August 9, 2002

Response to Women's Health Initiative Study Results by The American College of Obstetricians and Gynecologists

On July 9, 2002, the National Heart, Lung, and Blood Institute of the National Institutes of Health announced that it was halting the arm of the Women's Health Initiative (WHI) study evaluating combined estrogen and progestin use in postmenopausal women (1). This arm of the WHI study, a randomized placebo-controlled trial, assessed the effects of combined hormone replacement therapy (HRT) use in healthy postmenopausal women with an intact uterus. After review of reported data, the data and safety monitoring board of the study concluded that the risk of combined HRT use in this study population outweighed the benefits.

Study Analysis

This study is the first rigorously designed randomized controlled trial with a sufficiently large study population to investigate the relationship between HRT and the risk of cardiovascular disease and other vascular events, breast cancer, fractures, and other health outcomes. The study was not intended to measure the effect on vasomotor symptoms. To date, this study is the largest, most statistically valid, and well-analyzed research to evaluate the use of HRT in healthy postmenopausal women.

It is important to note that the results from this arm of the WHI study pertain only to women taking combined continuous conjugated equine estrogen (0.625 mg/d) and medroxyprogesterone acetate (2.5 mg/d) (Prempro®) and conclusions from this study can be applied reasonably only to this formulation. It is unclear whether these reported effects are similar for other hormone replacement regimens that differ in dosage, preparation or delivery method (eg, transdermal). However, other observational analyses indicate that caution is warranted for different preparations, and their safety should not be assumed in the absence of conclusive data. Therefore, all women taking HRT should be made aware of the reported increased risks, in particular those taking estrogen and progestin combinations.

The arm of the WHI study of estrogen-only use in women who had previously undergone hysterectomy is continuing with no reported increased risk of breast cancer. The data and safety monitoring board will continue to review data from this trial every six months.

Statistical Analysis

Statistical analysis in the current WHI study appears strong and valid. This randomized trial is the most epidemiologically robust study to date of the effects of combined continuous estrogen and progestin hormone replacement therapy on cardiovascular disease and breast cancer risk in healthy postmenopausal women. The following points about the reported results are important to note.

Concern has been expressed that a large proportion of women stopped taking the combined hormone replacement regimen during the study period. However, the rates of women discontinuing their study medication were similar both for women taking the combined estrogen and progestin and those taking placebo (42% versus 38%). This discontinuation rate of drop out also is similar to that seen in the general population of women prescribed HRT, and for both these reasons did not affect the accuracy of analysis.

Concern also has been raised that the majority of HRT is prescribed to women aged 50-59 years, but only 33% of study participants were aged 50-59 years. The reported results are applicable to this group, and the study authors are conducting further subset analyses that may clarify the risks and benefits for this younger cohort.

Although the mean age of study participants (63 years) also has been questioned, women were recruited in balanced age groups of 50-59 years, 60-69 years, and 70-79 years, This balance among ages was similar in both treatment and placebo groups, and there were ample percentages of women in the under age 60 group to make valid comparisons. This subset of women aged 50-59 is still the largest cohort of women this age to be studied in a randomized trial of HRT.

Study Results

Cardiovascular Disease

The WHI study showed no benefit for the prevention of coronary heart disease as the main outcome measure studied and, in fact, indicated a small but significant increased risk of cardiovascular events for women taking this combined estrogen and progestin therapy. Women taking the combined hormone therapy had a 22% increased risk of cardiovascular disease, including a 29% increased risk of coronary heart disease (hazard ratio 1.29 [95% confidence interval (CI) 1.02-1.63]). Although the risk is increased with estrogen and progestin use, the absolute increased risk for individual women is small, estimated to be 7 more coronary heart disease events (37 versus 30) per 10,000 women per year, and this risk is cumulative over time. Previous observational studies have suggested a cardiovascular benefit for women taking HRT. However, the positive effect seen for women taking HRT in these earlier studies now seems likely to be due to some other characteristic in the study group, in particular the possibility that those who self-selected to take HRT were healthier overall.

Breast Cancer

Results from this prospective randomized trial confirm an observed trend reported in previous research of an increased risk of breast cancer with HRT use. Based on the WHI study results, there is a 26% increased risk of invasive breast cancer with combined estrogen and progestin use (hazard ratio 1.26 [CI 1.00-1.59]). The rates of breast cancer in the study population increased over time at a faster rate than would be explained by an increase in a woman's age alone. It is important to note that although the individual increased risk for breast cancer is small, estimated at 8 additional new cases (38 versus 30) per 10,000 women per year, the impact from a public health perspective is significant, and this risk is cumulative over time.

Investigators illustrate results in Kaplan-Meier graphs of cumulative hazards (Fig. 1). The divergence of the Kaplan-Meier curves for breast cancer between the intervention and placebo groups after four years of follow-up shows a clinically apparent increase in the presence of invasive breast cancer for women taking combined estrogen and progestin. It cannot be inferred from this depiction of cumulative risk, however, that any period of use of combined continuous hormone therapy is absolutely safe and has no impact on the development of breast cancer in the first four years of treatment. Breast cancer takes several years to develop and in this trial it became clinically apparent at four years. Therefore, the biological effects of estrogen treatment on tumor growth may be important to consider but these effects are not addressed in this study.

Stroke and Pulmonary Embolism

A reported 41% increased risk of stroke (HR 1.41 [CI 1.07-1.85]) and a more than two-fold increased risk of pulmonary embolism (HR 2.13 [CI 1.39-3.25]) in women taking combined continuous estrogen and progestin therapy in the WHI study support results from previous research. And, as with other risks reported with combined estrogen and progestin, the absolute risk to individual women is low; 8 additional cases of stroke (29 versus 21), and 8 additional cases of pulmonary embolism (16 versus 8) per 10,000 women per year. However, this risk is cumulative. The elevated risk of stroke in the intervention group appears in the second year of the study, continues through year five, and is not explained by risk factors such as higher blood pressure, age, race, or ethnicity, as these were similar in both groups. It is important to note that for oral contraceptive use, the increased risk of thromboembolic events in the first year of use is often a result of genetic predisposition, and the risk with continued use diminishes thereafter. In contrast, the increased risks of stroke and pulmonary embolism appear to be a factor of increasing age coupled with combined estrogen and progestin use.

Fractures

Results of this study support previous research showing a decreased risk of vertebral and other osteoporotic fractures with HRT use. Rates of hip fracture were reduced by 34% (HR 0.66 [CI 0.45-0.98]) in this study, confirming the benefits of estrogen and progestin therapy on bone mineral density (2). There were fewer hip fractures in women taking combined HRT, 5 per 10,000 women per year (10 versus 15). The WHI study is the largest clinical trial to date that demonstrates the protective effect of HRT on hip fractures and total fractures.

Colon Cancer

The study results suggest a benefit in the prevention of colorectal cancer with combined

the women taking combined estrogen and progestin. The study analysis indicates 6 fewer cases (10 versus 16) of colorectal cancer per 10,000 women per year. The mechanism of this interaction in unclear, but appears to be biologically plausible.

Recommendations For Hormone Replacement Therapy Use

It is important to reemphasize that this trial from the WHI studied only one formulation of hormone replacement therapy (0.625 mg/d conjugated equine estrogen and 2.5 mg/d medroxyprogesterone acetate), and results are applicable only to this regimen. The ability to extrapolate results to other formulations is limited. The following recommendations are based on an ACOG expert panel review of the best currently available data.

The decision about use of HRT requires evaluation of the risks and benefits for each individual woman. For women currently using HRT, it is important to assess their reasons for use and to evaluate potential risks, benefits and alternatives.

In the past, short-term use has generally been defined as use of HRT for five years or less, most often prescribed to treat acute menopausal symptoms. There are no data from this study to establish clearly what constitutes safe short-term use. An increase in the diagnosis of invasive breast cancer appears after four years of use, but the influence of continuous estrogen and progestin therapy on breast cancer is unclear after even one year of use due to the biology of breast cancer.

Women who take HRT for the management of vasomotor symptoms should be encouraged to take it for as short a time as possible and to use the lowest effective dose. Long-term use of continuous combined estrogen and progestin therapy should be discontinued in asymptomatic patients. Patients interested in HRT for long-term use should be counseled about the risks and benefits of use, and about available alternatives. After counseling, women who want to continue taking HRT for general improvement in well-being may do so provided they understand the potential risks. In addition, for a postmenopausal woman with a uterus, switching from an estrogen and progestin combination to unopposed estrogen is not recommended, due to the increased risk of endometrial cancer (3). Women who choose to continue HRT for quality-of-life benefits should reevaluate the need for HRT periodically. If they decide to continue, they should be encouraged to use the lowest possible dose.

HRT has been shown to be the most effective treatment for symptomatic relief of vasomotor symptoms including hot flashes (4). For patients who decide not to use HRT, nonhormonal alternatives such as selective serotonin reuptake inhibitors, clonidine, or Bellergal-S may be helpful for this indication (5). Other agents such as black cohosh have been proposed; however there are conflicting data on effectiveness, and safety profiles are not established.

Based on the WHI data, combined continuous estrogen and progestin therapy is no longer recommended for the prevention of cardiovascular disease, and if previously prescribed for that purpose should be discontinued. In fact, the risk of stroke and pulmonary embolism appear to increase within the first two years of the study. Alternatives for improved cardiovascular health, including lifestyle modifications such as exercise, smoking cessation, and weight loss, should be

encouraged for all women. The use of cholesterol-lowering medications such as statins and the need for treatment of hypertension should be evaluated for each individual patient.

For patients with osteoporosis, other preventive therapies such as bisphosphonates and selective estrogen receptor modulators are available. However, for women at risk of osteoporosis who also have vasomotor menopausal symptoms, HRT can be of benefit.

For genitourinary symptoms associated with menopause, estrogen and progestin have been shown to be beneficial. Alternatives to oral delivery of estrogen, such as vaginal creams, tablets or rings, are usually effective. Although these delivery methods do not increase systemic estrogen levels appreciably, there are little data to assess the long-term safety of these alternatives.

For women with a family history of colorectal cancer, the risk-benefit ratio for use of combined estrogen and progestin remains unclear. While there appears to be a benefit with hormone use, the study results do not appear sufficiently robust to recommend its use solely for the prevention of colorectal cancer. In addition, routine periodic screening such as by fecal occult blood testing, flexible sigmoidoscopy, or colonoscopy will help to prevent colorectal cancer by identifying polyps that can be removed before they become cancerous.

The WHI study did not address possible cognitive indications for HRT such as the prevention of Alzheimer's disease, or mood disturbances. Other studies on these indications are inconclusive.

A determination of appropriate follow-up for patients who choose HRT is also important. Periodic reassessment of the need for HRT is recommended at least at every annual visit or more frequently if indicated.

Patients should use the lowest dose of HRT that provides relief of symptoms. Some limited data suggest that the adverse effects of HRT may be dose related (6). In addition, patients may find fewer adverse effects with discontinuation of use on a lower dose.

For women planning to discontinue use of hormone therapy, there are no definitive data to guide this process. Whether stopping abruptly or discontinuing use incrementally, some patients will develop vasomotor symptoms and will have to restart medication. Physicians should be aware that when discontinuing HRT, women may also experience vaginal bleeding, which may at times be heavy. If symptoms recur, more gradual withdrawal should be considered.

Glossary

Absolute Risk – The observed or calculated probability of an event in a population under study (7).

Confidence interval – Depicts the range within which the value being measured is likely to fall, within a specified probability. In general, the wider the confidence interval the less precise the estimate (8).

Nominal confidence interval – The traditional approach to presenting confidence intervals, used to describe the variability in the estimated effects. For a 95% nominal confidence interval, there is a 5% probability that this interval does not include the true value (1).

Adjusted confidence interval – A confidence interval that is modified to take into consideration factors that may cause errors in estimation by the experiment. Two corrections were incorporated--a Bonferroni correction that addresses multiple disease comparisons, and an O'Brien-Fleming correction that corrects for multiple analyses over time. These adjustments are designed to ensure that there is only a 5% chance that any of these intervals exclude the true value. Because both adjustments were used simultaneously, the confidence intervals are wider. This approach results in more conservative conclusions regarding actual differences between groups (1).

Global index – A summary measure of all of the events that were specified in the monitoring plan to be of interest: coronary heart disease, stroke, pulmonary embolism, breast cancer, endometrial cancer, colorectal cancer, hip fractures, and death from other causes. For simple frequencies, these were computed as the number of women who had any of these events. For survival type analyses, the response for each woman was the time from randomization to the first of any of these events (1).

Hazard ratios – Theoretical measure of the number of new cases that occur per unit of population time, eg, person-years at risk (7).

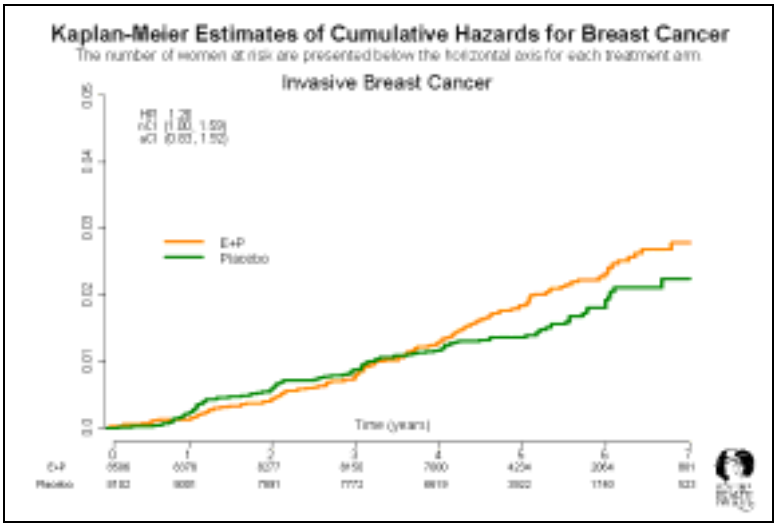
Kaplan-Meier method – a statistical method used in survival analysis to estimate the probability of experiencing an event, such as death, at different times in the study (9).

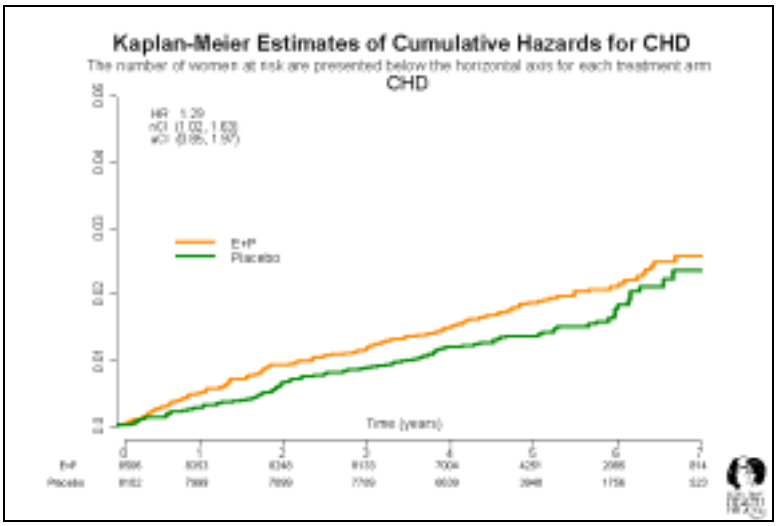
Observational study – An epidemiologic study that does not involve any intervention, experimental or otherwise. Such a study may be one in which natural history is observed or changes or differences in one characteristic are studied in relation to changes or differences in other(s), without the intervention of the investigator (7).

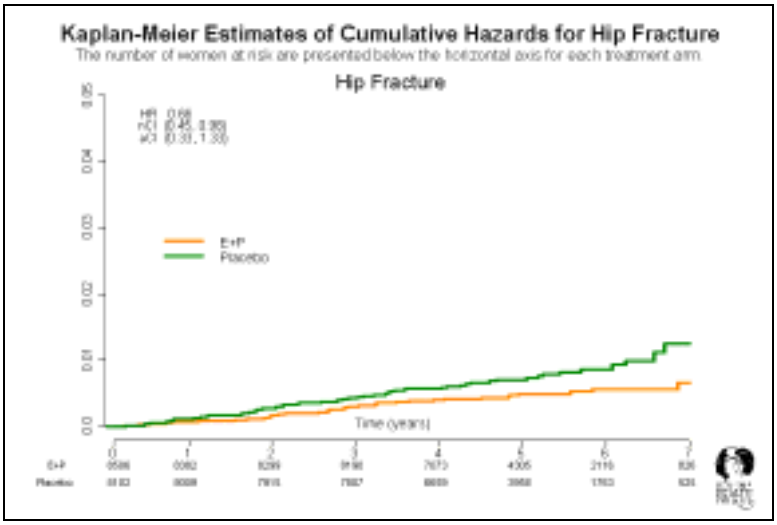
Randomized controlled trial – A clinical experiment in which subjects are prospectively, randomly allocated to receive (treatment) or not receive (control) a therapy or intervention. Within the limits of chance variation, random allocation should make the control and experimental groups similar at the start of an investigation and ensure that personal judgment and prejudices of the investigator do not influence allocation. Randomized controlled trials are generally regarded as the most scientifically rigorous method of hypothesis testing available in evidence-based medicine (7).

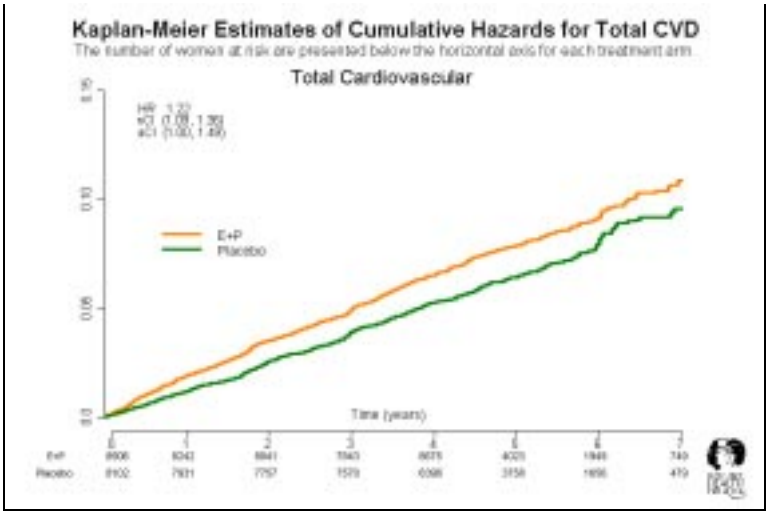
Relative risk – The ratio of disease or death rate among those exposed to a risk factor, compared with the risk among the unexposed. Alternatively, the ratio of the cumulative incidence rate in the exposed to the cumulative incidence rate among those not exposed. If the relative risk is above 1.0, then there is a positive association between the exposure and the disease; if it is less than 1.0, there is a negative association (7).

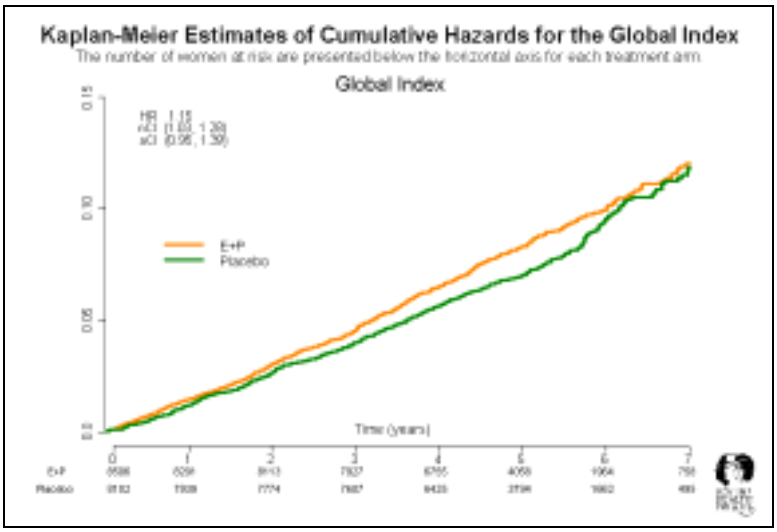
Figure 1


Kaplan-Meier Estimates of Cumulative Hazards for Breast Cancer
The number of women at risk are presented below the horizontal axis for each treatment arm
Invasive Breast Cancer
E+P
Placebo
Time (years)


Kaplan-Meier Estimates of Cumulative Hazards for CHD
The number of women at risk are presented below the horizontal axis for each treatment arm
CHD
E+P
Placebo
Time (years)


Kaplan-Meier Estimates of Cumulative Hazards for Hip Fracture
The number of women at risk are presented below the horizontal axis for each treatment arm
Hip Fracture
E+P
Placebo
Time (years)





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