
Abstract: CONTEXT: The effects of continuous combined hormone therapy on gynecologic cancers have not been investigated previously in a randomized trial setting. OBJECTIVE: To determine the possible associations of estrogen plus progestin on gynecologic cancers and related diagnostic procedures. DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, placebo-controlled trial of 16 608 postmenopausal women, who had not had a hysterectomy at baseline and who had been recruited from 40 US clinical centers between September 1993 and October 1998 (average follow-up, 5.6 years). INTERVENTION: One tablet per day containing 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate (n = 8506) or placebo (n = 8102). MAIN OUTCOME MEASURE: Incident invasive cancer of the ovary and endometrium. RESULTS: In 5.6 years of follow-up, there were 32 cases of invasive ovarian cancer, 58 cases of endometrial cancer, 1 case of nonendometrial uterine cancer, 13 cases of cervical cancer, and 7 cases of other gynecologic cancers. The hazard ratio (HR) for invasive ovarian cancer in women assigned to estrogen plus progestin compared with placebo was 1.58 (95% confidence interval [CI], 0.77-3.24). The HR for endometrial cancer was 0.81 (95% CI, 0.48-1.36). No appreciable differences were found in the distributions of tumor histology, stage, or grade for either cancer site. The incidence of other gynecologic cancers was low and did not differ by randomization assignment. More women taking estrogen plus progestin required endometrial biopsies (33% vs 6%; P<.001). CONCLUSIONS: This randomized trial suggests that continuous combined estrogen plus progestin therapy may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo. The increased burden of endometrial biopsies required to assess vaginal bleeding further limits the acceptability of this regimen. These data provide additional support for caution in the use of continuous combined hormones.


Abstract: CONTEXT: Despite decades of use and considerable research, the role of estrogen alone in preventing chronic diseases in postmenopausal women remains uncertain. OBJECTIVE: To assess the effects on major disease incidence rates of the most commonly used postmenopausal hormone therapy in the United States. DESIGN, SETTING, AND PARTICIPANTS: A randomized, double-blind, placebo-controlled disease prevention trial (the estrogen-alone component of the Women's Health Initiative [WHI]) conducted in 40 US clinical centers beginning in 1993. Enrolled were 10 739 postmenopausal women, aged 50-79 years, with prior hysterectomy, including 23% of minority race/ethnicity. INTERVENTION: Women were randomly assigned to receive either 0.625 mg/d of conjugated equine estrogen (CEE) or placebo. MAIN OUTCOME MEASURES: The primary outcome was coronary heart disease (CHD) incidence (nonfatal myocardial
infarction or CHD death). Invasive breast cancer incidence was the primary safety outcome. A global index of risks and benefits, including these primary outcomes plus stroke, pulmonary embolism (PE), colorectal cancer, hip fracture, and deaths from other causes, was used for summarizing overall effects. RESULTS: In February 2004, after reviewing data through November 30, 2003, the National Institutes of Health (NIH) decided to end the intervention phase of the trial early. Estimated hazard ratios (HRs) (95% confidence intervals [CIs]) for CEE vs placebo for the major clinical outcomes available through February 29, 2004 (average follow-up 6.8 years), were: CHD, 0.91 (0.75-1.12) with 376 cases; breast cancer, 0.77 (0.59-1.01) with 218 cases; stroke, 1.39 (1.10-1.77) with 276 cases; PE, 1.34 (0.87-2.06) with 85 cases; colorectal cancer, 1.08 (0.75-1.55) with 119 cases; and hip fracture, 0.61 (0.41-0.91) with 102 cases. Corresponding results for composite outcomes were: total cardiovascular disease, 1.12 (1.01-1.24); total cancer, 0.93 (0.81-1.07); total fractures, 0.70 (0.63-0.79); total mortality, 1.04 (0.88-1.22), and the global index, 1.01 (0.91-1.12). For the outcomes significantly affected by CEE, there was an absolute excess risk of 12 additional strokes per 10 000 person-years and an absolute risk reduction of 6 fewer hip fractures per 10 000 person-years. The estimated excess risk for all monitored events in the global index was a nonsignificant 2 events per 10 000 person-years. CONCLUSIONS: The use of CEE increases the risk of stroke, decreases the risk of hip fracture, and does not affect CHD incidence in postmenopausal women with prior hysterectomy over an average of 6.8 years. A possible reduction in breast cancer risk requires further investigation. The burden of incident disease events was equivalent in the CEE and placebo groups, indicating no overall benefit. Thus, CEE should not be recommended for chronic disease prevention in postmenopausal women.


Abstract: Over 24-25 February 2003 in Funchal, Madeira, Novo Nordisk gathered together 25 of the top international hormone replacement therapy (HRT) experts, in order to debate the results of the Women's Health Initiative (WHI) and interpret its possible implications for the future use of HRT. The meeting covered many interesting and controversial areas, addressing the complex and multifaceted issues with insight and realism. Some of the areas covered at the meeting were the use of HRT as a short- or long-term therapy for hot flushes, for general menopausal symptom relief and in osteoporosis prevention; the overall risk-benefit profile and specific breast cancer concerns were also discussed. The WHI data were reviewed and summarized, and, although it was generally agreed that the study was well designed and executed, its relevance to standard hormone therapy for clinical practice must be seriously called into question. The target population used in the WHI is not representative of the target population for whom menopausal HRT is normally considered. It is important to note that randomized controlled trials such as the WHI are really scientific tools for a group of research participants, not a form of individualized medical management. Since their publication, the relevance of the WHI study results for everyday clinical practice has been the subject of controversy. The WHI targeted a group of women who were much older than those normally treated and who had numerous other risk factors. These were not women for whom a practicing clinician would think about initiating hormone therapy with the regimen that was used. Putting a high-risk 70-year-old woman on 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate would not seem appropriate for any indication. With this in mind, we reviewed statements and guidance that followed the release of the WHI to the media, putting them in context.
with the actual results. Focusing on data taken out of context and without reference to subject profiles, the media created an emotive wave of uncertainty for patients and physicians, which needs to be addressed through realistic, factual communication. It is clear that hormone therapy is effective for postmenopausal symptoms and osteoporosis prevention. Timing is critical for the initiation of therapy and length of treatment. The individual's unique personal profile must be assessed. This leads to the paradox of osteoporosis prevention: therapy should be long-term, but it is long-term therapy that may increase breast cancer risk. The meeting reviewed the uncertain nature of the risks for breast cancer, although the evidence is becoming stronger that combinations of estrogen and progestogen cause a modest increase in risk after 5 years, while this seems not to be true for estrogen alone. Cardiovascular disease issues were also reviewed and discussed. This is perhaps the most misinterpreted result that came out of the WHI, given the population of women studied. Considering the vascular biology and effects of early interventions, the WHI finding that hormone therapy has no place in primary cardiovascular protection is an unwarranted conclusion. Other issues regarding the risk-benefit profile of HRT for the individual patient were also discussed. Additionally, presenters explored the possibility of class effects against the potential risk factors associated with particular estrogen and progestogen types. It is quite clear that CEE and 17beta-estradiol differ with respect to their source and composition; pharmacokinetic and metabolic data indicate that they differ in their total estrogenic potency, with CEE possessing greater estrogenic potency. Using 17beta-estradiol at the lowest dosage level can provide safe and effective therapy for most indications. The evidence for progestogen differences is even more clear. Medroxyprogesterone acetate and norethisterone acetate have different pharmacokinetic profiles and different activities on steroid receptors. Evidence from preclinical and clinical studies supports the conclusion that these differences result in different pharmacological and clinical effects in favor of norethisterone acetate. Having comprehensively discussed and reviewed all available evidence, a consensus was achieved with regard to appropriate therapy: HRT should be given to women with menopausal complaints to meet their individual needs, taking into account their individual risk profile and the overall therapeutic objectives.


Abstract: CONTEXT: In the Women's Health Initiative trial of estrogen-plus-progestin therapy, women assigned to active treatment had fewer fractures. OBJECTIVE: To test the hypothesis that the relative risk reduction of estrogen plus progestin on fractures differs according to risk factors for fractures. DESIGN, SETTING, AND PARTICIPANTS: Randomized controlled trial (September 1993-July 2002) in which 16,608 postmenopausal women aged 50 to 79 years with an intact uterus at baseline were recruited at 40 US clinical centers and followed up for an average of 5.6 years. INTERVENTION: Women were randomly assigned to receive conjugated equine estrogen, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n = 8506) or placebo (n = 8102). MAIN OUTCOME MEASURES: All confirmed osteoporotic fracture events that occurred from enrollment to discontinuation of the trial (July 7, 2002); bone mineral density (BMD), measured in a subset of women (n = 1024) at baseline and years 1 and 3; and a global index, developed to summarize the balance of risks and benefits to test whether the risk-benefit profile differed across tertiles of fracture risk. RESULTS: Seven hundred thirty-three women (8.6%) in the estrogen-plus-progestin group and 896 women (11.1%) in the
placebo group experienced a fracture (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.69-0.83). The effect did not differ in women stratified by age, body mass index, smoking status, history of falls, personal and family history of fracture, total calcium intake, past use of hormone therapy, BMD, or summary fracture risk score. Total hip BMD increased 3.7% after 3 years of treatment with estrogen plus progestin compared with 0.14% in the placebo group (P<.001). The HR for the global index was similar across tertiles of the fracture risk scale (lowest fracture risk tertile, HR, 1.20; 95% CI, 0.93-1.58; middle tertile, HR, 1.23; 95% CI, 1.04-1.46; highest tertile, HR, 1.03; 95% CI, 0.88-1.24) (P for interaction = .54). CONCLUSIONS: This study demonstrates that estrogen plus progestin increases BMD and reduces the risk of fracture in healthy postmenopausal women. The decreased risk of fracture attributed to estrogen plus progestin appeared to be present in all subgroups of women examined. When considering the effects of hormone therapy on other important disease outcomes in a global model, there was no net benefit, even in women considered to be at high risk of fracture.


Abstract: BACKGROUND: Breast cancer and its treatment may compromise bone health. We tested the hypothesis in the Women's Health Initiative Observational Study that postmenopausal survivors of breast cancer have a higher risk for fractures compared with women who have no cancer history. METHODS: A prospective cohort (5.1 years' follow-up) study design was used. Breast cancer survivors were women who reported a history of breast cancer (n = 5298). A reference group included women who had no cancer history at baseline (n = 80 848). Fracture occurrence was ascertained from annual self-reports. Hip fractures were confirmed by reviewing medical records. RESULTS: After adjustment for age, weight, ethnicity, and geographic region of enrollment, the hazard ratios (HRs) of breast cancer survivors to women in the reference group were 0.93 (95% confidence interval [CI], 0.64-1.33) for hip; 1.36 (95% CI, 1.16-1.59) for forearm or wrist; 1.31 (95% CI, 1.19-1.43) for eligible fractures other than hip, vertebral, and forearm or wrist; and 1.31 (95% CI, 1.21-1.41) for these fractures combined. The increased risk for clinical vertebral fracture was statistically significant only among survivors who had a breast cancer diagnosis before age 55 years (HR, 1.78; 95% CI, 1.28-2.46). After adjusting for factors related to hormone levels, risk of fall, fracture history, medication use, comorbidity, and lifestyle, the increased risk for all fractures studied among survivors was reduced to 15% (HR, 1.15; 95% CI, 1.05-1.25). CONCLUSIONS: Postmenopausal survivors of breast cancer are at increased risk for clinical fractures. Preventions and therapeutic interventions are needed to reduce fracture risk in this large and growing population.


Abstract: BACKGROUND: Breast cancer diagnosis and treatment may put women at higher risk for osteoporosis in later life. METHODS: In a subgroup of participants in the Women's Health Initiative Observational Study, authors of the current study investigated differences in bone mineral density (BMD, measured by dual-energy x-ray absorptiometry) between breast cancer survivors (n = 209) and a noncancer reference group (n = 5759). RESULTS: In comparison to the reference group, breast cancer survivors had significantly lower total body BMD value (0.989 vs. 1.013 g/cm(2), P = 0.001) and total hip BMD value (0.823 vs. 0.845 g/cm(2), P = 0.02) at baseline after adjustment for age, race/ethnicity,
years since menopause, and clinical center. These lower BMD levels were largely explained by lower usage of hormone therapy (HT) among survivors: after additional statistical adjustment for HT, hip BMD values were 0.834 versus 0.844 g/cm(2) (P = 0.26), and total body values were 1.005 versus 1.013 g/cm(2) (P = 0.33) for survivors and reference women, respectively. More than 77% of survivors with osteoporosis were undiagnosed by their healthcare providers, and this was similar to the undiagnosed rate in the reference group (85.7%). Longitudinally, breast cancer survivors in this study did not demonstrate an accelerated rate of bone loss compared with the reference population.

CONCLUSIONS: Associated with lower HT usage, postmenopausal survivors of breast cancer were more likely to have low BMD in comparison to other women of the same age; and many of these survivors with osteoporosis were undiagnosed.


Abstract: CONTEXT: The Women's Health Initiative trial of combined estrogen plus progestin was stopped early when overall health risks, including invasive breast cancer, exceeded benefits. Outstanding issues not previously addressed include characteristics of breast cancers observed among women using hormones and whether diagnosis may be influenced by hormone effects on mammography. OBJECTIVE: To determine the relationship among estrogen plus progestin use, breast cancer characteristics, and mammography recommendations. DESIGN, SETTING, AND PARTICIPANTS: Following a comprehensive breast cancer risk assessment, 16 608 postmenopausal women aged 50 to 79 years with an intact uterus were randomly assigned to receive combined conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d) or placebo from 1993 to 1998 at 40 clinical centers. Screening mammography and clinical breast examinations were performed at baseline and yearly thereafter. MAIN OUTCOME MEASURES: Breast cancer number and characteristics, and frequency of abnormal mammograms by estrogen plus progestin exposure. RESULTS: In intent-to-treat analyses, estrogen plus progestin increased total (245 vs 185 cases; hazard ratio [HR], 1.24; weighted P<.001) and invasive (199 vs 150 cases; HR, 1.24; weighted P =.003) breast cancers compared with placebo. The invasive breast cancers diagnosed in the estrogen plus progestin group were similar in histology and grade but were larger (mean [SD], 1.7 cm [1.1] vs 1.5 cm [0.9], respectively; P =.04) and were at more advanced stage (regional/metastatic 25.4% vs 16.0%, respectively; P =.04) compared with those diagnosed in the placebo group. After 1 year, the percentage of women with abnormal mammograms was substantially greater in the estrogen plus progestin group (716 [9.4%] of 7656) compared with placebo group (398 [5.4%] of 7310; P<.001), a pattern which continued for the study duration. CONCLUSIONS: Relatively short-term combined estrogen plus progestin use increases incident breast cancers, which are diagnosed at a more advanced stage compared with placebo use, and also substantially increases the percentage of women with abnormal mammograms. These results suggest estrogen plus progestin may stimulate breast cancer growth and hinder breast cancer diagnosis.


Abstract: CONTEXT: The Heart and Estrogen/progestin Replacement Study (HERS) was a randomized trial of estrogen plus progestin therapy after menopause. OBJECTIVE: To
examine the effect of long-term postmenopausal hormone therapy on common noncardiovascular disease outcomes. DESIGN AND SETTING: Randomized, blinded, placebo-controlled trial of 4.1 years' duration (HERS) and subsequent open-label observational follow-up for 2.7 years (HERS II), carried out between 1993 and 2000 in outpatient and community settings at 20 US clinical centers. PARTICIPANTS: A total of 2763 postmenopausal women with coronary disease and average age of 67 years at enrollment in HERS; 2321 women (93% of those surviving) consented to follow-up in HERS II. INTERVENTION: Participants were randomly assigned to receive 0.625 mg/d of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate (n = 1380) or placebo (n = 1383) during HERS; open-label hormone therapy was prescribed at personal physicians' discretion during HERS II. The proportions with at least 80% adherence to hormones declined from 81% (year 1) to 45% (year 6) in the hormone group and increased from 0% (year 1) to 8% (year 6) in the placebo group. MAIN OUTCOME MEASURES: Thromboembolic events, biliary tract surgery, cancer, fracture, and total mortality. RESULTS: Comparing women assigned to hormone therapy with those assigned to placebo, the unadjusted intention-to-treat relative hazard (RH) for venous thromboembolism declined from 2.66 (95% confidence interval [CI], 1.41-5.04) during HERS to 1.40 (95% CI, 0.64-3.05) during HERS II (P for time trend =.08); it was 2.08 overall for the 6.8 years (95% CI, 1.28-3.40), and 3 of the 73 women with thromboembolism died within 30 days due to pulmonary embolism. The overall RH for biliary tract surgery was 1.48 (95% CI, 1.12-1.95); for any cancer, 1.19 (95% CI, 0.95-1.50); and for any fracture, 1.04 (95% CI, 0.87-1.25). There were 261 deaths among those assigned to hormone therapy and 239 among those assigned to placebo (RH, 1.10; 95% CI, 0.92-1.31). Adjusted and as-treated analyses did not alter our conclusions. CONCLUSIONS: Treatment for 6.8 years with estrogen plus progestin in older women with coronary disease increased the rates of venous thromboembolism and biliary tract surgery. Trends in other disease outcomes were not favorable and should be assessed in larger trials and in broader populations.

Abstract: CONTEXT: Hormone replacement therapy (HRT) is widely considered to reduce fractures, but this belief is based on observational data; evidence from randomized trials is lacking. OBJECTIVE: To conduct a systematic review of all randomized trials of HRT that have reported or collected nonvertebral fracture data but that may not have focused on fracture prevention. DATA SOURCES: The MEDLINE, EMBASE, Science Citation Index, and Cochrane Controlled Trials Register databases were searched from 1997 through 2000 and a search was conducted of all recent systematic reviews to identify older studies. Authors were contacted to establish whether fracture data had been collected but not reported. Researchers in the field and pharmaceutical companies also were contacted to try to identify unpublished studies. STUDY SELECTION: Trials were included in which participants had been randomized to at least 12 months of therapy and data on nonvertebral fractures at any other site and due to any cause were available. Of 70 initially identified studies, 22 were included in the analysis. DATA EXTRACTION: Both investigators extracted data independently and appraised trial quality according to the Jadad scale, which assesses the methods of randomization, concealment allocation, and reporting of withdrawals and dropouts. Disagreements were resolved by discussion. DATA SYNTHESIS: There was an overall 27% reduction in nonvertebral fractures in a pooled analysis (reduction favoring HRT in relative risk [RR], 0.73; 95% confidence interval [CI],
This effect was greater among women randomized to HRT who had a mean age younger than 60 years (RR, 0.67; 95% CI, 0.46-0.98; P = .03). Among women with a mean age of 60 years or older, there was a reduced effect (RR, 0.88; 95% CI, 0.71-1.08; P = .22). For hip and wrist fractures alone, the effectiveness of HRT appeared more marked (RR, 0.60; 95% CI, 0.40-0.91; P = .02), particularly for women younger than 60 years (RR, 0.45; 95% CI, 0.26-0.79; P = .005). CONCLUSIONS: Our meta-analysis of randomized controlled trials of HRT noted a statistically significant reduction in nonvertebral fractures. However, this effect may be attenuated in older women.


Abstract: BACKGROUND: Antioxidant defenses are one possible mechanism for decreasing oxidative damage and its potentially negative effects on age-related bone mass. OBJECTIVE: This study cross-sectionally examined whether higher dietary intakes, total intakes, and serum concentrations of antioxidants may be associated with higher bone mineral density (BMD). DESIGN: Total hip (and subregions), spine, and total-body BMDs were measured in 11,068 women aged 50-79 y enrolled in the Women's Health Initiative Observational Study and Clinical Trial at 3 clinics. Antioxidant intakes from diet (vitamin A, retinol, beta-carotene, vitamin C, vitamin E, and selenium) were estimated by using a self-reported food-frequency questionnaire. Antioxidants from supplements were estimated with an interviewer-administered questionnaire. A random subset (n = 379) had serum concentrations of retinol, carotenoids, and tocopherols measured. RESULTS: After adjustment for important BMD-related covariates, increasing intakes of antioxidants were not independently associated with BMD. A significant interaction effect was observed between intake of total vitamin C (lower three-fourths compared with highest one-fourth) and use of hormone therapy (HT) (P < 0.01). The beneficial effect of current HT use on femoral neck BMD appeared to be greater in women with higher concentrations of total vitamin C. This interaction was also significant for total-body (P < 0.045), spine (P = 0.03), and total-hip BMDs (P = 0.029). CONCLUSIONS: Our results do not support independent associations between dietary intake, total intake, or serum concentrations of antioxidants and BMD in women participating in the Women's Health Initiative. The extent to which HT use may interact with vitamin C intake and BMD warrants further exploration.