Postmenopausal Hormone Replacement Therapy and Major Clinical Outcomes: A Focus on Cardiovascular Disease, Osteoporosis, Dementia, and Breast and Endometrial Neoplasia

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GOAL

To help physicians caring for postmenopausal women understand the current data regarding the effectiveness and safety of hormone replacement therapy (HRT).

LEARNING OBJECTIVES

After reading this article the reader should be able to:

1. Describe the effectiveness of HRT in the prevention and treatment of cardiovascular disease, osteoporosis, and dementia in postmenopausal women, and provide examples of alternative pharmacologic therapies.
2. Identify the major potential risks of HRT use: breast and endometrial neoplasia, and an early risk of cardiovascular and thromboembolic disease.

Current data suggest that hormone replacement therapy (HRT) might have a beneficial role in the prevention of cardiovascular disease (CVD), osteoporosis, and dementia in postmenopausal women, but other therapies should be considered for the treatment of these conditions. In this review we evaluated the potential benefits of HRT for CVD, osteoporosis, and dementia, and compared HRT with proven, effective therapies. In addition, we identified the potential risks of breast and endometrial neoplasia, and an early risk of CVD and thromboembolic disease associated with HRT use.

(Am J Manag Care 2002;8:95–104)

More than 30 million women in the United States are postmenopausal, and this number is rapidly increasing.[1] Multiple medical conditions have been associated with menopause including cardiovascular disease (CVD), osteoporosis, and dementia. Hormone replacement therapy (HRT) is highly effective in preventing and treating vasomotor and genitourinary symptoms associated with menopause. Epidemiological data suggest that HRT might also have a beneficial role in the medical management of CVD, osteoporosis, and dementia in postmenopausal women. However, HRT is also associated with breast and endometrial neoplasia.

Therefore, we reviewed the potential benefits of HRT for CVD, osteoporosis, and dementia and compared HRT with proven, effective pharmacologic therapies. In addition, we analyzed the risks of breast and endometrial neoplasia associated with HRT.

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This work was supported by funds from the Veterans Administration.

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··· CARDIOVASCULAR DISEASE ···

Cardiovascular disease is the leading cause of death of women in the United States.[2] The risk of CVD in premenopausal women is much lower than in age-matched men, but CVD mortality rates in postmenopausal women are similar to the levels in age-matched men.[3] These epidemiologic data have led to the hypothesis that the increasing risk of CVD in aging women is caused by declining estrogen levels associated with menopause, and that estrogen replacement should decrease this CVD risk. Although observational studies have supported this hypothesis,[4,5] recent randomized, placebo-controlled studies have not demonstrated a clear cardioprotective effect from HRT.[6,7]

Many large prospective studies have found an increased risk of CVD associated with natural menopause. The Framingham Heart Study reported that the 10-year incidence of CVD in women aged 50 to 59 years was 4.1% in those who had experienced natural menopause and 1% in those who were premenopausal.[8] Meta-analyses of case-control and observational studies have shown a 33% to 50% reduction in CVD risk among postmenopausal women who use HRT.[9] Barrett-Conner and Grady[9] estimated the relative risk for CVD to be 0.70 (confidence interval [CI] 0.65-0.75) among women who ever used estrogen compared with never-users of HRT and 0.66 (CI 0.53-0.84) among women who ever used combination estrogen-progestin regimens compared with nonusers of HRT. The Nurses' Health Study found a reduction of CVD with HRT use, with the benefits appearing to be greatest in women with known CVD.[10] Unfortunately, all these epidemiologic data share several potentially serious flaws: selection bias (unintended selection of healthy women), compliance bias (compliant patients have been shown to have a lower mortality), and surveillance bias (hormone users are more likely to be followed closely [surveillance], with disease being discovered and treated at an early stage, thus lowering mortality).

Several observational studies have investigated the association between HRT and CVD risk factors. Results from cross-sectional and longitudinal studies have shown unfavorable changes in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol in postmenopausal women not taking HRT.[2,3] The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, a large randomized, placebo-controlled study, demonstrated that estrogen replacement, with or without a progestin, significantly reduced LDL cholesterol approximately 11% from baseline.[11] Furthermore, this study showed that HDL cholesterol significantly increased approximately 9% with estrogen replacement alone, 7% with the addition of micronized progesterone, and 2% with the administration of cyclic or continuous medroxyprogesterone acetate.[11] Many other studies have also demonstrated effects of estrogen that would be expected to be cardioprotective, such as favorable changes in apolipoproteins, lipoprotein(a), plasminogen activator inhibitor-1, antithrombin III, endothelial function, vascular reactivity, blood flow, antioxidant activity, and calcium-channel activity.[12,13]

Secondary Prevention of Cardiovascular Disease

The Heart and Estrogen/progestin Replacement Study (HERS) was the first large, randomized, placebo-controlled clinical trial of HRT and CVD in women.[6] The study comprised women with established CVD and showed that the percentage of overall CVD events after 5 years did not significantly differ between the HRT and placebo groups (12.5% vs 12.7%), despite the expected significant favorable effects of HRT on LDL and HDL cholesterol (14% decrease vs 8% increase; $P < .05$). Moreover, CVD events were significantly more frequent in the first year of HRT compared with placebo (4% vs 2.7%; $P < .05$). The early CVD risk and later benefit observed with HRT has been proposed to be a result of tachyphylaxis, attrition of a susceptible cohort, random variation, or the documented early generalized increased risk of venous thrombosis with HRT use followed by a later benefit of atherosclerotic plaque stabilization from an estrogen-mediated lipid-lowering effect. (The HERS results showed an increased risk of thromboembolic events after 5 years of HRT use compared with placebo [2.5% vs 0.9%; $P < .05$], with approximately one third of the events associated with HRT occurring in the first year of treatment).[6,14] It has also been suggested that the absence of an overall CVD risk benefit could be due to an untoward effect of the progestin used in the study.[14] There are no prospective randomized controlled trial data showing that the incidence of CVD events is reduced with HRT, and the HERS results have raised concerns about the efficacy and safety of HRT for secondary prevention of CVD.

Current data suggest better alternatives to estrogen for the secondary prevention of CVD in women. Randomized trials have demonstrated an approximate 27% reduction of reinfarction and 32% reduction of sudden death with β-blocker use in studies that included women and men.[15] A database analysis found a 40% reduction in mortality in women and men with β-blocker use after a myocardial infarc-

tion.[16] Another study found a 1-year mortality rate of 7.7% for patients treated with β-blockers after a myocardial infarction compared with 12.6% for those who were not ($P < .001$; number needed to treat [NNT] = 20), a reduction that was similar for women and men.[17]

Cholesterol-lowering statins are also effective for secondary prevention of CVD. The Scandinavian Simvastatin Survival Study (4S), Cholesterol And Recurrent Events (CARE) study, and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study are large randomized secondary prevention trials that included a small number of women, and these trials showed a 23% to 34% reduction in CVD events with statin use (NNT = 11, 33, and 28 overall for the 4S, CARE, and LIPID studies, respectively).[18-20] Secondary prevention trials with aspirin have also reported consistent trends in reduction of CVD events in women and men. Meta-analysis of randomized trials showed that aspirin use for secondary prevention is associated with an approximate 30% reduction in recurrent nonfatal myocardial infarction, and women appear to benefit as much as men.[21] The role of raloxifene in the secondary prevention of CVD is currently being evaluated in a large, randomized, prospective trial—the Raloxifene Use for the Heart Trial.[22]

Primary Prevention of Cardiovascular Disease

Although the role of HRT for the treatment of established CVD has been cast in doubt, HRT might be useful for the primary prevention of CVD.[4] In a recently published observational study, Hu and colleagues[23] followed more than 85,000 women without CVD in the Nurses' Health Study and found that postmenopausal HRT was associated with a 9% decline in the incidence of CVD. The results of the Women's Health Initiative (WHI), a large randomized primary prevention trial of HRT in CVD, are expected in the year 2005. However, preliminary results of the WHI have already been reported to show a trend, similar to the HERS results, toward an early CVD risk with HRT use that diminishes with time.[24]

Available data suggest effective alternatives to estrogen for the primary prevention of CVD in women. The Air Force/Texas Coronary Atherosclerosis Prevention Study, a randomized primary prevention trial of women and men, showed a 37% reduction of CVD events with statin use (NNT = 49 overall; sex-specific data were not published).[25] Manson and colleagues[26] conducted a prospective cohort study with 87,000 women and found that the use of 1 to 6 aspirin tablets per week significantly reduced the risk of myocardial infarction (CI, 0.52-0.89). Combination regimens, such as HRT plus statins, have recently been reported to have a greater positive effect on HDL cholesterol and similar positive effects on LDL cholesterol in women compared with statins alone.[27] Raloxifene decreases LDL and fibrinogen, but raloxifene does not raise HDL cholesterol levels.[28]

In summary, the role for HRT in the secondary and primary prevention of CVD remains unclear. When used for secondary prevention of CVD, HRT appears to be associated with an early increased risk of CVD events followed by a decreased risk. Hormone replacement therapy, however, might be useful in primary prevention of CVD; results from ongoing and future randomized trials will be needed to establish this benefit. While awaiting these trial results, clinicians and patients need to make individual decisions about HRT based on available evidence. Women already taking HRT do not need to stop, whereas postmenopausal women with CVD who are considering starting HRT should not be prescribed HRT for the sole purpose of reducing CVD risk. β-Blockers, statins, and aspirin have proven benefits in the secondary prevention of CVD and should be included in the management of postmenopausal women with CVD. Use of any of these 3 drug classes, alone or in combination, should be considered in all women at high risk of CVD.

··· OSTEOPOROSIS ···

Osteoporosis is characterized by low bone mass, abnormal bone architecture, and increased fractures. The World Health Organization (WHO) defines osteoporosis as a bone mineral density (BMD) of at least 2.5 standard deviations (SD) below the mean peak values in young adults and osteopenia as a BMD between 1 and 2.5 SD below the mean peak values in young adults.[29] According to this definition, 15% of postmenopausal white women in the United States and 35% of women older than 65 years have osteoporosis.[29] The lifetime risk of osteoporotic fractures of the wrist, spine, and hip in 50-year-old white women is 30% to 40%.[30] Hip fractures are associated with a 15% increase in mortality in the first year and decreased function in more than 70% of the survivors.[31] Osteoporotic fractures create a significant economic cost, with more than 400,000 hospital admissions and 2.5 million physician visits per

year.[29] Thus, effective treatment and prevention of osteoporosis is essential.

The importance of estrogen in bone and mineral metabolism and the beneficial effects of postmenopausal estrogen replacement have been well established. The addition of progestins does not appear to negate, and might even enhance, the favorable effects of estrogen on bone homeostasis and mass.[32,33] The prospective, randomized, double-blind placebo-controlled PEPI trial demonstrated that vertebral and hip BMD increased significantly in postmenopausal women taking estrogen or combination estrogen and progestin compared with a decline in vertebral and hip BMD among women taking placebo.[32] Studies suggest that HRT should be started in early menopause and continued for at least 5 to 10 years to optimally decrease the risk of osteoporotic fractures; discontinuation of HRT for more than 5 years eliminates most of the benefit.[34-37]

A secondary analysis of the HERS trial regarding the effects of HRT on established CVD revealed that HRT use did not reduce the fracture risk compared with placebo. However, less than 20% of the participants had documented osteoporosis.[6] Thus, the HERS results only suggest that HRT has no effect on the prevention of fractures in nonosteoporotic postmenopausal women. A recent meta-analysis suggested that HRT reduces the risk of nonvertebral fractures by 27%; however, that study did not distinguish between participants with and without osteoporosis.[37] No large prospective studies have shown that estrogen prevents fractures; however, based on epidemiologic studies, it is estimated that current use of HRT, especially long-term use, is associated with a 30% to 50% reduction of hip, spine, and wrist fractures.[30]

Alternative therapies to HRT for the prevention and treatment of osteoporosis include potent bisphosphonates (alendronate or risedronate), the selective estrogen receptor modulators (eg, raloxifene), and calcitonin. Alendronate prevents bone loss in the spine and hip in women with and without osteoporosis.[38-41] In the Fracture Intervention Trial, 3 years of treatment with alendronate decreased the incidence of vertebral fractures by 47% (NNT = 14), clinically apparent vertebral fractures by 64% (NNT = 37), and any clinical fractures by 25% (NNT = 22) in postmenopausal women with osteoporotic fractures.[40] Similarly, 4 years of treatment with alendronate in women with osteoporosis (low BMD) but without a history of vertebral fractures resulted in significantly increased BMD and a 36% decreased incidence of clinically apparent fractures (NNT = 15).[40] Alendronate did not reduce the incidence of fractures in women with osteopenia. Recent randomized trials showed that alendronate plus HRT had an additive effect on BMD at both the spine and hip that was greater than either treatment alone.[42,43] Risedronate also has been shown to prevent bone loss in women with and without osteoporosis.[44,45] In a trial by Harris and colleagues,[45] risedronate therapy for 3 years in postmenopausal women with osteoporosis and a history of a vertebral fracture significantly increased BMD and decreased the risk of new vertebral fractures (11.3% vs 16.3%; $P = .003$; NNT = 20) and nonvertebral fractures (5.2% vs 8.4%; $P = .02$; NNT = 31) compared with placebo. Similarly, a recent trial by McClung and colleagues[46] showed a 41% (NNT = 77) reduction in hip fractures among elderly women with confirmed osteoporosis who used risedronate compared with placebo. No clinically significant difference in gastrointestinal toxicity was found between the potent bisphosphonates and placebo in the alendronate and risedronate trials.

The beneficial effects of selective estrogen-receptor modulators (SERMs) for the prevention and treatment of osteoporosis have been well documented, although their effects on BMD are less than those of HRT.[28,47-50] In a recent randomized clinical trial, 3 years of raloxifene use (60 or 120 mg/d) in postmenopausal women with osteoporosis significantly increased BMD in the spine and femoral neck and reduced the risk of vertebral fractures by 35% to 47% (NNT = 29-21), but there was no protection against hip fracture.[49] Raloxifene also appears to decrease the risk of breast cancer without an apparent increase in the risk of endometrial cancer; however, raloxifene is associated with an increased risk of venous thromboembolism (comparable with HRT) and hot flashes.[49,50] Calcitonin, parenterally and intranasally, prevents spinal bone loss in postmenopausal women, but because its effect on fracture risk appears to be modest, it is recommended as a second-line therapy or perhaps an adjuvant treatment of osteoporosis.[51,52]

Vitamin D and calcium supplementation has been shown to protect against nonvertebral bone loss and hip fracture in women at risk of vitamin D and calcium deficiency. In a randomized controlled trial, 800 IU of vitamin D and 1.2 g of calcium daily was associated with a 43% reduction in hip fractures and a 32% reduction in the total number of nonvertebral fractures in elderly women (NNT = 56 and 29, respectively).[53] The effect of either vitamin D or calcium alone on fracture risk is uncertain at this time. Their primary use is to prevent deficiencies of vitamin D or calcium, which are both common.

Therefore, vitamin D and calcium intake should be supplemented whenever dietary intake is inadequate. In general, most postmenopausal women will benefit from oral supplemental vitamin D (400 IU daily) and calcium (500 mg with meals 3 times daily). The updated guidelines from the American Association of Clinical Endocrinology on recommended intake of vitamin D and calcium can be found at http://www.aace.com/clin/guides/osteoporosis.html.

In summary, epidemiologic data provide strong evidence advocating the use of HRT in the prevention and treatment of osteoporosis, but the best evidence for a fracture risk reduction in established osteoporosis is associated with the potent bisphosphonates—alendronate or risedronate. Thus, pharmacologic prevention of osteoporosis is best accomplished by long-term HRT, a SERM, or a potent bisphosphonate. Hormone replacement therapy is the least expensive effective therapy for the prevention of osteoporosis (**Table**).[54] For the treatment of established osteoporosis and nonvertebral fracture risk reduction, the data are strongest for the potent bisphosphonates.

··· COGNITIVE FUNCTION AND DEMENTIA ···

Multiple studies have proposed that postmenopausal estrogen replacement therapy improves cognition in healthy women, reduces the risk for developing dementia, and lessens the severity of dementia. Although biological and physiological mechanisms can explain these beneficial effects, studies in women have produced contradictory results.

Table. Effectiveness, Adverse Effects, and Costs of Prescription Drugs for Osteoporosis

Drugs for Postmenopausal Osteoporosis	Treatment Effectiveness	Prevention Effectiveness	Adverse Effects	Costs*
Hormone replacement therapy (HRT)†	Effective	More effective	Bloating, breast tenderness, uterine bleeding, increased risk of endometrial cancer (if not taking a progestin), increased risk of thromboembolism,‡ increased risk of gallbladder disease,§ and possible slight increased risk of breast cancer.	Estrogen regimens: $7.00-$25.84 Estrogen-progestin regimens: $23.80-$27.72
Alendronate or risedronate	More effective	Effective	Heartburn, esophageal irritation, esophagitis, abdominal pain, diarrhea, and other adverse gastrointestinal effects.	$50.12-$54.88
Raloxifene	Effective	Effective	Hot flashes, leg cramps, increased risk of thromboembolism (comparable with HRT). No apparent increased risk of endometrial cancer. Decreased risk of breast cancer.	$56.56

*Average cost to the patient for 28 days' treatment based on data from retail pharmacies nationwide provided by Scott-Levin's *Source*™ *Prescription Audit* (SPA), July 1999-August 2000.[54]

†Estrogen and estrogen-progestin regimens appear to be equally effective therapies for osteoporosis.

‡The Heart and Estrogen/progestin Replacement Study (HERS)[4] results after 5 years showed an increased risk of thromboembolic events with HRT compared with placebo (2.5% and 0.9%, respectively), with approximately one third of the events associated with HRT occurring in the first year of treatment.

§The HERS[4] results showed a 38% higher risk of gallbladder disease with HRT compared with placebo.

Cognition

The prospective cohort study by Barrett-Connor and Kritz-Silverstein[55] is the largest and most methodologically sound epidemiologic study to date investigating the association between estrogen replacement therapy and cognition. They found that postmenopausal estrogen use among 800 normal women had no effect on standardized cognitive function tests. Contrary to this finding, several randomized trials have concluded that postmenopausal estrogen therapy improves cognitive function.[56-58] However, most of these studies had several confounding factors: small sample size, use of neuropsychological tests that are not validated or commonly used, lack of comparison to a placebo-treated group, and involvement of symptomatic postmenopausal women. A recent meta-analysis of 9 randomized controlled trials and 8 cohort studies provisionally concluded that HRT does not appear to consistently enhance performance on cognitive testing in women without postmenopausal symptoms; however, in symptomatic postmenopausal women, HRT possibly improves performance on cognitive tests, especially in tests of verbal memory, vigilance, reasoning, and motor speed.[59]

Epidemiologic data investigating the association between cognition and combination estrogen plus progestin therapy in postmenopausal women are limited. Studies have been small with multiple confounding factors. A prospective cohort study by Rice and colleagues[60] with more than 800 postmenopausal women reported that current-use HRT improved cognitive test scores for women using estrogen alone compared with never-users of HRT, but that use of combination estrogen plus progestin decreased cognitive test scores.

The results from cognitive testing in a large, randomized clinical trial of raloxifene were recently reported by Yaffe and colleagues.[61] Three years of raloxifene treatment in postmenopausal women with osteoporosis did not affect the overall cognitive scores compared with placebo.

Dementia

Multiple observational studies have investigated the role of estrogen replacement therapy in preventing the development of dementia, including Alzheimer's disease (AD). Results of these studies have ranged from suggesting a protective effect to no effect.

Two prospective cohort studies have found a decreased risk of dementia in estrogen users. In a study of 1124 women, Tang and colleagues[62] found that estrogen use was associated with a significant delay in the onset of AD and a decrease in the risk of developing AD (9 of 156 [5.8%] estrogen users developed AD vs 158 of 968 [16.3%] nonusers). In addition, women who used estrogen for longer than 1 year had a greater risk reduction compared with nonusers. Kawas and colleagues[63] studied 472 postmenopausal women enrolled in the Baltimore Longitudinal Study of Aging and found a similar reduction in the risk of developing AD associated with postmenopausal estrogen use. Although studies suggest that postmenopausal estrogen therapy delays or prevents the development of dementia, this epidemiologic evidence has many confounding factors. Large, randomized, controlled, double-blind trials are needed to confirm the role of estrogen in the prevention of dementia.

Randomized clinical trials investigating estrogen replacement therapy as a treatment of dementia have been published. Honjo and colleagues[64] studied 14 women with AD and found that those treated with estrogen for 3 weeks had greater improvement on only 1 of 3 dementia scales when compared with the placebo-treated group. Henderson and colleagues[65] studied 42 women with mild to moderate AD and found that those treated with estrogen for 16 weeks did not show improvement of AD symptoms. Mulnard and colleagues[66] obtained similar results from a study of 120 women with mild to moderate AD; they found that estrogen replacement therapy for 1 year did not slow the progression of AD.

The acetylcholinesterase inhibitors tacrine and donepezil, the only drugs approved for AD in the United States, show only small benefits in cognitive-test results and should be viewed as palliative treatment only.[67]

In summary, it is unclear whether HRT improves cognitive function in healthy postmenopausal women. Hormone replacement therapy does not appear to be an effective treatment of AD, but data from epidemiologic studies suggest that HRT might prevent AD. The WHI Memory Study is a randomized trial that will determine the effect of HRT (estrogen and estrogen plus progestin) on cognitive function and on the risk for developing dementia among approximately 8000 postmenopausal women. The results of this study will help clarify the role of HRT in cognition and dementia in postmenopausal women.

··· BREAST NEOPLASIA ···

After more than 50 years of HRT use in the United States and dozens of studies, controversy still surrounds the association between HRT and an

increased breast cancer risk. A considerable amount of epidemiologic evidence suggests a small increased risk of breast cancer with long-term use of HRT. A large combined analysis of 51 studies involving more than 160,000 women and representing about 90% of the worldwide data on the relation between HRT use and the risk of breast cancer showed the relative risk (RR) of breast cancer to be 1.35 (95% CI, 1.21-1.49) for women who used HRT for 5 years or more compared with never-users.[68] The risk of breast cancer increases with increasing duration of HRT use, but this increased risk disappears within 5 years of stopping HRT.[68] Based on these data, approximately 2, 6, and 12 extra cases of breast cancer would be diagnosed by the age of 70 for every 1000 women who started taking HRT at the age of 50 and continued it for 5, 10, and 15 years, respectively.[68,69] More recently, however, a large survey using the first National Health and Nutrition Examination Survey database, failed to find any increased risk of breast cancer among estrogen users.[70]

Controversy exists regarding the use of combination estrogen plus progestin and the risk of breast cancer. Most studies of HRT and breast cancer risk have not adequately distinguished the use of estrogen plus progestin from estrogen alone.[68] Recent studies, however, suggest that combination therapy increases the risk of breast cancer.[71-73] Schairer and colleagues[74] used data from 46,000 women who participated in the Breast Cancer Detection Demonstration Project in a retrospective cohort analysis to investigate the association between HRT and breast cancer risk. Based on more than 2000 breast cancer cases, the authors found that estrogen plus progestin was associated with a greater breast cancer risk than estrogen use alone. Furthermore, they reported that this increased risk was primarily limited to current or recent users and was directly related to duration of use. The relative risk was found to increase by 0.08 (95% CI, 0.002-0.16) for each year of combination therapy and by 0.01 (95% CI, 0.002-0.03) for each year of estrogen alone. This finding of an increased risk of breast cancer associated with combination estrogen plus progestin was found to be significant only in lean women.

Hormone replacement therapy appears to promote the growth of less aggressive tumors. In the meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer, breast cancers diagnosed in women who had used HRT were less clinically advanced than those diagnosed in never-users.[68] Similarly, in the Breast Cancer Detection Demonstration Project, Shairer and colleagues[75] found an increased risk of in situ breast cancer among women who used HRT compared with never-users, but no association between duration of HRT use and an increased risk of invasive carcinoma. From the Iowa Women's Health Study, a large population-based, prospective, cohort study with more than 37,000 healthy postmenopausal women aged 55 to 69 years, Gapstur and colleagues[76] concluded that exposure to HRT was associated most strongly with an increased risk of invasive breast cancer with "favorable prognosis." Hormone replacement therapy use was associated with an increased risk of invasive carcinoma with a favorable prognosis, with RRs of 1.81 (95% CI, 1.07-3.07) and 2.65 (95% CI, 1.34-5.23) for short- (5 years or less) and long-term (more than 5 years) users, respectively. For current users of HRT, the RRs were 4.42 (95% CI, 2.00-9.76) and 2.63 (95% CI, 1.18-5.89) for short- and long-term users, respectively. When all the tumors were combined and stratified by duration of use, HRT was not associated with an increased risk of breast cancer in either the short- or long-term users (RR 1.07 [95% CI, 0.94-1.22] and 1.11 [95% CI, 0.92-1.35], respectively).

In summary, HRT might slightly increase the risk of breast cancer, but use of HRT appears to be associated with more benign tumors. This observation provides a plausible explanation for the lower breast cancer mortality rates among HRT users compared with nonusers reported in some epidemiologic studies.[77]

··· ENDOMETRIAL NEOPLASIA ···

A substantial amount of evidence supports the causal relationship between postmenopausal estrogen replacement and both endometrial hyperplasia and endometrial cancer. In the randomized, double-blind, placebo-controlled PEPI trial, unopposed estrogen therapy was associated with a 34% increased risk of endometrial hyperplasia.[11] In a meta-analysis, Grady and colleagues[78] examined 37 studies and found that the risk of endometrial cancer increased substantially with long durations of unopposed estrogen use (RR 2.3 [95% CI, 2.1-2.5] with ever-estrogen use, RR 9.5 [95% CI, 7.4-12.3] with 10 or more years of use), and this increased risk persisted for 5 or more years after discontinuation of estrogen use. Although endometrial cancer is uncommon, long-term unopposed estrogen use might increase the risk of this disease 10-fold, with up to 20% of women treated with unopposed estrogen for more than 10 years developing endometrial cancer.[75]

The risk of endometrial cancer appears to be significantly increased with estrogen replacement therapy, but the risk of developing invasive cancer or dying from endometrial cancer does not seem to be similarly increased. Grady and colleagues[78] demonstrated a higher risk of developing noninvasive than invasive cancer with an RR of 6.2 (95% CI, 4.5-8.4) and 3.8 (95% CI, 2.9-5.1), respectively, and no significant increased risk of death from endometrial cancer. The reason for the absence of an increased risk of invasive cancer and death is not clear. Perhaps tumors associated with estrogen use are less aggressive or women using estrogen might have their tumors detected at an earlier stage.

The addition of a cyclic progestin to estrogen replacement therapy has been shown to eliminate the increased risk of endometrial hyperplasia.[11,79] A case-control study by Voigt and colleagues[80] suggested that the cyclic monthly addition of progestins should last for at least 10 days to minimize the endometrial cancer risk associated with estrogen. Continuous combined regimens with daily addition of a progestin to estrogens have been shown to reduce endometrial cancer risk when compared with no HRT use.[81] Because the risk of endometrial cancer does not appear to be substantially increased with combination therapy and there might indeed be a protective effect, all postmenopausal women with an intact uterus should strongly consider the addition of a progestin if they opt for HRT.

··· CONCLUSIONS ···

Multiple medical conditions need to be considered when deciding whether to begin postmenopausal HRT. Hormone replacement therapy provides no clear benefit in terms of secondary prevention of CVD, but possibly a small benefit in primary prevention of CVD. Thus, proven effective treatment and prevention regimens for CVD should be considered first for postmenopausal women who have established CVD or who are at high risk of CVD. Epidemiologic data have demonstrated that HRT is effective in the treatment and prevention of osteoporosis, but only potent bisphosphonates have been shown to reduce vertebral and nonvertebral fractures in randomized, controlled trials of older women with osteoporosis. Hormone replacement therapy does not appear to be an effective treatment of dementia; however, epidemiologic studies suggest that HRT might prevent dementia. The risk of breast cancer and thromboembolic disease appears to be slightly increased with HRT use, but the risk of endometrial cancer is not increased when combination estrogen plus progestin therapy is used. To conclude, current data suggest that HRT might have a beneficial role in the *prevention* of CVD, osteoporosis, and dementia in postmenopausal women, but other therapies should be considered for the definitive *treatment* of these conditions.

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CME QUESTIONS: TEST #070004

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Instructions

After reading the article "Postmenopausal Hormone Replacement Therapy and Major Clinical Outcomes: A Focus on Cardiovascular Disease, Osteoporosis, Dementia, and Breast and Endometrial Neoplasia," select the best answer to each of the following questions. In order to receive 1 CME credit, at least 7 of the 10 answers must be correct. Estimated time for this activity is 1 hour. CME credits are distributed on a yearly basis.

1. Death from cardiovascular causes is more common in older men than age-matched postmenopausal women.

a) true
b) false

2. The Heart and Estrogen/progestin Replacement Study (HERS) showed that hormone replacement therapy (HRT) in postmenopausal women with established cardiovascular disease (CVD) was associated with:

a) an early decreased risk of CVD events followed by an increased risk
b) an early increased risk of CVD events followed by a decreased risk
c) an overall increased risk in CVD events
d) an overall decreased risk in CVD events

3. HRT has proved to be as effective as β-blockers, statins, and aspirin in the secondary prevention of CVD.

a) true
b) false

4. Ten percent of women older than 65 years of age in the United States have osteoporosis.

a) true
b) false

5. Epidemiologic data suggest that HRT decreases fracture risk by 30% to 50% in postmenopausal women.

a) true
b) false

6. The best evidence for a fracture risk reduction in postmenopausal women with established osteoporosis is associated with:

a) long-term HRT
b) raloxifene
c) alendronate or risedronate
d) calcitonin

CME TEST FORM
AJMC Test #070004
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(Test valid through December 31, 2002. No credit will be given after this date.)

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3. **a b**
4. **a b**
5. **a b**
6. **a b c d**
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9. **a b c d**
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7. HRT does not appear to be an effective treatment of Alzheimer's disease (AD) in postmenopausal women, but it might prevent AD.

a) true
b) false

8. HRT has been estimated to increase the number of extra cases of breast cancer in postmenopausal women by 25 for every 1000 women who use HRT for more than 10 years.

a) true
b) false

9. The addition of progestin to estrogen replacement therapy:

a) reduces the effectiveness of estrogen in the prevention and treatment of osteoporosis
b) enhances the favorable effects of estrogen on CVD risk factors
c) eliminates the increased risk of endometrial cancer associated with estrogen replacement therapy alone
d) reduces the risk of breast cancer

10. Data from HERS suggest that postmenopausal women who use HRT do not have an increased risk of thromboembolism.

a) true
b) false