial, which examined HT regimens using 17β-estradiol with or without cyclic MPA (46).

Primary prevention RCTs The strongest evidence regarding primary prevention of CHD comes from RCTs with clinical event outcomes; in such trials, there is little evidence of benefit from E/PT (26) or ET (47). Only the WHI trials had clinical cardiovascular outcomes as primary end points and sufficient power to evaluate benefit or risk.

In the WHI E/PT primary prevention trial (26), there were 37 and 30 CHD events per 10,000 woman-years in the E/PT and placebo groups, respectively, indicating that E/PT was associated with a small but significant increase in CHD risk (HR 1.29; 95% CI, 1.02–1.63). The increased CHD risk occurred despite a significant 12.7% reduction in low-density lipoprotein cholesterol and 7.3% increase in high-density lipoprotein cholesterol with E/PT relative to placebo. Most of the excess CHD risk was in nonfatal MI events, excluding silent MI (HR 1.30; 95% CI, 1.01–1.67) (48). Deaths due to cardiac disease were not significantly increased (15 and 13 per 10,000 woman-years in E/PT and placebo-treated groups, respectively). In the final analysis of the WHI E/PT trial, the
HR was lower and less significant: 1.24 (95% CI, 1.00–1.54). A significantly higher risk was observed only in the first year of E/PT treatment (HR 1.81; 95% CI, 1.09–3.01), and risk did not correlate with age at study entry, body mass index, presence of vasomotor symptoms, or use of aspirin or statins. An excess risk of CHD was observed in E/PT-treated women who were more than 20 years postmenopausal at the time of study entry or had higher baseline levels of low-density lipoprotein cholesterol (48). In the WHI ET primary prevention trial (47), there were similar numbers of CHD events in the ET and placebo groups, 53 and 56 per 10,000 woman-years, respectively, indicating that ET did not cause a significant increase in CHD risk (HR 0.95; 95% CI, 0.79–1.16).

One criticism of the WHI study is that the primary reports provided no specific information about cardiovascular risks among women who started to use hormones soon after menopause, before atherosclerotic heart disease was established. The WHI addressed the timing of the initiation of HT in a secondary pooled analysis of both hormone trials (49). The CHD risk was lower when HT was started within 10 years compared with more than 10 years after menopause (P=.02), but the trend in CHD risk by age was not statistically significant.

The CHD risks with either ET or E/PT use by age and by years from menopause are shown in Figure 1. The 95% confidence intervals for each pair of ET and E/PT risks of CHD overlap, although the overall adjusted CHD risk was lower with ET than E/PT (P=.02). An effect on coronary artery plaque calcification may be a mechanism for the effect of years from menopause, as shown in an analysis of computed tomography of coronary arteries in 1064 women aged 50 to 59 years from the WHI unopposed estrogen trial. The likelihood of coronary artery plaque calcification was significantly reduced in the unopposed estrogen group, and the risk reduction was greatest for the most severe calcification scores (50).

The findings of a meta-analysis of pooled data from 30 trials involving a total of 26,708 participants are pertinent to issues concerning age and years after menopause (51). In the trials with younger women, there were 14 deaths per 10,000 women, and in the trials with older women, there were 175 deaths per 10,000 women. Hormone therapy reduced total mortality in trials among younger women (mean age <60 years) (OR 0.61; CI, 0.3–0.95) but not in those among older women (mean age >60 years) (OR 1.03; CI, 0.90–1.18).
The pooled WHI hormone trial analysis is reassuring about the CHD risk with hormone use within 10 years of menopause (49). Data from a large cohort study in the United Kingdom were consistent with the WHI trial results and confirm that ET is associated with a lower likelihood of MI among women less than 60 years of age compared with E/PT (52, 53). Although these data support the relevance of WHI results to similar women in the population, the data do not support using either ET or E/PT for the primary prevention of CHD. More importantly, however, there is little risk of CHD in prescribing ET or E/PT for healthy women 50 to 60 years of age for the treatment of menopausal symptoms.

Secondary prevention Among women with a history of MI or clinically significant coronary artery disease, secondary prevention of CHD is an important goal. Because clinical events are more frequent in women with heart disease, these trials can achieve the required power with a smaller sample size. Among the secondary prevention trials, only two had clinical cardiovascular outcomes as primary end points: the HERS trial of E/PT reported in 1998 (24) and the Estrogen for Prevention of ReInfarction Trial (ESPRIT) of ET reported in 2002 (19).

The HERS secondary prevention trial involved 2,763 women aged 55 to 80 years (mean age: 66.7 years) with coronary artery disease who were postmenopausal and had an intact uterus (24). During an average follow-up of 4.1 years, treatment with oral E/PT (0.625 mg of CEE plus 2.5 mg of MPA) had no effect on MI or CHD death (relative hazard 0.99; 95% CI, 0.80–1.22). There was a pattern of early increase in CHD events with a time trend toward fewer CHD events in years 4 and 5. HERS II, a follow-up open-label observational study of 2.7 years’ duration, showed that the lower rates of CHD events observed among women in the final years of HERS did not persist during the additional years of observation (54). After 6.8 years, E/PT did not reduce the risk of cardiovascular events in women with preexisting coronary artery disease.

The smaller ESPRIT study randomized 1017 postmenopausal women aged 50 to 69 years of age (mean age: 62.6 years) with a recent first MI to placebo or ET (2 mg of estradiol valerate daily) for 2 years. The frequency of nonfatal reinfarction or cardiac death did not differ between the two groups (rate ratio 0.99; 95% CI, 0.70–1.41) (19). The results of HERS and HERS II suggest that E/PT should not be used for secondary prevention of cardiac events in women with CHD. Secondary analysis of HERS identified a substantial underutilization by the study participants of medications proven effective for secondary prevention, such as aspirin, β-blockers, and statins (54). Data from ESPRIT suggest that ET administered soon after recovery from a first MI does not reduce the risk of subsequent cardiac events (19).

Alternative CHD prevention strategies The keys to prevention of CHD in women are fitness, healthy diet, and appropriate body weight (55, 56). Lipid lowering therapy remains unproven in women. A systematic review of all lipid lowering trials in women included six RCTs and 11,435 women (57); the RRs (95% CI) were 0.61 (0.22–1.68) for nonfatal MI and 1.07 (0.47–2.40) for CHD mortality. The value of aspirin also remains unproven in women less than 65 years of age. In the Women’s Health Study, 39,786 healthy women were allocated to low-dose acetylsalicylic acid (aspirin) or placebo for a 10-year follow-up period (58). Although there was no evidence of benefit with respect to fatal or nonfatal MI (RR 1.02; 95% CI, 0.84–1.25), aspirin significantly reduced the risk of ischemic stroke and MI in the subgroup of women 65 years of age or older.

Summary of CHD-prevention studies Hormone therapy is not indicated for primary or secondary prevention of CHD. However, when used to treat symptoms in perimenopausal women, HT does not increase the risk of nonfatal or fatal MI. The prevention of heart disease remains an important goal. Myocardial infarction is rare within 10 years of menopause, and preventive strategies therefore should rely on maintaining fitness, eating a healthy diet, and keeping body weight within healthy limits. Older women may benefit from standard therapies for primary and secondary prevention such as aspirin and antihypertensive drugs (54). Although prescriptions for HT may include different formulations and routes of administration, the effects of most hormone products used over the last 15 years should be similar to those observed in the WHI studies (59).

Colon Cancer

The incidence of colorectal cancer in postmenopausal women is approximately 16 cases per year per 10,000 women (26, 27). Age, family history, and diet are risk factors, and the use of oral contraception, ET, and E/PT has been associated with reduced risks (60). One possible biological rationale for reduced risk would be a decrease in the concentrations of secondary bile acids, which are potentially tumor-promoting, a hypothesis based on the lower risk observed among women who have been pregnant or taking HT. Another possibility is linked to the dominant estrogen receptor (ER) subtype in the colonic mucosa, which is ERβ. Evidence has emerged that this subtype is significantly decreased in colonic tumors from women.

The epidemiologic evidence was summarized in a meta-analysis that included 25 studies and distinguished between risk of colon cancer and risk of rectal cancer (60). Rectal cancer incidence was not affected by HT use. However, recent use of HT was associated with a 33% reduction in the risk for colon cancer (RR 0.67; 95% CI, 0.59–0.77). In a second meta-analysis, current users of HT had a 34% lower risk of colon cancer (RR 0.66; 95% CI, 0.59–0.74) (61).

Two of three trials that include data relating to this question are consistent with a potentially reduced risk. After 6.8 years in the HERS trial and the follow-up period, there were 2.5 and 3.1 colon cancer cases per 1000 woman years in the E/PT and placebo groups, respectively (relative hazard [RH] 0.81; 95% CI, 0.46–1.45) (62). In the WHI E/PT trial, there were 9 and
16 new invasive colorectal cases per 10,000 woman-years in the E/PT and placebo groups, respectively (RH 0.56; adjusted 95% CI, 0.38–0.81) (63). The reduction in risk was mainly due to a decrease in local as opposed to regional or metastatic cancers. Within the category of regional and metastatic disease, the E/PT group had a greater number of positive lymph nodes (3.6 vs. 1.6). In the WHI ET trial, there were 17 and 16 new colorectal cases per 10,000 woman-years in the ET and placebo groups, respectively (RH 1.08; adjusted 95% CI 0.63–1.86) (27). Although the trial findings remain promising for E/PT, reduced colorectal cancer risk currently is not an indication to prescribe ET or E/PT.

More research is needed into the mechanisms by which estrogen and progestogen might influence the development of colon cancer. Results might guide focused trials to evaluate whether the observed reduced incidence is due to hormone use or alternative actions.

DISORDERS THAT MAY BE MORE FREQUENT WITH HORMONE TREATMENT

Stroke

The incidence of stroke among otherwise healthy postmenopausal women is approximately 2 per 1000 per year, and approximately 75% of strokes are ischemic (26, 27, 64, 65). There was no conclusive evidence for a beneficial or harmful effect of HT on stroke risk in 29 different epidemiologic studies, although the stroke end points and HT definitions were inconsistent (66). The Nurses’ Health Study reported a trend toward increased risk with combined continuous E/PT. Only a small nonsignificant increase in risk was observed for ET (RR 1.18; 95% CI, 0.95–1.46), but for E/PT the risk was 1.45-fold higher (95% CI, 1.10–1.92) for any type of stroke compared with never-users (64).

Stroke risk associated with E/PT has been addressed as a secondary outcome in the HERS and WHI studies. In HERS and HERS II, combined continuous E/PT was not associated with an increased risk for transient ischemic attack (RH 0.90; 95% CI, 0.84–1.43) or ischemic stroke (RH 1.18; 95% CI, 0.84–1.43) compared with placebo, but HERS lacked the necessary power to evaluate these small relative changes in risk (65). Overall, the RH for any stroke was 1.23 (0.89–1.70), which was not a statistically significant increase.

About 1% of HERS patients at baseline had atrial fibrillation, which increases stroke risk, often due to cardioembolism (67). Stroke risk was increased by more than six-fold in these patients, but HERS did not have the power to assess an interaction between HT and atrial fibrillation. In a trial among patients with atrial fibrillation receiving warfarin with or without aspirin, ET was associated with a 3.2-fold (95% CI, 1.4–7.5) increased risk of ischemic stroke compared with nonusers. The risk associated with E/PT was similar (68).

The WHI E/PT primary prevention trial (26) reported 29 and 21 strokes per 10,000 woman-years in the E/PT and placebo groups, respectively, an increase in stroke risk that was not statistically significant when adjusted for multiple comparisons (HR 1.41; 95% CI, 0.86–2.31). In all, 151 women (1.8%) in the E/PT group and 107 (1.3%) in the placebo group had strokes (69), 80% of which were ischemic. The HR was 1.44 (95% CI, 1.09–1.90) for ischemic stroke and 0.82 (95% CI, 0.43–1.56) for hemorrhagic stroke. There were 26 and 18 ischemic strokes per 10,000 woman-years in the E/PT and placebo groups, respectively.

Stroke risk with ET has been addressed also as a secondary outcome in three RCTs. In the ESPRIT trial among women who had a history of MI, stroke risk with estradiol valerate treatment was 1.64 (95% CI, 0.60–4.47) compared with placebo treatment (19). In the WHI ET trial, there were 44 and 32 cases of stroke per 10,000 women per year in the ET and placebo groups, respectively, an increased risk that was verging on statistical significance after adjusting for multiple statistical testing (HR 1.39; adjusted 95% CI, 0.97–1.99) (27). Another secondary prevention trial, the Women’s Estrogen for Stroke Trial (WEST), involved 664 postmenopausal women with recent stroke or transient ischemic attack; ET (1 mg of micronized 17β-estradiol per day) did not reduce the risk of subsequent stroke or mortality over the 2.8-year follow-up period (RR 1.1; 95% CI, 0.8–1.6) (70).

In all five trials, the point estimate indicated increased stroke risk with HT, although no estimate was statistically significant. The pooled RR is 1.25 (95% CI, 1.03–1.51), which is consistent with an increase in absolute risk from 20 cases to 25 cases per year among 10,000 otherwise healthy postmenopausal women. Note that the incidence rates were 32 and 21 per 10,000 women per year in the placebo groups of the WHI ET and E/PT trials, respectively. The effect of HT on stroke risk appears to involve mainly the risk of ischemic stroke. Little is known about the characteristics of the patients who are at greatest risk of stroke while using HT (50).

Venous Thromboembolism

Venous thromboembolism (VTE) is an uncommon but important risk for women receiving HT. The incidence among healthy postmenopausal women is 16 to 22 cases per 10,000 women per year (26, 71). Data from epidemiologic studies and RCTs consistently demonstrate an increased risk of VTE events in postmenopausal women who use ET or E/PT (24, 26, 71, 72). In five epidemiologic studies published between 1992 and 1997 involving 592 cases of VTE of which 130 (22.0%) were current HT users, the risk of VTE was increased approximately two-fold (typical OR 2.3; 95% CI, 1.7–3.0) (73–77). In the HERS trial, the relative risk of VTE was similar in magnitude: 2.66 (95% CI, 1.41–5.04) (62). The excess risk was 3.9 per 1000 woman-years, and the number needed to cause harm in one additional woman with established heart disease (average age, 66.7 years) was 256 (95% CI, 157–692). Venous thromboembolism is not confined to the first year of HT use, but the increased risk declines from approximately four-fold in the first year to less than two-fold after the third year of use.
(23, 73, 76, 77). In HERS II, the VTE risk declined to a non-significant level during the 2.7-year unblinded follow-up period (RH 1.40; 95% CI, 0.6–3.0) (62).

The WHI studies confirmed the magnitude and timing of the VTE risk estimates from previous studies (26, 71). In the E/PT study, there were 34 and 16 VTE events per 10,000 woman-years in the E/PT and placebo groups, respectively, an increase that was statistically significant after adjusting for multiple statistical testing (HR 2.11; adjusted 95% CI, 1.26–3.55). The relative hazards for pulmonary embolism (2.13) and deep venous thrombosis (2.07) were similar. The VTE events decreased over time during the study \((z = -2.46; P = .014)\) (26). In the ET trial, there were 30 and 22 VTE events per 10,000 woman-years in the ET and placebo groups, respectively, and the risk increase was no longer statistically significant after adjusting for multiple statistical testing (HR 1.32; adjusted 95% CI, 0.99–1.75). The VTE risk was highest in the first 2 years (71). The excess risks of VTE including pulmonary embolism and venous thrombosis (approximately 1 and 2 cases, respectively, per 1000 women per year in the ET and E/PT studies) were significantly higher with use of E/PT (71).

The risks for VTE may vary with the route of administration of HT because oral estrogens have greater impact on coagulation factors than do transdermal or vaginal routes of administration (73, 76, 78, 79). A meta-analysis of observational studies found that oral estrogen, but not transdermal estrogen, was associated with an increased risk for VTE (80). The odds ratios (95% CI) for first-time VTE were 2.5 (1.9, 3.4) in current users of oral estrogen and 1.2 (95% CI, 0.9–1.7) in current users of transdermal estrogen, compared with nonusers.

Continuing research on the prevalence and effects of procoagulation factors and the genetics of VTE risk may identify screening procedures to reduce overall risk among women using HT. At present, routine screening of women for thrombophilias is not indicated before initiating HT.

**Endometrial Cancer**

The incidence of endometrial cancer in postmenopausal women is approximately 6 cases per 10,000 women per year (26). Epidemiologic studies since 1975 have consistently shown that unopposed estrogen increases the risk of endometrial cancer among women who have a uterus. Data from 30 case-control studies and seven cohort studies suggest that risk among ever-users of ET is increased approximately 2.8-fold (95% CI, 2.6–3.0) over that in never-users (81). Moreover, there is a significant trend toward increasing risk of endometrial cancer with increasing duration of ET; the risk is 2.0-fold higher (95% CI, 1.8–2.2) with less than 5 years of use and 6.7-fold higher (95% CI, 5.9–7.6) with longer durations of ET. After discontinuation of ET, the RR remains elevated; the risk is still 3.5 times higher (95% CI, 3.0–4.0) for up to 5 years after treatment ends and 2.5 times higher (95% CI, 1.9–3.2) for 5 and more years after discontinuing ET. The ET-associated endometrial cancer risk is similar for different estrogen preparations, and higher doses are associated with a small additional increase in risk (81, 82).

Combining estrogen with continuous progestogens appears to reduce the risk of endometrial cancer associated with ET. The Million Women Study, reporting on 716,738 menopausal women who had not had a hysterectomy, found that endometrial cancer risk was increased when the last hormone use reported was unopposed estrogen (1.45; 95% CI, 1.02–2.06). The risk was lower with last use of continuous combined E/PT (0.71; 95% CI, 0.56–0.90) but not with cyclic E/PT (1.05; 95% CI, 0.91–1.22). The type of progestogen did not affect the risk (82).

The WHI E/PT trial confirmed that continuous E/PT has no effect on risk for developing endometrial cancer. In the WHI trial, five and six cases of endometrial cancer were observed per 10,000 woman-years in the E/PT and placebo groups, respectively, yielding a small decrease in risk that was not statistically significant (RH 0.83; adjusted 95% CI, 0.29–2.32) (26).

**Breast Cancer**

Breast cancer incidence in postmenopausal women is approximately 30 cases per 10,000 women per year (26). An association between breast cancer and hormone use would be plausible because breast cancer incidence is increased by hormonal factors such as early menarche and late menopause (83). In a 1997 reanalysis of 51 epidemiologic studies on breast cancer and hormone use, breast cancer risk increased by 2.3% per year of hormone use (mostly estrogen use) compared with an increased risk of 2.8% per year of natural delay in the onset of the menopause (84). Since then, data have accumulated in RCTs involving more than 30,000 women and in epidemiologic studies involving more than 1.8 million women (85).

With use of ET, the average risk of invasive breast cancer was 0.81 (95% CI, 0.63–1.03) in four randomized trials involving 12,643 women (19, 46, 70, 86). With use of E/PT, the average breast cancer risk was 1.24 (95% CI, 1.03–1.50) in four randomized trials involving 19,756 women (43, 62, 87, 88). For the 19 epidemiologic studies published after 1997, the average breast cancer risks were 1.18 (95% CI, 1.03–1.50) with ET and 1.70 (95% CI, 1.36–2.17) with current use of E/PT (85). In the epidemiologic studies, the increased breast cancer risk diminished soon after discontinuing hormones and normalized within 5 years (85).

The higher average risks in the epidemiologic studies may reflect the intent-to-treat analyses of the WHI studies (which dominate the RCT results). With intent-to-treat analyses in which women who discontinue using their assigned HT are analyzed as hormone users, the hormone group has a mixture of current users and past users (Table 5). For example, the RH for breast cancer among women adherent to E/PT (RH 1.49; 95% CI, 1.13–1.96) was higher than the RH in the intent-to-treat analysis (RH 1.24; 95% CI, 1.01, 1.54) (87). Combined analyses of the WHI trial and observational studies indicate
that, for women who initiate hormone use soon after the menopause, there is no clear evidence that ET has an impact on breast cancer risk, whereas E/PT increases risk by 1.64-fold over 5 years (95% CI 1.00, 2.68) (89, 90). The broad coherence between the randomized and observational findings suggests that both sources of evidence should be considered.

Ethnicity has not been studied in detail for other risks of HT, but breast cancer risk appears to differ according to ethnicity. Among 156,570 postmenopausal women participating in the WHI observational and randomized studies, breast cancer risk was lower in minority women compared with Caucasian non-Hispanic women. Adjustment for breast cancer risk factors accounted for the differences observed in Hispanic, American Indian/Alaskan Native, and Asian/Pacific Island women, but among African Americans the lower risk persisted after adjustment. The hazard rate was 0.75 (95% CI, 0.61–0.92), corresponding to 29 cases and 44 cases per 10,000 person years for African American and white women, respectively (91). In the Black Women’s Health Study, there were 615 breast cancer cases during follow-up of 32,559 women 40 years or older over 182,629 person-years. The RR for ET alone was 1.10 (95% CI, 0.85–1.41) and for E/PT 1.28 (95% CI, 0.98–2.70). The association of breast cancer with female hormone use was stronger among leaner women (body mass index <25) than among heavier women. Isolating prolonged recent use of ET or E/PT (for durations of 10 or more years), the incidence rate ratio was 3.08 (95% CI, 1.70–5.56) in the leaner women, compared with 1.43 and 0.91 in women with body mass indices of 25 to 29 and 30 or greater, respectively, neither of which was statistically significant (92). Thus, although African American women have a lower risk of developing breast cancer, the effects of hormones are also indicate that E/PT increases the risk of lobular more than ductal breast cancer, but the number of studies remains limited. In the collaborative study, HT did not add to the risk associated with a family history of breast cancer (84). In breast cancers that arise during HT, the stage and grade do not differ significantly from those in nonusers, but breast cancers in E/PT users are statistically significantly more likely to be ER-positive (85). Breast cancer mortality tends to be lower in observational studies among patients who were HT users (97), but in the early results from the WHI study, mortality was not better among users of E/PT (26). In an RCT involving 434 women with breast cancer who required treatment for menopausal symptoms, recurrence was 3.5-fold more likely (95% CI, 1.5–8.1) with hormone use than with alternative treatments (98).

Relative risks in the range of the 1.5-fold higher risk of invasive breast cancer associated with current E/PT are considered as relatively moderate breast cancer risk factors (RR <2). Other risk factors in this range include alcohol consumption, obesity, and nulliparity (99). Higher risks are associated with a family history of breast cancer, early menarche, and delayed menopause (100) (Fig. 2). The absolute effect of E/PT in the WHI and HERS trials adds 8 and 17 cases per 10,000 women per year, respectively, to the natural risk (26, 62).

In summary, breast cancer risk is increased with E/PT more than with ET, the risk returns to normal within 5 years after discontinuation of HT, and the epidemiologic evidence is generally consistent with the trial findings. However, many uncertainties remain, such as the role of progestogen, reasons for the effects on lobular cancer, the effect of receptor status, and the impact of HT on prognosis and mortality in breast cancer.

### Epithelial Ovarian Cancer

Invasive ovarian cancer incidence in postmenopausal women is approximately 3 cases per 10,000 women per year (21, 101). Epithelial ovarian cancer shares certain reproductive and hormonal risk factors with endometrial cancer; it is less common in parous women and in those who have used oral contraceptives or had an early menopause (102, 103). Use of hormones during menopause has been associated

<table>
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<th>TABLE 5</th>
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<tr>
<td><strong>Estimates of hormone-associated breast cancer risk by study type</strong> (85).</td>
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<tr>
<td><strong>Estrogen alone</strong></td>
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<tr>
<td><strong>RR or RH</strong></td>
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<tr>
<td>WHI RCTs (RH)</td>
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<tr>
<td>Epidemiologic studies (RR)</td>
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<tr>
<td>Current-use</td>
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<tr>
<td>Ever-use</td>
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CI: confidence interval; RH: relative hazard; RR: relative rate; RTCs: randomized controlled trials.

Source: Collins et al., 2005 (85).

with higher ovarian cancer incidence, but there may be confounding factors because ovarian cancer rates are higher among well-educated women and those in the highest social classes who are most able to pay for HT (104). During 5.6 years of follow-up in the WHI trial of E/PT and placebo, there were 20 and 12 new invasive ovarian cancer cases (4 and 3 per 10,000 woman-years) in the E/PT and placebo groups, respectively (RH 1.58; 95% CI, 0.77–3.24) (21). This RCT result is valid, and the sample was large, but the WHI study lacked the power needed for a precise estimate. Results of epidemiologic studies mainly provide similar results. A meta-analysis of 15 case-control studies published in 2000 found heterogeneous risk estimates, and the ovarian cancer risk was not significantly higher for HT users (summary OR 1.1; 95% CI, 0.9–1.3) (105). In a pooled analysis of data from five European case control studies involving 2501 women published in 2002, the ovarian cancer risk was 1.28-fold higher (95% CI, 1.05–1.56) for ever-users of HT compared with never-users (106).

Two cohort and three case-control studies have appeared since these meta-analyses were published. In a 2002 Swedish case-control study, epithelial ovarian cancer risk was increased with ever-use of ET (adjusted OR 1.43; 95% CI, 1.02–2.00) or sequential E/PT (OR 1.54; 95% CI, 1.15–2.05) (107). Ever-use of continuous E/PT, however, was not associated with increased risk (OR 1.02; 95% CI, 0.73–1.43). Another 2002 report of a cohort analysis of ovarian cancer incidence during 19 years of follow-up in the Breast Cancer Detection Demonstration Project estimated that ovarian cancer risk was 1.6-fold higher (95% CI, 1.2–2.0) in ET users but not significantly increased in E/PT users (adjusted RR = 1.1; 95% CI, 0.64–1.7) (108). Increased duration of ET use for 10 or more years was associated with a significantly increased risk of ovarian cancer (RR 1.8; 95% CI, 1.1–3.0). In a 2002 American case-control study, adjusted ORs for invasive epithelial ovarian cancer were 0.90 (95% CI, 0.61–1.33) with ever-use of conjugated estrogens and 0.52 (95% CI, 0.25–1.10) with other estrogens (109). Odds ratios for HT with ever-use of progestogens combined with conjugated estrogens and other estrogens were 1.06 (95% CI, 0.74–1.52) and 1.08 (95% CI, 0.59–2.00), respectively. A 2004 cohort study, women using ET at baseline had a higher risk of epithelial ovarian cancer during 15 years of follow-up (adjusted OR 1.72; 95% CI, 1.07–2.75) (110). In a 2004 case-control study from Denmark, the adjusted OR for ovarian cancer was 1.06 (95% CI, 1.00–1.11) for each additional gram of cumulative estrogen but was unrelated to progestogen dosage (111). In a prospective study of 944 fatal cancers, ovarian cancer mortality was higher among users of ET (OR 1.5; 95% CI, 1.2–2.0), but the data reported for long-term ever users did not include exposure information after study initiation in 1982 (112).

Overall, the results of the WHI study, the epidemiologic studies, and the mortality study are consistent with an increased risk of ovarian cancer associated with use of ET, a risk that appears to be nullified when estrogen is combined with progestin. Although epithelial ovarian cancer is an uncommon disease, the mortality ratio is high.

At the present time, it is uncertain whether the observed effects of HT on epithelial ovarian cancer reflect bias, chance, or reality. Further studies on long-term ET and E/PT will need to address the impact of dose, duration, and prescription schedule.

**SUMMARY AND CONCLUSIONS**

- Hot flushes occur in over 50% of women entering menopause, and their frequency declines to 30% after 3 years. However, symptoms may persist in up to 16% of women at 67 years of age.
- Hormone therapy is the most effective treatment for moderate to severe vasomotor symptoms. The average patient is a woman aged 45 to 60 years, and the most common duration of use is less than 3 years.
- Hormone therapy is an effective treatment for urogenital atrophy but may worsen urinary incontinence.
- Both ET and E/PT are associated with side effects that include breast tenderness, vaginal discharge, and uterine bleeding. Weight gain is not more common in HT users.
- Hormone therapy reduces the risk of osteoporotic fractures of the hip, vertebrae, and other sites. However, the effect on hip fracture is small, and HT is not warranted solely for fracture prevention.
- Although estrogen was associated with a 34% reduction in the risk of senile dementia in epidemiologic studies, WHIMS failed to corroborate these observations.
- Hormone therapy is not indicated for the primary or secondary prevention of coronary artery disease events. At the same time, perimenopausal women treated with hormones have no increased risk of CHD.
- Keeping fit and maintaining a healthy diet and body weight are the best strategies for prevention of CHD at all ages. Women more than 10 years after menopause

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**FIGURE 2**

Hormone-related indicators of the risk of breast cancer. Data from Singletary 2003 (99) and Clemons and Goss 2001 (100).

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Relative Risk</th>
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<tr>
<td>Use of OCs</td>
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<tr>
<td>Estrogen use</td>
<td></td>
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<tr>
<td>Estrogen-Progesterin Use</td>
<td></td>
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<tr>
<td>No breast feeding</td>
<td></td>
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<tr>
<td>No children</td>
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<tr>
<td>Menarche before 12 years</td>
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<tr>
<td>Menopause after 55 years</td>
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<tr>
<td>Family history of breast cancer</td>
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<tr>
<td>First child after 30 years</td>
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<tr>
<td>Increased bone density</td>
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<tr>
<td>Highest quartile estradiol</td>
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<td>Increased breast density</td>
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also should receive treatment with aspirin and antihypertensive drugs, when indicated.

- Risk of VTE is increased among women using E/PT and declines during continuing use. Route of administration may affect the magnitude of risk.
- In the WHI study, ET treatment among women with a hysterectomy was associated with fewer invasive breast cancer cases per year per 10,000 women than placebo treatment (26 new cases compared with 33 in the placebo group), a difference that was not statistically significant.
- In the epidemiologic studies, current use of ET for 5 years is associated with a small increased risk of breast cancer (RR = 1.18). The increase in risk disappears 5 years after discontinuing therapy.
- E/PT treatment has a small but significant effect on breast cancer risk equivalent to 8 new cases per year per 10,000 women (41 and 33 invasive cases, respectively, in E/PT and placebo groups).
- The increased risk of breast cancer associated with E/PT use is observed after 5 years of current use, is within the range of natural hormone-associated risks such as delayed menopause, and disappears several years after discontinuing therapy.
- Epidemiologic studies suggest that there is a small but significant increased risk of epithelial ovarian cancer with ET use that is not observed with E/PT. The effect is significant in women who take ET for 10 or more years.

Acknowledgments: This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine and as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee of the American Society for Reproductive Medicine and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

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