# HORMONE THERAPY IN SELECTED POSTMENOPAUSAL WOMEN AT RISK FOR OSTEOPOROSIS

## Introduction

In 2002, the National Osteoporosis Foundation estimated that 30 million women age 50 years or older in the United States have low bone mass and, of these, 8 million have osteoporosis.[1] Half of all postmenopausal women will have an osteoporosis-related fracture during their lives, including one quarter who will develop a vertebral deformity.[2] The lifetime risk of hip fracture alone for a 50-year-old woman is 17.5%.[2,3]

There is significant disability, morbidity and mortality associated with vertebral and hip fractures.[4-7] The overall mortality within 1 year following a hip fracture is estimated to be 20%.[8,9] The annual public health costs of osteoporosis in general in the U.S. are over $10 billion.[7,10] Approximately $13.8 billion dollars were spent in 1995 for the management of fractures in the U.S. The size of the older population is expected to increase remarkably during the next decades, and the costs related to postmenopausal osteoporotic fractures are expected to increase correspondingly, both in the U.S. and worldwide.[11,12]

# BENEFICIAL EFFECTS OF POSTMENOPAUSAL HORMONE THERAPY ON BONE MINERAL DENSITY AND FRACTURE RISK

This section summarizes recent data on the effects of postmenopausal hormone therapy on BMD and the risk of fracture. Alternative therapies are also discussed. Approximately 50 studies were considered in this analysis. The majority of the studies were randomized and placebo controlled; however, several meta-analyses and observational studies are also included.

## Bone Mineral Density

Low bone mineral density (BMD) is the single best predictor of fracture risk in postmenopausal women.[13] There is strong evidence that postmenopausal estrogen/progestin therapy, especially oral CEE/MPA, has a positive effect on BMD in the lumbar spine, forearm, and hip. This is based on the findings of several randomized, placebo-controlled trials, including the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial[14] and the Women's Health, Osteoporosis, Progestin, Estrogen (Women's HOPE) study,[15] as well as a recent meta-analysis by the Osteoporosis Research Advisory Group (ORAG).[16] These studies show that postmenopausal hormone therapy increases BMD of the spine by 3.5% to 7%, increases hip BMD by 2% to 4%, and increases forearm BMD by 3% to 4.5%.[14,16] Increases in BMD became apparent within the first year of hormone therapy.

Bone loss is most rapid in the years immediately following menopause, when circulating estradiol levels drop precipitously.[17-19] Data from randomized, placebo-

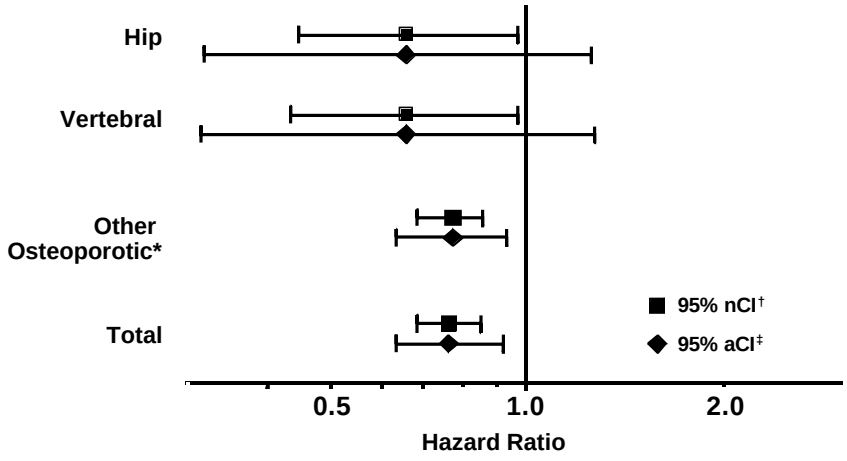
controlled trials,[20] observational studies,[21,22] and meta-analyses[23] suggest that the beneficial impact on BMD is greatest when postmenopausal estrogen/progestin therapy is begun within 5 years of menopause. However, significant increases in BMD may still be seen when therapy is initiated at older ages.[24]

## Fracture Risk

Postmenopausal hormone therapy is efficacious for the prevention of fractures. The decrease in fracture risk with postmenopausal hormone therapy has been demonstrated in several large observational studies, including the Framingham Study and the Study of Osteoporotic Fractures (SOF).[21,22] Two recent meta-analyses reported a decreased rate of both vertebral and nonvertebral (i.e., wrist and hip) fractures in women taking postmenopausal hormone therapy.[23,25] Most recently, the WHI confirmed, in a clinical trial setting, that postmenopausal estrogen/progestin therapy (CEE/MPA) significantly reduced the incidence of hip, vertebral and other osteoporotic fractures.[26]

The CEE(0.625mg)/MPA(2.5mg) component of the WHI[26] is by far the largest randomized, placebo-controlled trial to date evaluating fracture risk. After a mean follow-up period of 5.2 years, significant reductions in the relative hazard for hip fractures (hazard ratio [HR], 0.66; 95% nominal confidence interval [nCI], 0.45–0.98) and vertebral fractures (HR, 0.66; 95% CI, 0.44–0.98) were observed with CEE/MPA (Figure 1).

**Figure 1. Women's Health Initiative (WHI): Fracture Outcomes**




***Includes all fractures other than chest/sternum, skull/face, fingers, toes, and cervical vertebrae, as well as hip and vertebral fractures reported separately.**
**†nCI = nominal confidence interval (shows variability based on simple trial for single outcome).**
**‡aCI = adjusted confidence interval (corrects for multiple analyses over time).**
**Adapted from Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-33.[26]**

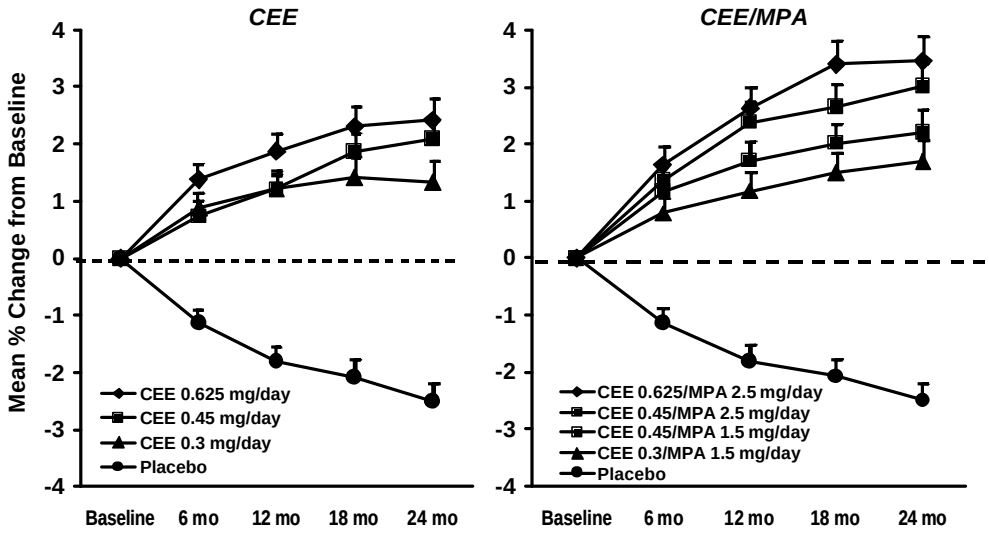
Significant reductions in relative hazards for other osteoporotic fractures (HR, 0.77; 95% CI, 0.69–0.86) and total fractures (HR, 0.76; 95% CI, 0.69–0.85) were also observed.

The WHI finding of decreased fracture risk with postmenopausal estrogen/progestin therapy is remarkable for several reasons. First, it is unusual to observe a significant reduction in fractures at multiple sites (i.e., hip, vertebral and other osteoporotic) in a single study. Second, the vertebral fracture end point consisted of documented clinical fractures and not radiographically defined fractures. It is estimated that only about one third of vertebral fractures are detected by radiography. Radiographic fractures tend to be more prevalent and therefore are the more commonly studied fracture endpoint. Additionally, this reduced fracture risk was observed in a study population that was not selected to be at high risk for fracture, possibly underestimating the potential benefit of postmenopausal estrogen/progestin therapy in a high-risk population.

## Effect of Dose

In the Women's HOPE study, a randomized, placebo-controlled study that investigated the efficacy of various lower doses of CEE and CEE/MPA, doses as low as 0.3 mg/d of CEE significantly increased spine and hip BMD from baseline within 2 years of therapy (Figure 2).[15]

**Figure 2. The Women's HOPE Trial: Changes in Spine BMD**




**Intent-to-treat population only.**
**HOPE = Heart, Osteoporosis, Progestin, Estrogen.**
**Lindsay R, et al. *JAMA.* 2002;287:2668-76.[15]**

Data from the ORAG meta-analysis suggested that lower doses significantly increase BMD at the lumbar spine, femoral neck, and forearm compared with placebo controls; however, significant differences were observed between low-dose (equivalent to CEE 0.3 mg/d) and high-dose (equivalent to CEE 0.9 mg/d) groups at the lumbar spine and the femoral neck.[16]

## Effect of Type of Estrogen, Progestin, or Regimen

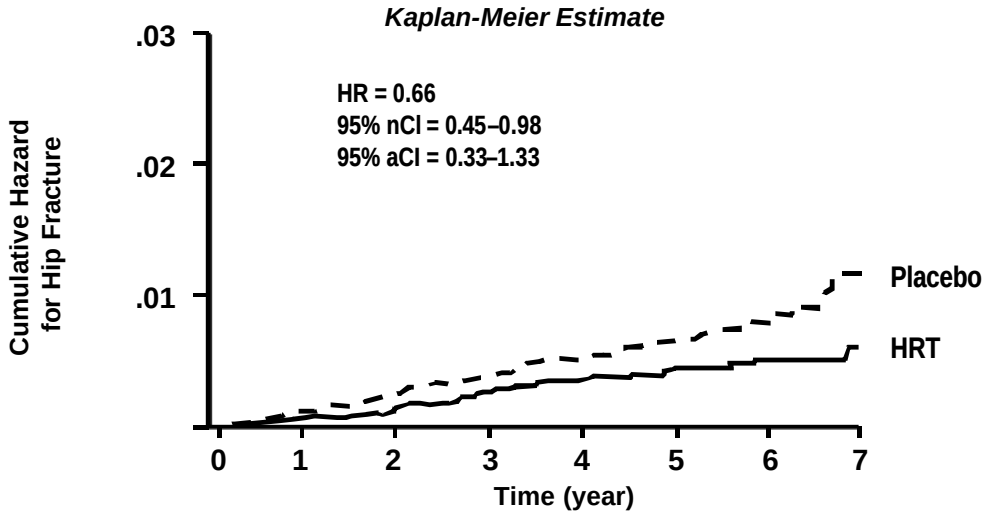
The data do not suggest a difference in effect on BMD among various formulations of postmenopausal estrogen therapy or among various formulations or regimens of postmenopausal estrogen/progestin therapy. However, there is some suggestion from the Women's HOPE study that combination estrogen/progestin therapy may produce greater increases in BMD than estrogen-only therapy.[15] Data from the ORAG meta-analysis, which included randomized clinical trials other than the WHI, did not suggest differences between various postmenopausal hormone therapy combinations.[16]

With regard to fracture, other than the WHI, the data on the effectiveness of postmenopausal hormone therapy in fracture prevention are mostly limited to observational studies, which included a variety of estrogens, progestins, and estrogen-progestin regimens.

## Effect of Duration of Use

In the WHI, the protective effect of CEE/MPA on fractures became evident within the first year of therapy initiation (Figure 3). However, the beneficial effect of hormone therapy may have been underestimated because some patients (approximately 25%, including 6% current users) had been taking postmenopausal estrogen/progestin therapy before entering the study.[26]

**Figure 3. WHI: Effect of HRT on Risk of Hip Fracture**




**HR = hazard ratio; nCI = nominal confidence interval; aCI = adjusted confidence interval.**
**Writing Group for the Women's Health Initiative Investigators. *JAMA.* 2002;288:321-33.[26]**

A randomized clinical trial[15] and the ORAG meta-analysis[16] indicate that

significant increases in BMD with postmenopausal hormone therapy can be observed by 1 year of treatment.

## Effect of Past Use/Discontinuation of Therapy

There are limited studies that directly address the question of the long-term effects on bone protection associated with short-term postmenopausal hormone therapy use. The large National Osteoporosis Risk Assessment (NORA) study of over 200,000 women showed a decreased incidence of osteoporosis in former users.[27] Data from the PEPI trial[28] indicate that BMD after discontinuation of therapy decreases at relatively slow rates. Two recent studies examined changes in BMD following discontinuation of postmenopausal hormone therapy. Both studies found BMD levels after discontinuation that were well above those of placebo. One double-blind, placebo controlled discontinuation trial measured BMD 1 year after stopping hormone therapy that had been taken for 2 years. Compared to the 3-year placebo group, the group that was switched to placebo after 2 years of hormone treatment had a BMD that was 2.9% higher at the spine (P <0.05), 2.9% higher at the trochanter (P =<0.001) and 2.1% higher at the hip. The other study[30] reported significantly higher BMD levels 2 years after discontinuation in women who had used hormone therapy for 3 years. Spine BMD in the presence (P <0.05) or absence of calcitrol remained well over the BMD levels of the placebo group. BMD of the femoral neck also remained substantially higher than placebo levels. Since fracture risk is inversely related to BMD, increases in BMD secondary to short-term use of postmenopausal hormone therapy should result in a decreased risk of fracture for some time following treatment discontinuation.

## Alternative Therapies

Alternative therapies for the prevention and treatment of osteoporosis include alendronate,[31-38] risedronate,[39-42]raloxifene,[43-46] and calcitonin.[47] Two randomized, placebo-controlled studies have compared the effects of postmenopausal hormone therapy and alendronate on BMD.[32,33] One 2-year trial that compared the effects of postmenopausal hormone therapy on BMD to those of alendronate 5 mg/d included 2 cohorts: a US cohort, which used continuous CEE 0.625/MPA 2.5, and a European cohort, which used sequential estradiol 2 mg/norethindrone acetate (NETA) 1 mg.[32] In the US cohort, the response to CEE/MPA was slightly, but not significantly greater than the response to alendronate in the spine (4.0% vs 2.9%, *P* = .06) and in the hip (1.8% vs 1.3%, *P* = .21). In the European cohort, the response to estradiol/NETA was significantly greater than the response to alendronate (spine: 5.1% vs 3.3%, *P* = .008; hip: 3.2% vs 1.6%, *P* < .002). Another 2-year trial[32] demonstrated that CEE 0.625 produced increases in BMD in the spine and femoral neck that were similar to those of alendronate 10 mg/d. In clinical practice, the predominant adverse effects associated with alendronate and risedronate include gastrointestinal symptoms (i.e., dyspepsia, esophageal irritation, and ulceration). Alendronate and risedronate should be used with caution in patients with esophageal disease.

The effects of raloxifene and postmenopausal estrogen therapy on BMD have also been compared.[43,44] In a 2-year placebo-controlled trial, both CEE 0.625 mg/d and raloxifene increased BMD at the hip compared to baseline and to placebo.[44] However,

patients taking CEE experienced significantly greater changes from baseline and placebo compared with raloxifene. A 24-week study showed that treatment with CEE or cyclic CEE/MPA resulted in a significantly greater increase in spinal BMD than raloxifene.[43] The predominant adverse effects associated with raloxifene include an increase in or the development of vasomotor symptoms, which may limit its utility in the early menopausal population. It also is associated with an increased relative risk of venous thromboembolic events.

Although there are data on the effects of all of these alternative therapies on hip fracture, only alendronate has strong evidence for a reduced risk of hip fracture. Moreover, studies evaluating long-term use are either lacking or limited for alternative therapies; therefore, conclusions regarding long-term safety cannot be made.

# RISKS OF POSTMENOPAUSAL HORMONE THERAPY

## Breast Cancer

### *Breast Cancer Risk*

A review of the available studies evaluating breast cancer incidence with postmenopausal hormone therapy yields mixed results: some studies have reported an increased relative risk while others have not. In those studies that observed an overall increase in relative risk of breast cancer, the relative risk is generally less than 2.0. Some studies with women taking long-term therapy have seen an effect of duration of hormone use and have observed an increase in the relative risk for breast cancer somewhere after 5 years of postmenopausal hormone therapy use.[26, 48-55]

The Collaborative Group reanalysis[48] suggests that the relative risk of breast cancer increases 1% to 3% for each year of use. Using modeling techniques, the authors estimate that among 1,000 women initiating postmenopausal estrogen/progestin therapy at age 50 years and continuing for 5 years, 10 years, or 15 years, there would be 2, 6, and 12 additional cases of breast cancer, respectively, by age 70 years.[48] This is in addition to an estimated cumulative incidence over the same period of 45 cases per 1,000 women based on incidence rates in the general population.

The Million Women Study[56] reported an adjusted relative breast cancer risk of 1.66 (95% CI, 1.58-1.75) for current users at recruitment. The study reported on various types of estrogen and progestin, as well as tibolone, and was not limited to CEE/MPA. The risk was greater when progestin was added to estrogen [RR; 2.00 (95% CI, 1.88-2.12)]. Past users were not at increased risk of incident or fatal breast cancer.

Although the WHI was designed as a randomized controlled trial, the study was limited in duration and included women with prior use of postmenopausal hormone therapy. Care must therefore be taken in generalizing the results to women who are initiating hormone therapy for the first time. The larger body of evidence from observational studies must be taken into account.

The WHI reported an overall increase in the incidence of breast cancer among women (mean age= 63 years) randomized to CEE/MPA compared with those randomized to placebo, with an overall relative risk of 1.26 (95% CI, 1.00–1.59) after an average of 5.2 years of follow-up.[26] A recent re-analysis of the data [57], extending the follow-up period to an average 5.6 years, yielded a hazard ratio for total breast cancer of 1.24 (95% CI, 1.02-1.50). The increase in breast cancer became evident about 4 years after randomization.[57] This finding is consistent with some observational studies,[49, 50, 52-55, 58,59] suggesting an association between postmenopausal estrogen/progestin therapy and breast cancer. However, care must be taken in extrapolating these results to other populations of women, in particular newly menopausal women initiating postmenopausal estrogen/progestin therapy for the first time. Since, in general, it can take years for a new tumor to develop, it is possible that the breast cancers observed in WHI had begun to develop prior to the start of the study, and were not initiated by the hormone therapy.

The question remains whether hormone therapy in some way alters or facilitates the growth of existing tumors.

The WHI also included subjects at risk for breast cancer, such as first-degree relatives with breast cancer (about 12% of the subjects). The therapy-related breast cancer risk found in WHI may therefore be lower in a risk-free population.

The relative risk that would be relevant to early postmenopausal women initiating estrogen/progestin therapy for the first time would be that derived from an analysis limited to the women in the WHI with no CEE/MPA exposure prior to randomization. In this subgroup, which includes 75% of the original cohort, the overall relative risk is 1.06 (95% CI, 0.81–1.38).[26] This is less than the 1% to 3% increase per year reported by the Collaborative Group. Conversely, the relative risks for subgroups with prior use are greater than the overall relative risk of 1.26.

Because both the background rate of breast cancer (273 cases per 100,000 in women aged 50 to 54 years[60]) and the relative risk associated with short-term use are low in early postmenopausal women, the absolute risk with hormone therapy for the treatment of menopausal symptoms is low. Therefore, the excess risk of 8 per 10,000 women per year reported in the WHI, which included older women with long-term prior use, is likely to be a significant overestimate of risk for women initiating postmenopausal hormone therapy for the first time. For women without previous hormone use in the WHI, invasive breast cancer rates were lower for the initial 2 years in the CEE/MPA group compared with placebo, and similar in the third year.

***Breast Cancer Mortality***

To date, WHI has seen no difference in breast cancer mortality between the CEE/MPA and placebo groups.[57] In the Million Women Study[56], there is a suggestion of an increased relative risk of mortality due to breast cancer (RR=1.22; 95% CI; 1.00 – 1.48) for current users compared to never users. In general, the previous observational studies as well as WHI have not demonstrated an increased mortality risk; to the contrary, the WHI investigators noted in the breast cancer reanalysis[57] that, overall, most of the available data suggests a better prognosis for women on hormone therapy [see FNs 20-25 in BC reanalysis].

***Past Use and Time Since Last Use***

In studies which showed increased risk of breast cancer and which evaluated the incidence of breast cancer following discontinuation of hormone therapy, the risk appears to decrease towards baseline, especially after 5 years of non-use, at which time the relative risk of breast cancer approaches 1.0. In the Collaborative Group's reanalysis,[48] the relative risk of breast cancer was no longer increased when 5 or more years had elapsed since the last use of postmenopausal hormone therapy, regardless of how long therapy was used (RR, 0.90 for 5 to 9 years of use; RR, 0.95 for ≥10 years of use). Several recent observational studies that evaluated the relationship between past use of postmenopausal hormone therapy and relative risk of breast cancer, including the

Million Women Study, found no increase in the relative risk of breast cancer among past users.[50, 54, 56, 61-63]

### *Effect of Different Hormone Regimens on Breast Cancer*

Current information indicates that the relative risk of breast cancer associated with hormone therapy does not differ by hormone regimen.

Of the recent observational studies that differentiated between postmenopausal estrogen therapy and combination estrogen/progestin therapy, three studies reported an increased relative risk for breast cancer with current postmenopausal estrogen/progestin therapy (RRs, 1.39–1.49),[49, 50, 52] while only one study reported an increased relative risk of breast cancer with current postmenopausal estrogen therapy use (RR, 1.25; 95% CI, 1.08–1.45).[49] More recently, the Million Women Study[56] reported an increased breast cancer risk in estrogen-only users, [RR 1.30; 95% CI, 1.21-1.40]. Addition of progestin to estrogen further increased that risk (RR 2.00; 95% CI 1.88-2.12]. The study included estradiol, norethindrone, or levonorgestrel regimens as well as CEE/MPA. An increased risk was also reported for tibolone.[56]

In the Collaborative Group reanalysis of 51 observational studies,[48] the authors noted that the relative risk of breast cancer did not vary according to the type or dose of estrogen used. In addition, a case-control study, which evaluated predominantly 17β-estradiol compounds, reported an increased odds ratio (OR) for breast cancer (OR, 1.65; 95% CI, 1.43–1.89).[55] The study also evaluated breast cancer risk by type of progestin and found that ever-use of progestins derived from progesterone, such as MPA, was not associated with an increased relative risk of breast cancer (OR, 1.14; 95% CI, 0.69–1.88), while ever-use of progestins derived from testosterone, such as norethindrone acetate (NETA), had an increased relative risk (OR, 1.68; 95% CI, 1.39–2.03) that occurred with either sequential or continuous regimens.[55] The relative risk associated with cyclic testosterone-derived progestins increased with increasing duration of use (OR, 1.08 per year of use; 95% CI, 1.03–1.13).

## Coronary Heart Disease

Until recently, the majority of published observational studies as well as preclinical and surrogate marker data, suggested a lower incidence of CHD among users of postmenopausal estrogen therapy or estrogen/progestin therapy compared with nonusers. However, the results from the WHI[26] and the earlier secondary prevention trial, the Heart and Estrogen/progestin Replacement Study (HERS),[64, 65] have led to a re-examination of whether postmenopausal hormone use is associated with cardiovascular benefit or risk.

The following section is based on a review of the literature on postmenopausal hormone therapy use and CVD with an emphasis on the end points of CHD (incidence and mortality), stroke, and venous thromboembolic events (VTE). More than 45 studies have been published since 1966 on the primary or secondary prevention of CVD or CHD.

***Coronary Heart Disease Risk***

While the vast majority of published observational studies reported a lower incidence of CHD among postmenopausal hormone therapy users, recent randomized clinical trials have observed an increased risk of CHD in the first year of use, which decreases thereafter.

The WHI trial,[26] although labeled as a primary prevention study, included a small subset of women with conditions characteristic of a secondary prevention study, such as a history of cardiovascular disease, myocardial infarction, revascularization procedures, transient ischemic attack, and/or carotid endarterectomy/angioplasty. The authors of the report[26] state that this subset of women (n=400) reported conditions at baseline that would have made them eligible for the HERS study. Moreover, a number of women in the trial had risk factors for CHD, including high BMI, smoking (past or current), and treatment for high cholesterol, high blood pressure and diabetes.[26] The original WHI publication reported a relative risk of 1.29 (95% nCI, 1.02–1.63) for CHD. Most of the excess risk was from nonfatal MI. The incidence of CHD was low in both treatment groups: 1.5% in the placebo group and 1.9% in the postmenopausal estrogen/progestin therapy group. The small increase in relative risk for the CEE/MPA group appeared in year 1 and subsequently decreased towards 1.0 with the exception of year 5, which appears to be an outlier. The increased relative risk in year 5 is attributable to a marked decrease in the event rate for the placebo group.

Compared to the original WHI publication[26], the data from the most recent WHI CHD publication[66] reflect the central adjudication of primary coronary heart disease (CHD; non-fatal MI, CHD deaths). The follow-up period was extended to an average of 5.6 years from 5.2 years in the original report. The combined number of CHD cases in the two groups changed from 286 to 335. This has resulted in changes in the overall hazard ratios for CHD in the therapy vs. placebo groups to HR = 1.24 (95% nCI, 1.00-1.54). The increased risk was due mainly to an increase in nonfatal MIs (HR, 1.28; 95% nCI, 1.00-1.63). A significant increase in the risk of CHD in the CEE/MPA group was reported in year 1 (HR, 1.81; 95% nCI, 1.09-3.01). Smaller and non-significant excess risks were observed in years 2 through 5. In year 6 and beyond, the increased rates in the placebo group resulted in an apparent reduction in relative risk. The trend toward a decreasing relative risk over time was statistically significant.

Overall, no subgroup of women except those with higher LDL-cholesterol levels showed evidence of a different CHD risk compared to that of all women, although the power to draw subgroup conclusions was limited. Age, body mass index, presence or absence of coronary risk factors and other variables did not significantly modify the risk of CHD related to hormone therapy. For women < 10, 10-19, and ≥20 years post menopause, the HR's for hormone therapy were 0.89; 1.22 and 1.71, respectively. These data suggest that women within 10 years of menopause are not at increased risk for CHD with the use of hormone therapy.

The finding of early risk with a trend towards a decreasing risk after the first year was also seen in HERS,[64] a secondary prevention study in women with established CHD. In HERS there was an increased risk of CHD in year 1 that tended to decrease with

continued postmenopausal estrogen/progestin therapy use (RR for year 1, 1.52; 95% CI, 1.01–2.29). Similar trends for women with established CHD were found in post hoc analyses of several prospective observational cohorts.[67-69] Analysis of the Nurses' Health Study (NHS)[68] subjects with CHD reported relative risks of 1.25 (95% CI, 0.78–2.00) for initiation of postmenopausal hormone therapy within 1 year of MI, and relative risks of 0.55 (95% CI, 0.13–2.27) and 0.38 (95% CI, 0.22–0.66) for the second and subsequent years of use, respectively. Another study[67] suggested that use of postmenopausal estrogen/progestin therapy within the first 60 days of an MI was associated with a relative risk of 2.16 (95% CI, 0.94–4.95), with evidence of a decreasing trend in relative risk, 0.92 (95% CI, 0.40–2.12), and 0.76 (95% CI, 0.42–1.36) for use up to one year and greater than 1 year, respectively. Retrospective analysis of the CARS database[69] reported a relative risk of 1.44 (95% CI, 1.05–1.99) for recurrent first year events of either cardiac death, MI, or unstable angina. Relative risks for longer use were not reported.

The WHI report of an early increased relative risk for CHD, contrasts with the over 30 observational studies that examined the association of MI and other cardiovascular outcomes with postmenopausal hormone use. These studies show apparent protective associations between estrogen and CHD, with significant relative risk estimates from 12 studies that ranged from 0.21 to 0.82.[63, 68, 70-79] However, several aspects of the most recent WHI CHD publication, including the evidence of a significant trend toward decreasing relative risk over time, is consistent with the observational data.

The explanation for the difference between observational and controlled clinical trials remains unclear. One suggestion is that the observational studies may be subject to bias if women using postmenopausal hormone therapy are different from non-users. A recent meta-analysis that included studies rated as good or fair quality found that among the observational studies that adjusted for socioeconomic status (SES), there was no association between any postmenopausal estrogen/progestin therapy use and CHD events (RR, 0.88; 95% CI, 0.64–1.21).[80]

Another explanation for the contrast between the WHI study and observational study results is that the WHI study was not conducted in an early postmenopausal population. The average starting age of women in the WHI trial was considerably older, (mean age = 63.3 years, with two thirds of the women >60 years) than the age at onset of menopause, a number of women exhibited risk factors for CHD, and a small subset of women (n=400) reported conditions at baseline that would have made them eligible for the HERS study. Data from studies in non-human primates[80a] and in postmenopausal women[80b] suggest that early initiation of hormone therapy may prevent the development of atherosclerosis.[80c] Thus, it is not known whether the results of the WHI are applicable to healthy, younger, postmenopausal women. Given the low background rate of CHD in early postmenopausal women, the same relative risk would be expected to yield a substantially lower absolute risk in this population.

***Coronary Heart Disease Mortality***

Of those observational studies that evaluated mortality,[63, 68, 70-74, 77, 81-87] most show a lower mortality due to CHD among postmenopausal hormone therapy users. In these studies the observational period ranged from 1.3 to 20 years, with an apparent trend

toward a reduction in cardiovascular mortality in postmenopausal hormone therapy users (RRs ranged from 0.17 to 1.94). Furthermore, a modest decrease in mortality remains after adjusting for SES. A recent meta-analysis that adjusted for SES[80, 88] reported a summary relative risk for current users of postmenopausal hormone therapy of 0.64 (95% CI, 0.44–0.93) and 0.62 (95% CI, 0.40–0.90) for CVD and CHD mortality, respectively. In the WHI there was no significant difference in CHD mortality between the treatment groups, although the overall number of events was small.[26] The overall mortality was not affected by CEE/MPA therapy during the trial.[26]

***Stroke***

The majority of observational studies and clinical trials did not observe an increased risk of stroke.[89] However, an increased risk has been found in some studies; the relative risk reported in those studies was generally less than 2.0. In studies where the type of stroke was evaluated, the increased risk was predominantly observed for thromboembolic strokes.

A recent meta-analysis,[88] which pooled results from 9 observational studies,[63, 82, 90-96] reported that the relative risk for overall stroke incidence was slightly increased among ever users (RR, 1.12; 95% CI, 1.01–1.23). Relative risk was elevated for thromboembolic stroke (RR, 1.20; 95% CI, 1.01–1.40), but not for subarachnoid or intracerebral stroke.[88]

In the WHI trial the overall hazard ratio for stroke (fatal and nonfatal) was 1.41 (95% nominal CI, 1.07–1.85), after an average of 5.2 years of follow-up.[26] The increased risk of stroke appeared in year 2 and persisted to the end of the study. When separated into fatal or nonfatal events, the increase in stroke was statistically significant for nonfatal stroke, but not for fatal stroke.

The original WHI publication[26] data were recently updated.[97] The average follow-up period was extended from 5.2 years to 5.6 years, the stroke events were subjected to central adjudication, and new cases were added (258 vs. 212). The overall hazard ratio for stroke (ischemic and hemorrhagic) reported in the updated study was 1.31 (95% nCI, 1.02-1.68). The increased risk resulted exclusively from an increase in ischemic stroke [HR 1.44; (95% nCI, 1.09-1.90)]. The relative risk of hemorrhagic stroke was decreased [HR 0.82; (95% nCI 0.43-1.56)]. Hormone users had an increased risk for non-fatal stroke, but not for fatal stroke. The adjusted hazard ratios for overall stroke were similar across age groups.

***Venous Thromboembolism***

Evidence supports an increased relative risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) with postmenopausal hormone therapy.[26, 64, 98-100] Evidence from randomized controlled trials in women with and without established cardiovascular disease,[26, 64, 98] supports an association between postmenopausal hormone therapy and an increased risk of VTE (RR range, 2.08 to 2.89).

A number of observational studies have examined the risk of venous thromboembolism with postmenopausal hormone therapy. A recent meta-analysis of 12

studies[101] found that current use of postmenopausal estrogen was associated with a 2-fold increased risk for VTE (RR, 2.14; 95% CI, 1.64–2.81). Pooled data from 6 studies[64, 79, 102-105] indicated that the risk was highest during the first year of use (RR, 3.49; 95% CI, 2.33–5.59), with a lower increased risk persisting (RR, 1.91, 95% CI, 1.18–3.52) thereafter using different estrogens and progestins.[101] The increased DVT risk associated with hormone therapy appears to be dose-dependent and has been seen with multiple regimens.[102-104]

***Cognitive Functions***

Global cognitive functions and incidence of probable dementia were evaluated in 4381 postmenopausal women 65 years or older. The study participants were recruited from the WHI Study. Women in the CEE/MPA - treated group did not exhibit as much improvement over time as women in the placebo group in the Modified Mini-Mental State Examination, a standard instrument used to screen for dementia. This difference was significant (P = .008) when compared to placebo.[106] The incidence of dementia and mild cognitive impairment was reported in another study[107] of the above population plus an additional 151 subjects. The hazard ratio for probable dementia in the hormone treated group was higher than in the placebo group [HR 2.05; (n95% CI, 1.21-3.48)]. Alzheimer's disease was the most common classification of dementia in both study groups. Treatment effects on mild cognitive impairment did not differ between groups. The WHI authors note that these results contrast with prior observational data showing a reduction in Alzheimers disease and dementia for women using hormone therapy. [107]

## Limitations of the WHI Study

To date, Wyeth has not had access to the full data underlying the WHI publications, and thus has not been able to analyze that data completely. There are, moreover, a number of factors which limit both the interpretation and generalizability of the WHI results. A non-exhaustive list is set forth below.

The WHI[26] recruited women of relatively old age (age range at study start: 50-79 years; mean age 63.2 years in the CEE/MPA group and 63.3 in the placebo group). Approximately 66% of the study population was ≥60 years old. By comparison, the onset of menopause occurs on average at 51 years, an age when hormone therapy is indicated for many women and when the risks associated with hormone therapy can be expected to be substantially lower than observed in WHI. Indeed, the study excluded women with severe menopausal symptoms that would have been inconsistent with assignment to placebo.[108] Moreover, while only 400 women had previously diagnosed CHD, a number of participants were overweight, smokers (past or current), and being treated for high cholesterol, high blood pressure and diabetes.[26] The study thus examined a population unrepresentative of the women for whom the product is principally indicated.

The WHI study population included about 25% of prior and current hormone users and therefore had been exposed to potential risk factors associated with hormone therapy for longer than the duration of the study. About 30% of prior and current users had taken therapy for longer than 5 years. Therefore, risk factors ascribed to CEE/MPA therapy in WHI may have been overestimated.

A further limitation of WHI is the relatively high rate of unblinding (approximately 40%) and discontinuation (42%) in the active treatment arm, and the relatively high rate of crossover to active treatment in the placebo arm (10.7%).

WHI studied only one strength of CEE/MPA. The risk profile observed in WHI may therefore not apply to lower CEE/MPA doses or to other types of hormones.

## Conclusion

- The overall benefit of hormone therapy must be evaluated against the overall risk associated with the therapy. The efficacy of postmenopausal hormone therapy to relieve menopausal symptoms, prevent osteoporosis and reduce fractures has been well documented both in observational studies and in the recent WHI study. The CEE/MPA component of the WHI study is by far the largest randomized, placebo-controlled clinical trial to date evaluating fracture risk. Hormone therapy resulted in significant reductions in the risk of both vertebral and hip fractures, and in significant reductions in the risk of colorectal cancer.

- After a mean follow-up of 5.2 years, the WHI Data and Safety Monitoring Board recommended to discontinue CEE/MPA treatment because the breast cancer rates exceeded the predefined stopping boundary. The board concluded that the overall risks exceeded the benefits, as measured by using the global index. However, the global index was originally intended as a monitoring tool, and not as an overall risk/benefit measure. The index is based on selected risks and selected benefits and not on all risks and all benefits. For example, it includes hip fractures but not vertebral fractures or menopausal symptoms. Vertebral fractures are associated with substantial rates of disability, morbidity and mortality; and menopausal symptoms can be debilitating and detrimental to everyday life. The global index does not contain a measure of quality of life (less disability) associated with reduced rates of vertebral fractures, menopausal symptoms and other factors. Therefore, the global index, as used in the WHI, does not truly represent a comprehensive measure of risks vs. benefits that is applicable to the general population of postmenopausal women receiving estrogen/progestin treatment.

- It is important to offer different treatment options to physicians and patients. Hormone therapy represents an important option for use in relieving menopausal symptoms and concomitant prevention of osteoporosis in women with high risk of osteoporosis/fractures but without significant risk factors for cardiovascular disease or breast cancer for whom alternative therapies to prevent osteoporosis cannot be used or have not been effective.

- Postmenopausal hormone therapy is the only intervention that is simultaneously effective in the treatment of menopausal symptoms and the prevention of osteoporosis. The use of postmenopausal hormone therapy for the treatment of menopausal symptoms should be limited to the lowest dose and shortest duration consistent with treatment goals and risks for the individual woman.

- When using hormone therapy solely for the prevention of postmenopausal osteoporosis, therapy should be considered only for women at significant risk of osteoporosis, and non-estrogen medications, such as alendronate, risedronate or raloxifene, should be carefully considered as a first-line treatment option. For older women, use in combination with a progestin should only be considered for women who failed on, or were intolerant of, non-estrogen medication. Potential long-term risks of postmenopausal hormone therapy should be evaluated when using this therapy for the prevention of osteoporosis. The decision regarding

therapy should take into account the individual woman's underlying risk factors for cardiovascular disease and breast cancer. Because individual treatment goals and risks change over time, the use of postmenopausal hormone therapy should be periodically re-evaluated. These re-evaluations are especially important when longer durations of therapy, particularly greater than 5 years, are considered.

- The adverse effects associated with alternative therapies, such as esophageal ulceration, gastrointestinal symptoms, lower extremity cramping or vasomotor symptoms should be carefully evaluated and should be balanced against the risks associated with hormone therapy. Studies evaluating long-term use are either lacking or limited for alternative therapies; therefore, conclusions regarding long-term safety cannot be made.

- Alternative therapies may also have limitations regarding their efficacy. Fracture reduction studies of alendronate or risedronate therapy have been conducted primarily in osteoporotic women. However, the National Osteoporosis Risk Assessment (NORA) study identified nearly 40% osteopenic (i.e., non-osteoporotic, non-symptomatic) women among its study population, indicating that there are large numbers of women with osteopenia in the general population. The NORA study found substantial fracture rates associated with osteopenia.

- The WHI study was conducted in non-osteoporotic women and thus the significant reduction of fracture risk observed in the WHI study may be more relevant to the general population than the observations from trials of alternative therapies conducted in osteoporotic women. Moreover, the efficacy of risedronate to protect against hip fractures may be limited.

- The WHI study was conducted largely in an older population of postmenopausal women who are not typical hormone therapy users.

- Patient counseling is an essential part of any treatment decision. When making decisions about initiating or continuing postmenopausal hormone therapy, counseling women about the potential benefits and risks is particularly important. Healthcare providers who counsel women about postmenopausal hormone therapy should be familiar with the differences between relative risk and absolute risk so that treatment decisions can be based on the individual patient's benefit/risk profile. Women should participate in the decision-making process with an understanding of the potential risks and benefits of postmenopausal hormone therapy, and they should be reassured that their choice of therapy will be periodically reevaluated.

## References


1. National Osteoporosis Foundation. *America's Bone Health: The State of Osteoporosis and Low Bone Mass in Our Nation*. Washington, DC: National Osteoporosis Foundation; 2002:1-55.

2. Melton LJI, Chrischilles EA, Cooper C, et al. Perspective: How many women have osteoporosis now? J Bone Miner Res. 1992;7:1005-1010.

3. Melton LJI, Crowson CS, O'Fallon WM. Fracture incidence in Olmsted County, Minnesota: comparison of urban with rural rates and changes in urban rates over time. Osteoporos Int. 1999;9:29-37.

4. Oleksik A, Lips P, Dawson A, et al. Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. J Bone Miner Res. 2000;15:1384-1392.

5. Cauley JA, Thompson DE, Ensrud KC, et al. Risk of mortality following clinical fractures. Osteoporos Int. 2000;11:556-561.

6. Papaioannou A, Watts NB, Kendler DL, et al. Diagnosis and management of vertebral fractures in elderly adults. Am J Med. 2002;113:220-228.

7. American Association of Clinical Endocrinologists. American association of clinical endocrinologists 2001 medical guidelines for clinical practice for the prevention and management of postmenopausal osteoporosis. Endocr Pract. 2001;7:293-312.

8. Keene GS, Parker MJ, Pryor GA. Mortality and morbidity after hip fractures. BMJ. 1993;307:1248-1250.

9. Cummings SR, Kelsey JL, Nevitt MC, et al. Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev. 1985;7:178-208.

10. Hoerger TJ, Downs KE, Lakshmanan MC, et al. Healthcare use among U.S. women aged 45 and older: total costs and costs for selected postmenopausal health risks. J Womens Health Gend Based Med. 1999;8:1077-1089.

11. Fox NF, Chan JK, Thamer M, Melton J. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: Report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12:24-35.

12. Johnell O. The socioeconomic burden of factures: Today and in the 21st Century. Am J Med 1997;103(2A):20S-26S.

13. Kanis JA. Diagnosis of osteoporosis. Osteoporos Int. 1997;7:S108-S116.

14. Writing Group for the PEPI Trial. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA. 1996;276:1389-1396.

15. Lindsay R, Gallagher JC, Kleerekoper M, et al. Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. JAMA. 2002;287:2668-2676.

16. Wells G, Tugwell P, Shea B, et al. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. Endocr Rev. 2002;23:529-539.

17. Nilas L, Christiansen C. The pathophysiology of peri- and postmenopausal bone loss. Br J Obstet Gynaecol. 1989;96:580-587.

18. Slemenda C, Longcope C, Peacock M, et al. Sex steroids, bone mass, and bone loss—a prospective study of pre-, peri-, and postmenopausal women. J Clin Invest. 1996;97:14-21.

19. Slemenda C, Hui SL, Longcope C, et al. Sex steroids and bone mass. A study of changes about the time of menopause. J Clin Invest. 1987;80:1261-1269.

20. Lindsay R, Aitken JM, Anderson JB, et al. Long-term prevention of postmenopausal osteoporosis by oestrogen: evidence for an increased bone mass after delayed onset of oestrogen treatment. Lancet. 1976;1(7968):1038-1041, May 15, 1976..

21. Cauley JA, Seeley DG, Ensrud K, et al. Estrogen replacement therapy and fractures in older women. Ann Intern Med. 1995;122:9-16.

22. Kiel DP, Felson DT, Anderson JJ, et al. Hip fracture and the use of estrogens in postmenopausal women. The Framingham study. N Engl J Med. 1987;317:1169-1174.

23. Torgerson DJ, Bell-Syer SEM. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. JAMA. 2001;285:2891-2897.

24. Villareal DT, Binder EF, Williams DB, et al. Bone mineral density response to estrogen replacement in frail elderly women. A randomized controlled trial. JAMA. 2001;286:815-820.

25. Torgerson DJ, Bell-Syer SEM. Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials. BMC Musculoskeletal Disorders. 2001;2:7-10.

26. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from

the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321-333.

27. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the national osteoporosis risk assessment. JAMA. 2001;286:2815-2822.

28. Greendale GA, Espeland M, Slone S, et al. Bone mass response to discontinuation of long-term hormone replacement therapy: results from the postmenopausal estrogen/progestin interventions (PEPI) safety follow-up study. Arch Intern Med. 2002;162:665-672.

29. Greenspan SL, Emkey RD, Bone HG, Weiss SR, Bell NJ, Downs RW, et al. Significant differential effects of alendronate, estrogen, or combination therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis. Ann Intern Med 2002;137:875-883.

30. Gallagher JC, Rapuri PB, Haynatzki G, Detter JR. Effect of discontinuation of estrogen, calcitriol, and the combination of both on bone density and bone markers. J Clin Endocrinol Metab 2002;87:4914-4923.

31. Ravn P, Bidstrup M, Wasnich RD, et al. Alendronate and estrogen-progestin in the long-term prevention of bone loss: four-year results from the early postmenopausal intervention cohort study. A randomized, controlled trial. Ann Intern Med. 1999;131:935-942.

32. Hosking D, Chilvers CED, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. N Engl J Med. 1998;338:485-492.

33. Bone HG, Greenspan SL, McKeever C, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. J Clin Endocrinol Metab. 2000;85:720-726.

34. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet. 1996;348:1535-1541.

35. Black DM, Thompson DE, Bauer DC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. J Clin Endocrinol Metab. 2000;85:4118-4124.

36. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the fracture intervention trial. JAMA. 1998;280:2077-2082.

37. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med. 1995;333:1437-1443.

38. Karpf DB, Shapiro DR, Seeman E, et al. Prevention of nonvertebral fractures by alendronate: a meta-analysis. JAMA. 1997;277:1159-1164.

39. ACTONEL® risedronate sodium tablets [package insert]. Aventis Pharmaceuticals. 2002.

40. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. 1999;282:1344-1352.

41. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. N Engl J Med. 2001;344:333-340.

42. Reginster J-Y, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Osteoporos Int. 2000;11:83-91.

43. Prestwood KM, Gunness M, Muchmore DB, et al. A comparison of the effects of raloxifene and estrogen on bone in postmenopausal women. J Clin Endocrinol Metab. 2000;85:2197-2202.

44. EVISTA® raloxifene hydrochloride 60 mg tablets [package insert]. Eli Lilly and Company. 2002.

45. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. Results from a 3-year randomized clinical trial. JAMA. 1999;282:637-645.

46. Lufkin EG, Whitaker MD, Nickelsen T, et al. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. J Bone Miner Res. 1998;13:1747-1754.

47. Miacalcin® (calcitonin-salmon) Nasal Spray. Prescribing information. Novartis Pharmaceuticals Corp. 2000.

48. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. Lancet. 1997;350:1047-1059.

49. Newcomb PA, Titus-Ernstoff L, Egan KM, et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2002;11:593-600.

50. Chen C-L, Weiss NS, Newcomb P, et al. Hormone replacement therapy in relation to breast cancer. JAMA. 2002;287:734-741.

51. Ross RK, Paganini-Hill A, Wan PC, et al. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J Natl Cancer Inst. 2000;92:328-332.

52. Schairer C, Lubin J, Triosi R, et al. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA. 2000;283:485-491.

53. Persson I, Thurfjell E, Bergstrom R, et al. Hormone replacement therapy and the risk of breast cancer: nested case-control study in a cohort of Swedish women attending mammography screening. Int J Cancer. 1997;72:758-761.

54. Persson I, Weiderpass E, Bergkvist L, et al. Risks of breast and endometrial cancer after estrogen and estrogen-progestin replacement. Cancer Causes Control. 1999;10:253-260.

55. Magnusson C, Baron JA, Correia N, et al. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. Int J Cancer. 1999;81:339-344.

56. Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. Lancet. 2003;362:419-427

57. Chlebowski RT, Hendrix SL, Langer, RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women The Women's Health Initiative randomized trial. JAMA 2003;289:3243-3253.

58. Manjer J, Malina J, Berglund G, et al. Increased incidence of small and well-differentiated breast tumours in post-menopausal women following hormone-replacement therapy. Int J Cancer. 2001;92:919-922.

59. Tavani A, Braga C, La Vecchia C, et al. Hormone replacement treatment and breast cancer risk: an age-specific analysis. Cancer Epidemiol Biomarkers Prev. 1997;6:11-14.

60. Ries LAG, Eisner MP, Kosary CL, et al. SEER Cancer Statistics Review, 1973-1999. Bethesda, Md: National Cancer Institute; 2002.

61. Moorman PG, Kuwabara H, Millikan RC, et al. Menopausal hormones and breast cancer in a biracial population. Am J Public Health. 2000;90:966-971.

62. Brinton LA, Brogan DR, Coates RJ, et al. Breast cancer risk among women under 55 years of age by joint effects of usage of oral contraceptives and hormone replacement therapy. Menopause. 1998;5:145-151.

63. Sourander L, Rajala T, Raihi I, et al. Cardiovascular and cancer morbidity and mortality and sudden cardiac death in postmenopausal women on oestrogen replacement therapy (ERT). Lancet. 1998;352:1965-1969.

64. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998;280:605-613.

65. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: heart and estrogen/progestin replacement study follow-up (HERS II). JAMA. 2002;288:49-57.

66. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;349:523-534.

67. Heckbert SR, Kaplan RC, Weiss NS, et al. Risk of recurrent coronary events in relation to use and recent initiation of postmenopausal hormone therapy. Arch Intern Med. 2001;161:1709-1713.

68. Grodstein F, Manson JE, Stampfer MJ. Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study. A prospective, observational study. Ann Intern Med. 2001;135:1-8.

69. Alexander KP, Newby LK, Hellkamp AS, et al. Initiation of hormone replacement therapy after acute myocardial infarction is associated with more cardiac events during follow-up. J Am Coll Cardiol. 2001;38:1-7.

70. Bush TL, Barrett-Connor E, Cowan LD, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. Circulation. 1987;75:1102-1109.

71. Wolf PH, Madans JH, Finucane FF, et al. Reduction of cardiovascular disease-related mortality among postmenopausal women who use hormones: Evidence from a national cohort. Am J Obstet Gynecol. 1991;164:489-494.

72. Folsom AR, Mink PJ, Sellers TA, et al. Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. Am J Public Health. 1995;85:1128-1132.

73. Ettinger B, Friedman GD, Bush T, et al. Reduced mortality associated with long-term postmenopausal estrogen therapy. Obstet Gynecol. 1996;87:6-12.

74. Cauley JA, Seeley DG, Browner WS, et al. Estrogen replacement therapy and mortality among older women: the study of osteoporotic fractures. Arch Intern Med. 1997;157:2181-2187.

75. Hammond CB, Jelovsek FR, Lee KL, et al. Effects of long-term estrogen replacement therapy: I. Metabolic effects. Am J Obstet Gynecol. 1979;133:525-536.

76. Falkeborn M, Persson I, Adami H-O, et al. The risk of acute myocardial infarction after oestrogen and oestrogen-progestogen replacement. Br J Obstet Gynaecol. 1992;99:821-828.

77. Ross RK, Paganini-Hill A, Mack TM, et al. Menopausal oestrogen therapy and protection from death from ischaemic heart disease. Lancet. 1981;1:858-860.

78. Psaty BM, Heckbert SR, Atkins D, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. Arch Intern Med. 1994;154:1333-1339.

79. Varas-Lorenzo C, Garcia-Rodriguez LA, Perez-Gutthann S, et al. Hormone replacement therapy and incidence of acute myocardial infarction: a population-based nested case-control study. Circulation. 2000;101:2572-2578.

80. Humphrey LL, Chan BKS, Sox HC. Postmenopausal hormone replacement therapy and the primary prevention of cardiovascular disease. Ann Intern Med. 2002;137:273-284.

80. a. Williams JK, Anthony MS, Honore EK, et al. Regression of atherosclerosis in female monkeys. Arterioscler Thromb Vasc Biol 1995;15:827-836.

80. b. Hodis HN, Mack WJ, Lobo RA, et al. Estrogen in the prevention of atherosclerosis. Ann Intern Med 2001;135:939-953.

80. c. Hodis HN, Mack WJ, Azen SP, et al. Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. N Engl J Med 2003;349:535-545.

81. Criqui MH, Suarez L, Barrett-Connor E, et al. Postmenopausal estrogen use and mortality. Results from a prospective study in a defined, homogeneous community. Am J Epidemiol. 1988;128:606-614.

82. Wilson PWF, Garrison RJ, Castelli WP. Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50: the Framingham Study. N Engl J Med. 1985;313:1038-1043.

83. Petitti DB, Perlman JA, Sidney S. Noncontraceptive estrogens and mortality: long-term follow-up of women in the Walnut Creek Study. Obstet Gynecol. 1987;70:289-293.

84. Henderson BE, Paganini-Hill A, Ross RK. Estrogen replacement therapy and protection from acute myocardial infarction. Am J Obstet Gynecol. 1988;159:312-317.

85. Talbott E, Kuller LH, Detre K, et al. Biologic and psychosocial risk factors of sudden death from coronary disease in white women. Am J Cardiol. 1977;39:858-864.

86. Adam S, Williams V, Vessey MP. Cardiovascular disease and hormone replacement treatment: a pilot case-control study. BMJ. 1981;282:1277-1278.

87. Beard CM, Kottke TE, Annegers JF, et al. The Rochester coronary heart disease project: effect of cigarette smoking, hypertension, diabetes, and steroidal estrogen use on coronary heart disease among 40- to 59-year-old women, 1960 through 1982. Mayo Clin Proc. 1989;64:1471-1480.

88. Nelson HD, Humphrey LL, Nygren P, et al. Postmenopausal hormone replacement therapy: scientific review. JAMA. 2002;288:872-881.

89. Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: a statement for healthcare professionals from the stroke council of the American Heart Association. Circulation. 2001;103:163-182.

90. Thompson SG, Meade TW, Greenberg G. The use of hormonal replacement therapy and the risk of stroke and myocardial infarction in women. J Epidemiol Community Health. 1989;43:173-178.

91. Pfeffer RI, Whipple GH, Kurosaki TT, et al. Coronary risk and estrogen use in postmenopausal women. Am J Epidemiol. 1978;107:479-497.

92. Grodstein F, Manson JE, Colditz GA, et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med. 2000;133:933-941.

93. Petitti DB, Sidney S, Quesenberry CP, et al. Ischemic stroke and use of estrogen and estrogen/progestogen as hormone replacement therapy. Stroke. 1998;29:23-28.

94. Pedersen AT, Lidegaard O, Kreiner S, et al. Hormone replacement therapy and risk of non-fatal stroke. Lancet. 1997;350:1277-1283.

95. Fung MM, Barrett-Connor E, Bettencourt RR. Hormone replacement therapy and stroke risk in older women. J Womens Health. 1999;8:359-364.

96. Finucane FF, Madans JH, Bush TL, et al. Decreased risk of stroke among postmenopausal hormone users: results from a national cohort. Arch Intern Med. 1993;153:73-79.

97. Wassertheil-Smoller S, Hendrix, S, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women. JAMA. 2003;289:2673-2689.

98. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: heart and estrogen/progestin replacement study follow-up (HERS II). JAMA. 2002;288:58-66.

99. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. N Engl J Med. 2000;343:522-529.

100. Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. JAMA. 1995;273:199-208.

101. Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive services task force. Ann Intern Med. 2002;136:680-690.

102. Daly E, Vessey MP, Hawkins MM, et al. Risk of venous thromboembolism in users of hormone replacement therapy. Lancet. 1996;348:977-980.

103. Jick H, Derby LE, Myers MW, et al. Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. Lancet. 1996;348:981-983.

104. Pérez Gutthann S, García Rodríguez LA, Castellsague J, et al. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. BMJ. 1997;314:796-800.

105. Hoibraaten E, Abdelnoor M, Sandset PM. Hormone replacement therapy with estradiol and risk of venous thromboembolism: a population-based case-control study. Thromb Haemost. 1999;82:1218-1221.

106. Rapp SR, Espeland MA, Shumaker SA, Henderson VW, Brunner RL, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women. The Women's Health Initiative Memory Study: A randomized controlled trial. JAMA 2003;289:2663-2684.

107. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. JAMA 2003;289:2651-2662.

108. The Women's Health Initiative Study Group. Design of the Women's Health Initiative Clinical Trial and Observational Study. Controlled Clin Trials 1998;19:61-109.