Health Risks and Benefits 3 Years After Stopping Randomized Treatment With Estrogen and Progestin

The WHI Investigators
Background:
WHI Hormone Program Design

Hysterectomy

YES
N= 10,739

Conjugated equine estrogen (CEE) 0.625 mg/d
Placebo

NO
N= 16,608

CEE 0.625 mg/d + medroxyprogesterone acetate (MPA) 2.5 mg/d
Placebo
Women’s Health Initiative Trial of Estrogen + Progestin

Summary Overview
WHI Estrogen+Progestin Trial
Purpose

• To test the hypothesis that estrogen+progestin will reduce rates of CHD and osteoporosis-related fracture.

• To determine the balance of risks and benefits of estrogen+progestin on the overall health of postmenopausal women.
Profile of the Women’s Health Initiative Randomized Trial of Estrogen Plus Progestin in Women With an Intact Uterus

- **Initiated screening (N = 373,092)**
- **Provided consent and reported no hysterectomy (N = 18,845)**
- **Randomized (N = 16,608)**

**Estrogen + Progestin (N = 8,506)**
- **Status on 4/30/02**
  - Alive/outcomes data submitted in last 18 months (n = 7,968)
  - Unknown vital status (n = 307)
  - Deceased (n = 231)

**Placebo (N = 8,102)**
- **Status on 4/30/02**
  - Alive/outcomes data submitted in last 18 months (n = 7,608)
  - Unknown vital status (n = 276)
  - Deceased (n = 218)
“On May 31, 2002, after a mean of 5.6 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs. placebo 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.”

Writing Group for the Women’s Health Initiative Investigators
JAMA 2002;288:321-333
WHI Estrogen+Progestin Trial Results: Attributable Risks

- **Excess risk per 10,000 person-years on E+P**
  - 7 more women with CHD
  - 8 more women with stroke
  - 8 more women with PE
  - 8 more women with breast cancer

- **Risk reduction per 10,000 person-years on E+P**
  - 6 fewer colorectal cancer
  - 5 fewer hip fractures
Why was the E+P Arm of the WHI Trial Stopped?

The trigger for early stopping was

- A weighted logrank test = -3.19 for invasive breast cancer that exceeded the pre-specified (O’Brian-Flemming) boundary for harm, and

- Test statistics of - 1.62 (weighted) and - 2.38 (unweighted) exceeding the pre-specified boundary for the global index in an adverse direction
Why was the E+P Arm of the WHI Trial Stopped?

- Thus, early stopping was based on each of invasive breast cancer and the global index meeting criteria in the adverse direction.
- The adverse statistic for the global index was due to unfavorable cardiovascular disease results for the E+P intervention (each of CHD, stroke and PE).
- The DSMB also had available data from WHIMS on cognitive impairment (none, minor cognitive impairment, or probable dementia) to inform their early stopping discussion.
Post-Intervention Follow-up

After the trial was stopped early, WHI followed the study participants through the planned termination of the trial (March 31, 2005).

Except for stopping the intervention and unmasking, the same trial protocol was followed, such as semi-annual monitoring to identify and classify study outcomes.
Post-Intervention Follow-up - Results

• On March 5, 2008 the WHI investigators reported on health outcomes at three years after the intervention was stopped (mean of 2.4 years of follow-up)

• This is a planned point of analysis to evaluate the effects of stopping hormone therapy

• Post intervention information for the period July 8, 2002 to March 31, 2005 was available on 95% of the women
Post-Intervention Follow-up - Results

• As for the intervention phase of the trial the primary endpoints were coronary heart disease and invasive breast cancer

• A global index (GI) was used to summarize the balance of risks and benefits

• The GI includes the two primary endpoints plus stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture and death due to other causes
Pulmonary embolism

Overall

![Graph showing the proportion of pulmonary embolism over years with CEE+MPA and Placebo groups. The hazard ratio (HR) is 1.66 (1.22 - 2.25).]

After Intervention

![Graph showing a reduced proportion of pulmonary embolism over years after intervention. The hazard ratio (HR) is 1.07 (0.62 - 1.86).]

No. at Risk

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Invasive Breast Cancer

Overall

HR = 1.27
(1.06 - 1.51)

No. at Risk
CEE + MPA  Placebo
8506     8102
8328     7912
8108     7717
7794     7459
3922     3670

After Intervention

HR = 1.27
(0.91 - 2.78)

7854     7533
7466     7190
Colorectal Cancer

Overall

HR = 0.75
(0.57 - 1.00)

CEE+MPA
Placebo

After Intervention

HR = 1.08
(0.66 - 1.77)

No. at Risk

CEE + MPA
Placebo

0 1 2 3 4 5 6 7 8
Years

0 1 2
Years

8506 8353 8191 7949 4036
8102 7943 7769 7547 3728

8014 7616 7660
7294
Hip Fracture

Overall

HR = 0.78
(0.60 - 1.00)

No. at Risk
CEE + MPA 8506 8350 8186 7936 4031
Placebo 8102 7942 7771 7528 3717

After Intervention

HR = 0.92
(0.64 - 1.34)
All Cause Mortality

Overall

HR = 1.04
(0.91 - 1.18)

No. at Risk
CEE + MPA  Placebo
8506  8102
8366  7963
8218  7816
7988  7608
4066  3769

After Intervention

HR = 1.15
(0.95 - 1.39)

No. at Risk
CEE + MPA  Placebo
8052  7678
7718  7370
Global risk index

Overall

HR = 1.66
(1.22 - 2.25)

No. at Risk
CEE + MPA  Placebo
8506   8102
8158   7796
7805   7483
7363   7095
3629   3423

After Intervention

HR = 1.07
(0.62 - 1.86)

No. at Risk
CEE + MPA  Placebo
7429   7185
6930   6721
Post-Intervention – Overview of Results

• In the 3 years after stopping intervention women who previously used E+P no longer had an increased risk of heart disease, stroke, and blood clots compared with women on placebo

• The lower risk of colorectal cancer seen during the trial in women who used E+P disappeared after stopping intervention

• The benefit for fractures in women who had used E+P also disappeared after stopping hormone therapy
Post-Intervention – Overview of Results

The risk of all malignancies increased from 1.03 (0.92, 1.15) during the intervention phase to 1.24 (1.04, 1.48) in the post-intervention period (p-diff=0.08)

• This was due to increases in a variety of cancers, including lung cancer (33 lung cancer events in the E+P vs. 15 in the placebo group)

• Additional follow-up to enable more refined analyses is needed
Post-Intervention – Overview of Results

• During intervention phase excess risk of invasive breast cancer with E+P use emerged ~fourth year (HR 1.26; 1.02, 1.55)

• Post intervention, more breast cancers were diagnosed in the E+P group (HR 1.27; 0.91,1.78) but a downward inflection in the temporal trend in cumulative HRs for breast cancer was observed

• The change in HR of breast cancer post intervention is not statistically significant
Post-Intervention – Overview of Results

- After stopping the intervention all-cause mortality was somewhat higher in women who previously used E+P compared with placebo.
- Most deaths were cancer related (101 in E+P vs. 69 in placebo).
- Only 27 deaths in the E+P and 16 deaths in the placebo group were associated with breast, colorectal, endometrial, or ovarian cancer (pre-specified cancer outcomes).
Post-Intervention – Overview of Results

• Thus, the "other cancers" category accounted for a larger absolute number of deaths with a similar pattern of association

• Among the “other cancers” most were lung cancer events (33 in the CEE+MPA vs. 15 in the placebo group)

• Reflecting these individual results, the global index of risks and benefits was unchanged from randomization through the end of the post-intervention follow-up (HR=1.12, CI 1.03-1.21)
Suppl. Slides
Sensitivity analysis of the post-intervention effects

- A sensitivity analysis of post-intervention effects was requested by the journal reviewers.
- At the time the E+P trial was stopped, the mean follow-up was 5.6 years (range 3.5 – 8.5 years).
- At that point 58% of the women assigned to CEE+MPA and 62% of the women assigned to placebo were taking their study pills.
Sensitivity analysis - Continued

Population eligible for sensitivity analyses

• Women in the trial who had never stopped participating, were adherent at 80% or greater of study medications through the stopping date of July 7, 2002 and never took non-study HT were analyzed

• This corresponds to 41% of those assigned to active treatment and 47% of those assigned to placebo
Sensitivity analysis - Continued

Among the women adherent to study medication, the HR (95% CI) for combined post-intervention endpoints were as follows:

- All cardiovascular events 1.05 (0.81, 1.36)
- All cancers 1.34 (1.02, 1.76)
- All fractures 0.87 (0.69, 1.10)
- The global index 1.19 (0.95, 1.49)

Although less precise, these results are fully consistent with the estimated HRs for the entire group.
Sensitivity analysis - Continued

• The single exception was an increased risk of death from all causes during the post intervention phase for adherers originally assigned to E+P (HR=1.53, 95% CI 1.04, 2.24) compared to those assigned to placebo.

• The cumulative, annualized mortality among adherers in the active treatment and placebo groups were 0.82% and 0.61%, respectively.