The Women's Health Initiative (WHI) Clinical Trial of Estrogen plus Progestin in Postmenopausal Women

Funded by the National Heart, Lung, and Blood Institute
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Conducted by 40 Clinical Centers and a Clinical Coordinating Center
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SUMMARY OF THE WOMEN'S HEALTH INITIATIVE (WHI)

Rationale for WHI Trials of Hormone Therapy

The National Institutes of Health launched the WHI program in 1991 in response to concerns about unanswered questions of importance to women's health. A number of clinical trials were designed to provide clear answers to promising but unproven prevention strategies. Two of these trials centered on the efficacy and safety of long term hormone therapy for prevention of chronic diseases.

While in prior decades these hormones were primarily used for the treatment of (FDA-approved) menopausal symptoms and vaginal atrophy, from the late 1980s and early 1990s long term hormone therapy was being used with increasing frequency for the prevention of fractures and coronary heart disease. For fracture prevention, this use was based on the proven (and FDA-approved) benefit for osteoporosis prevention, and on observational studies of fractures. For coronary heart disease prevention, this use was based on improvements in lipids found in clinical trials, observational studies, animal studies, and studies of mechanism. However, there was no clinical trial evidence proving that hormone therapy would prevent fractures, or prevent coronary heart disease, and these indications were not approved by the FDA. Similarly, there was no clinical trial evidence that any benefits would not be offset by harms. It was known that estrogen increased the risk of endometrial cancer (an effect which could be abrogated by progestins). It was suspected that hormone therapy increased the risk of breast cancer, based on observational and animal studies. At the time, the effect of hormones on stroke was unknown, as was the effect on venous thrombosis. In summary, the trials of hormone therapy were needed, because use of hormone therapy for the prevention of chronic disease was rising, and the diseases for which benefit was being assumed (or the harms which it could cause) were of considerable public health importance. The WHI trials were not designed to test the benefits and risks of short term hormone therapy at the time of menopause, but did include postmenopausal women in a wide age range in order to extend their generalizability.

Choice of Subjects and Drug Therapy

The age range of postmenopausal women included in these trials was 50-79 to encompass the age range for which hormones were being prescribed for prevention of chronic diseases. The choice of estrogen was dictated by the knowledge that Premarin (conjugated equine estrogen) was the most commonly prescribed hormone in the US in the early 1990s, that most of the prescriptions were for the 0.625 mg daily dose, and by the fact that most of the observational data suggesting benefit for coronary heart disease were based on this drug at this dose. Premarin at this dose was also the most commonly prescribed estrogen when used in combination with a progestin. The most commonly prescribed progestin was medroxyprogesterone, typically as cyclic therapy of 10 mg for 10-12 days in the month, or (increasingly) as continuous-combined therapy with daily 2.5 mg of medroxyprogesterone. Initially, continous-combined therapy was prescribed as two separate pills, however from 1995 onwards the combination pill Prempro became the dominant combination therapy. Compared to epidemiologic data on Premarin alone, there was relatively little data on Premarin combined with medroxyprogesterone. However, what data existed appeared to support

benefit for coronary heart disease of about the same extent as for Premarin alone. Observational data from Europe, where different estrogens and progestins predominate, were consistent with the U.S. data. The scanty data also supported a risk for breast cancer for the combination therapy, and a benefit for osteoporosis prevention. After the WHI trials were launched, reports of increased risk for venous thrombosis on estrogen alone or combined with progestins surfaced, and in 1998 the Heart and Estrogen/Progestin Study (HERS) published its findings of no benefit for coronary heart disease prevention in women with existing coronary disease.

Design and Timeline of Randomized Controlled Clinical Trials of Hormone Therapy

The trials were designed to test whether hormone therapy would prevent coronary heart disease, and whether the benefits would outweigh the risks, when given for several years to generally healthy postmenopausal women aged 50-79. The primary outcome for benefit was coronary heart disease, and the main outcome for harm was breast cancer. A global index was constructed as a summary measure of overall benefit or harm. The monitored outcomes included in the global index were coronary heart disease, stroke, pulmonary embolism, hip fracture, breast cancer, colorectal cancer, endometrial cancer (in women with a uterus), and death from other causes.

A randomized controlled trial of estrogen (E-Alone) in 10,739 women who had had a hysterectomy enrolled participants in the period 1993-1998 and is planned to continue to 2005, after an average of 8.5 years of follow-up. The estrogen is Premarin (conjugated equine estrogen) 0.625 mg daily, compared to matching placebo. A separate randomized controlled trial of estrogen plus progestin (E+P) in 16,608 women who had an intact uterus had the same timeline and was also originally planned to continue to 2005. The drug used in the E+P trial was Prempro (conjugated equine estrogen 0.626 mg plus medroxyprogesterone 2.5 mg daily). However, this trial was stopped in July, 2002 after 5.2 years of follow up when the independent Data and Safety Monitoring Board concluded that the pre-designated boundary for harm from breast cancer had been crossed, and that there was overall harm as assessed by a summary measure of important clinical outcomes. Note that in 2000 and again in 2001 women in the E-Alone as well as women in the E+P trials were notified of an increased risk of coronary heart disease, stroke, and venous thrombosis in the active treatment arms.

MAIN FINDINGS FROM THE COMPLETED E+P TRIAL

These findings are summarized below, and links to abstracts of published articles are provided. The first publication reported the major locally adjudicated outcomes as of April 30, 2002, representing an average of 5.2 years of follow-up. Subsequent publications include centrally adjudicated outcomes reported up to the closing of the trial on July 7, 2002 and represent an average of 5.6 years of follow up. These subsequent publications also provide more detailed subgroup analyses. The summary findings are reported here as hazard ratios (HR) with the traditional nominal confidence (CI) intervals; however, the various articles also report more conservative CIs adjusted for sequential monitoring and/or multiple outcomes, as appropriate.

OVERALL RISKS AND BENEFITS

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the Women's Health Initiative Investigators

JAMA 2002;288:321-333

After a mean of 5.2 years of follow-up, the trial was stopped because because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits.

Hazard ratios (nominal 95% confidence intervals) were as follows:

- CHD: 1.29 (1.02-1.63) with 286 cases
- Breast cancer: 1.26 (1.00-1.59) with 290 cases;
- Stroke: 1.41 (1.07-1.85) with 212 cases;
- Pulmonary embolism: 2.13 (1.39-3.25) with 101 cases
- Colorectal cancer: 0.63 (0.43-0.92) with 112 cases
- Endometrial cancer: 0.83 (0.47-1.47) with 47 cases
- Hip fracture: 0.66 (0.45-0.98) with 106 cases
- Death due to other causes: 0.92 (0.74-1.14) with 331 cases
- Total mortality: 0.98 (0.82-1.18)
- Global index: 1.15 (1.03-1.28).

Absolute excess risks per 10 000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more pulmonary emboli, and 8 more invasive breast cancers, while absolute risk reductions per 10 000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10 000 person-years.

Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

Abstract: http://jama.ama-assn.org/cgi/content/abstract/288/3/321

CORONARY HEART DISEASE

Estrogen plus Progestin and the Risk of Coronary Heart Disease

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NEJM 2003;349:523-534

As noted above, this and all subsequent reports include the centrally adjudicated (rather than locally adjudicated) outcomes over the entire 5.6 year (rather than 5.2 year) duration of the trial.

- A total of 335 cases of CHD were included in this final analysis, and with 188 vs 147 cases the HR was 1.24 (95% CI 1.00 - 1.54) for E+P compared to placebo
- This corresponds to an excess of 6 cases CHD for every 10,000 women treated for one year, on average.
- In adherent women the HR for CHD was 1.50 (1.14-1.97)
- The elevation in risk was most apparent at one year with a HR of 1.81 (1.09 - 3.01); the risks of CHD for years 2 through 6+ were 1.34, 1,27, 1.25, 1,45, and 0.70
- In year 6 and beyond, increased rates in the placebo group resulted in an apparent risk reduction
- E+P did not increase or decrease the risks for angina, CABG or PTCA, and congestive heart failure
- No subgroup (e.g., by age, years since menopause, presence of symptoms, BMI) with lowered risk of CHD on E+P could be identified
- Higher base-line levels of low-density lipoprotein cholesterol were associated with an excess risk of CHD among women who received E+P, but higher base-line levels of C-reactive protein, other biomarkers, and other clinical characteristics did not significantly modify the treatment-related risk of CHD

Estrogen plus progestin does not prevent CHD, and may increase the risk of CHD among generally healthy postmenopausal women, especially during the first year after the initiation of hormone use. This treatment should not be prescribed for the prevention of cardiovascular disease.

Abstract: http://content.nejm.org/cgi/content/short/349/6/523

BREAST CANCER

Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women

The Women's Health Initiative Randomized Trial

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- After a mean follow-up of 5.6 years, the hazard ratios (95% confidence intervals) for breast cancer associated with E+P compared to placebo were as follows:
    - Total breast cancer (245 vs 185 cases), HR 1.24 (1.02-1.50), weighted *P*<.001*
    - Invasive breast cancer (199 vs 150 cases), HR 1.24 (1.01-1.54), weighted *P* = .003
    - In situ breast cancer (47 vs 37 cases), HR 1.18 (0.77-1.82), weighted *P* = 0.09.
- The invasive breast cancers diagnosed in the E+P group were similar to those in the placebo group in respect of histology (including proportions of ductal and lobular cancers), estrogen and progestin receptor status, and grade of malignancy
- However, the cancers in the E+P group 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.
- For all study periods after the baseline examination, the percentages of women with abnormal mammograms were substantially higher in the E+P group than in the placebo group
- In adherent participants, the HR for invasive breast cancer was 1.49 (1.13-1.96), *P* <.001
- The findings were statistically consistent across multiple subgroups (e.g., by age, BMI, Gail Risk Assessment category)
- Women with no prior menopausal hormone use had a HR for invasive breast cancer of 1.09 (0.86-1.39), while women with <5 years prior use had a HR of 1.70 (0.99-2.91), and those with >5 years prior use had a HR of 2.27 (1.00-5.15), weighted *P* value for interaction = 0.15
- In the placebo group, women with no prior menopausal hormone use appeared to have somewhat higher risk of breast cancer compared to women with prior use
- On the other hand, the risk from E+P emerged later in women with no prior use; their HRs for invasive breast cancers were 0.48, 0.65, and 0.96 in years 1 through 3, and 1.45, 1.61, and 1.24 in years 4 through 6+. In women with prior use, the HRs were 0.90, 1.10, 3.09, 2.16, 3.56, and 1.99 in years 1 through 6+.

Relatively short-term E+P use increases the risk for 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. The results suggest E+P stimulates breast cancer growth and delays breast cancer diagnosis. Apparent differences by prior hormone use status need further investigation.

* weighting, as specified in the design, varied linearly from zero at time of randomization to a maximum of 1 beginning at follow up year 10

Abstract: http://jama.ama-assn.org/cgi/content/abstract/289/24/3254

STROKE

Effect of Estrogen Plus Progestin on Stroke in Postmenopausal Women

The Women's Health Initiative: A Randomized Trial

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JAMA 2003:289;2673-2684

- All strokes were centrally adjudicated by stroke-trained neurologists for this report
- 151 participants in the E+P and 107 in the placebo groups had strokes.
- For combined ischemic and hemorrhagic strokes, the HR for estrogen plus progestin vs placebo was 1.31 (95% CI, 1.02-1.68); with adjustment for adherence, the HR was 1.50 (95% CI, 1.08-2.08).
- The excess risk for stroke appeared in the second year after randomization and persisted thereafter
- Overall 79.8% of strokes were ischemic; the HR for ischemic stroke was 1.44 (95% CI, 1.09-1.90)
- There was no effect of E+P on hemorrhagic stroke, HR 0.82 (95% CI, 0.43-1.56)
- Although E+P raised systolic blood pressure slightly (between 1 and 2 mm Hg), this did not explain the excess risk
- The excess risk of all stroke was apparent in all age groups, in all categories of baseline stroke risk, and in women with and without hypertension, prior history of cardiovascular disease, or prior use of hormones
- Use of statins or aspirin did not modify the increased risk of stroke due to E+P
- Years since menopause and presence or absence of hot flashes and/or night sweats did not modify the effect of E+P on stroke risk
- Higher levels of inflammatory factors (IL-6, CRP, and E-selectin) predicted stroke, but did not modify the effect of E+P on stroke risk.
- Other risk factors for stroke, including smoking, blood pressure, diabetes, lower use of vitamin C supplements, higher white blood cell count, and higher hematocrit levels also did not modify the effect of E+P on stroke risk

Estrogen plus progestin increases the risk of ischemic stroke in generally healthy postmenopausal women. Excess risk for all strokes attributed to estrogen plus progestin appeared to be present in all subgroups of women examined. Inflammatory factors appear to play a role in stroke, but did not modify the effect of E+P on stroke risk.

Abstract: http://jama.ama-assn.org/cgi/content/abstract/289/20/2673

DEMENTIA

Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women

The Women's Health Initiative Memory Study: A Randomized Controlled Trial

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JAMA 2003:289;2651-2662

The Women's Health Initiative Memory Study (WHIMS) is an ancillary study to WHI funded by Wyeth. It enrolled women aged 65 and older who were participating in the WHI trial of E+P. WHIMS enrolled 92.6% of the 4894 WHI participants who were age-eligible and free of dementia in 39 of the 40 WHI clinical centers. WHIMS ascertained the incidence of probable dementia (primary outcome) and mild cognitive impairment (secondary outcome) through a structured clinical assessment. The mean (SD) time between the date of randomization into WHI and the last Modified Mini-Mental State Examination (3MSE) for all WHIMS participants was 4.05 (1.19) years.

- Overall, 61 women were diagnosed with probable dementia, 40 (66%) in the estrogen plus progestin group compared with 21 (34%) in the placebo group.
- The HR for probable dementia was 2.05 (95% CI, 1.21-3.48)
- In adherent women the HR for probable dementia was 3.22 (95% CI, 1.25-8.29)
- Absolute rates were 45 vs 22 per 10 000 person-years, *P* = .01; on average, this increased risk would result in an additional 23 cases of dementia per 10 000 women per year of treatment with E+P.
- Alzheimer disease was the most common classification of dementia in both study groups
- Age, education, and baseline 3MSE score related to risk of probable dementia, but did not modify the effect of E+P
- Prior use of hormones, statins, or aspirin did not modify the effect of E+P
- Mild cognitive impairment did not differ between E+P and placebo groups (HR, 1.07; 95% CI, 0.74-1.55; 63 vs 59 cases per 10 000 person-years; *P* = .72)

E+P therapy increased the risk for probable dementia in postmenopausal women aged 65 years or older. In addition, estrogen plus progestin therapy did not prevent mild cognitive impairment in these women. These findings, in conjunction with previously reported WHI data, support the conclusion that the risks of estrogen plus progestin outweigh the benefits.

Abstract: http://jama.ama-assn.org/cgi/content/abstract/289/20/2651

COGNITIVE FUNCTION

Effect of Estrogen Plus Progestin on Global Cognitive Function in Postmenopausal Women

The Women's Health Initiative Memory Study: A Randomized Controlled Trial

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The study population for this report was essentially the same as that for the companion report on dementia, only excluding some 151 participants without a valid post-enrollment assessment of cognitive function. WHIMS participants completed an annual assessment of global cognitive function, as measured with the Modified Mini-Mental State Examination (3MSE).

- 3MSE mean total scores in both groups increased slightly over time (mean follow-up of 4.2 years), probably due to the "learning effect" of repeated administration
- Women in the estrogen plus progestin group had smaller average increases in total scores compared with women receiving placebo (P = .03), but these differences were not clinically important
- Re-analysis after removing women by censoring them after adjudicated dementia, mild cognitive impairment, or stroke, and nonadherence to study protocol, did not alter the findings
- Prior hormone therapy use and duration of prior use did not affect the interpretation of the results, nor did timing of prior hormone therapy initiation with respect to the final menstrual period
- More women in the estrogen plus progestin group had a substantial and clinically important decline (≥ 2 SDs) in 3MSE total score (6.7%) compared with the placebo group (4.8%) (P = .008)

Among postmenopausal women aged 65 years or older, estrogen plus progestin did not improve cognitive function when compared with placebo. While most women receiving estrogen plus progestin did not experience clinically relevant adverse effects on cognition compared with placebo, a small increased risk of clinically meaningful cognitive decline occurred in the estrogen plus progestin group.

Abstract: http://jama.ama-assn.org/cgi/content/abstract/289/20/2663

QUALITY OF LIFE

Effects of Estrogen plus Progestin on Health-Related Quality of Life

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NEJM 2003:348;1839-54

Quality-of-life measures were collected at base line and at one year in all women and at three years in a subgroup of 1511 women enrolled in the trial of E+P.

- E+P treatment compared to placebo did not have any effects on general health, vitality, mental health, depressive symptoms, or sexual satisfaction
- E+P treatment was associated with a statistically significant but small and not clinically meaningful benefits for sleep disturbance, physical functioning, and bodily pain after one year (for sleep disturbance the mean benefit was 0.4 point on a 20-point scale, for physical functioning 0.8 point on a 100-point scale, and for bodily pain it was 1.9 points on a 100-point scale)
- These small benefits were no longer apparent at three years, and there were no significant benefits in terms of any of the other quality-of-life outcomes, in the subgroup with data at 3 years
- The findings were similar in women aged 50-59 and in older women, and there were no differences in any subgroup (e.g., by body mass index, race or ethnicity, presence of menopausal symptoms, or previous use of hormone therapy)
- Among 574 women aged 50 to 54 years with moderate-to-severe vasomotor symptoms at base line, E+P improved vasomotor symptoms and resulted in a small benefit for sleep disturbance but no benefit for the other quality-of-life outcomes

In this trial in postmenopausal women, estrogen plus progestin did not have a clinically meaningful effect on health-related quality of life. If present, symptoms of hot flashes and night sweats improved, but there were no clinically significant improvements in other domains of quality of life.

Abstract: http://content.nejm.org/cgi/content/abstract/NEJMoa030311v1

FRACTURES

The effects of Estrogen Plus Progestin on the Risk of Fracture and Bone Mineral Density
The Women's Health Initiative Clinical Trial

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JAMA 2003: 290;1729-1738

The trial was designed to test the effect of E+P on fractures in a population of postmenopausal women otherwise at low risk of fracture. All confirmed osteoporotic fractures that occurred during 5.6 years of the trial were included in this report. Hip fractures were designated as a secondary outcome of the trial, and were centrally adjudicated. Other osteoporotic fractures were locally adjudicated, using radiology reports to confirm initial self-report. Bone mineral density (BMD) was measured in a subset of women (n=1024) at baseline and years 1 and 3.

- 733 women in the E+P group and 896 in the placebo group experienced a fracture, HR 0.76 (95% CI 0.69-0.83)
- On average, 10,000 women treated for one year with E+P would experience 47 fewer osteoporotic fractures than women on placebo
- 52 women in the E+P group and 73 in the placebo group experienced a hip fracture, HR 0.72 (95% CI 0.47-0.96)
- On average, 10,000 women treated for one year with E+P would experience 5 fewer hip fractures than women on placebo
- The HRs in adherent women were similar to those in the groups overall; HR for total fracture was 0.71 (95% CI, 0.64-0.81), and HR for hip fracture was 0.63 (95% CI, 0.38-1.06)
- The effect of E+P on fractures did not differ significantly by age, years since menopause, BMI, BMD, prior hormone use, or fracture risk score
- For hip fracture, E+P reduced the risk more markedly in the subgroup of women with a baseline calcium intake of >1200 mg/day than in women with a lower intake (*P* for interaction = 0.02); however, this was not true for total fracture
- E+P lowered the risk of hip fracture in women with baseline BMIs of <25 and 25-<30, but not in women with a BMI of $\geq$30, but the interaction of therapy with baseline BMI was not statistically significant; E+P reduced the risk of total fracture to a similar degree across all groups of baseline BMI
- Total hip BMD increased by 3.7% after 3 years, compared to 0.14% in the placebo group, p<0.0001
- The HR for the global index ranged from 1.20 in the lowest fracture risk tertile to 1.03 in the highest tertile (the global index includes coronary heart disease, stroke, pulmonary embolism, hip fracture, breast cancer, colorectal cancer, endometrial cancer, and death from other causes)

E+P increases BMD and reduces risk of osteoporotic fractures in healthy postmenopausal women. However, even in the highest fracture risk tertile there was no net benefit from treatment, as assessed by the global index. Given the overall unfavorable risk/benefit ratio and the availability of other agents to prevent and treat osteoporosis, E+P cannot be recommended for the prevention or treatment of osteoporosis.

GYNECOLOGIC CANCERS

Gynecologic Cancers and Associated Diagnostic Procedures in the Women's Health Initiative Randomized Trial of Estrogen Plus Progestin

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JAMA 2003: 290;1739-1748

The effects of continuous combined E+P on gynecologic cancers have not previously been described in a clinical trial setting. The main outcome measures of this report were incident invasive cancer of the ovary and endometrium.

- The hazard ratio (HR) for invasive ovarian cancer in women assigned to estrogen plus progestin relative to placebo was 1.58 (95% CI: 0.77-3.24) with 32 cases.
- The HR for endometrial cancer was 0.81 (95% CI: 0.48-1.36) with 58 cases.
- No appreciable differences were found in the distributions of tumor histology, stage or grade for either cancer site
- The HR for cervical cancer was 1.44 (95% CI 0.47-4.42) with 13 cases, and the Pap smear results yielded slightly more mild displasia, low grade squamous intra-epithelial lesions, or atypia than the placebo arm and fewer normal results ($p<0.0001$)
- The incidence of other gynecologic cancers (uterus, other gynecologic organs) was low and did not differ by treatment arm
- More women on E+P required endometrial biopsies (33% vs 6%, $p<0.0001$)

The data suggest that continuous combined E+P may increase the risk of ovarian cancer, but not that of endometrial cancer, over an average follow up period of 5.6 years. The increased rates of endometrial biopsy required to assess and manage vaginal bleed further limits the acceptability of this treatment.

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Further information on the WHI Program can be found at http://www.whi.org/ and at http://www.nhlbi.nih.gov/whi/

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