

## Oh No! Not Another Scare about Hormone Therapy and Breast Cancer!

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In October 2010, many of you have heard the ominous headlines proclaiming “hormone therapy doubles risk of death from breast cancer” all over the television and internet. Unfortunately, this represented yet another example of the news media reporting data in a skewed manner, adding to the already deep confusion about menopausal hormone therapy.

While I certainly would not minimize the seriousness of breast cancer risk, it is vitally important to take a critical look at the recent study in question so that women are well equipped to make their own informed decision about hormone therapy.

### Study:

- "Estrogen Plus Progestin and Breast Cancer Incidence and Mortality in Postmenopausal Women", published in JAMA on 10/20/10 (Chlebowski RT, et al)
- This new publication from the WHI focused on breast cancer incidence and mortality associated with using combined conjugated equine estrogens and medroxyprogesterone acetate (Prempro; CEE 0.625 mg/d plus MPA 2.5 mg/d), a mean intervention time of 5.6 years (range, 3.7-8.6 years) and followed a mean total of 11 years.

### Design, Setting, and Participants:

- A total of 16 608 postmenopausal women aged 50 to 79 years with no prior hysterectomy from 40 US clinical centers were randomly assigned to receive combined conjugated equine estrogens (Premarin) 0.625 mg/d plus medroxyprogesterone acetate (Provera) 2.5 mg/d, or placebo pill.
- After the original trial completion date (March 31, 2005), re-consent was required for continued follow-up for breast cancer incidence and was obtained from 12 788 (83%) of the surviving participants.

### Findings:

- After a total mean follow-up of 11 years, there was an increased finding of invasive breast cancer in women taking estrogen plus progestin compared with placebo (385 cases [0.42% per year] vs 293 cases [0.34% per year], respectively; Hazard Ratio (HR), 1.25; 95% confidence interval [CI], 1.07-1.46;  $P = .004$ ). Frequency of mammography was the same in both the combined hormone and placebo groups (86%).
- A significantly larger proportion of women with breast cancers had positive lymph nodes in the combined hormone therapy group compared with the placebo group (81 [23.7%] vs 43 [16.2%], respectively, with a HR of 1.78; 95% CI, 1.23-2.58;  $P = .03$ ). The breast cancers detected were similar in histology and grade to breast cancers in the placebo group.
- Breast cancer mortality was increased in women taking combined estrogen plus progestin compared with women taking placebo. The study reported 25 deaths [0.03%

per year] vs 12 deaths [0.01% per year], with a Hazard ratio of 1.96; 95% CI, 1.00-4.04;  $P = .049$ ). This represents an absolute risk of 2.6 deaths from breast cancer (in the combined hormone group) vs 1.3 deaths (in the placebo group) per 10,000 women per year.

- There were more deaths from all causes occurring after a breast cancer diagnosis (51 deaths [0.05% per year] vs 31 deaths [0.03% per year]; HR, 1.57; 95% CI, 1.01-2.48;  $P = .045$ ) in women taking combined estrogen and progestin compared with placebo. This represents 5.3 vs 3.4 deaths per 10,000 women per year, respectively.

According to the North American Menopause Society (NAMS) statement, “the primary finding was of 1 to 2 extra deaths from breast cancer per 10,000 women per year. Specifically, for every 10,000 women in the study who were randomized to placebo, there were 1.3 deaths from breast cancer per year. For every 10,000 women randomized to combined hormone therapy, there were 2.6 deaths from breast cancer per year. These results apply to combination estrogen plus progestin and not to estrogen alone. The WHI found no increase in breast cancer risk with estrogen alone (without a progestin) among women with hysterectomy over an average of 7 years of randomized treatment.”

NAMS further advised in their statement that “clinicians can help women put the breast cancer risk into perspective by informing them that the increased risk of breast cancer using estrogen plus progestogen for 5 years is very similar to the increased risk of breast cancer associated with having menopause 5 years later. This increased risk of breast cancer occurs with a woman’s own internal, natural estrogen and progesterone.”

**Dr. James Simon, medical director of [www.menopausewise.com](http://www.menopausewise.com) added this information:**

“The big problem with the primary data set first reported in 2002, and this publication as well is that the Estrogen + Progestogen treated group did not have an equal breast cancer risk to the placebo group at baseline (when they entered the study). When baseline risk for breast cancer is considered and adjusted for, the 5.6 years of E+P treatment did NOT show an increased risk of getting breast cancer. It isn’t clear whether the mortality increase in this manuscript can likewise be attributed to the differences in baseline breast cancer risk or not.”

**Dr. Huang’s comments:**

First of all, the study in the spotlight was NOT a new study. It was a follow-up study of the WHI (Women’s Health Initiative). Remember the Women’s Health Initiative (WHI) study that was all over the news in 2002 and scared many US women off hormone therapy? The study that had subsequently been criticized for its multiple flaws, the main one being the average age of study participants being 63 with majority being 10-20 years beyond their last menstrual period? Yes, the new information that created the recent headlines stemmed from THAT study!

Here is a reminder of the flaws in the WHI study:

- The average age of WHI participants was 63, with the oldest participant being aged 79 at the beginning of the study. On average study participants were 12 years after their menopause. Approximately 70% were 60-79 years old. Only 15% of the participants were in the first 5 years post-menopause.
- The women assigned to HT (hormone therapy) were not so “healthy”. 35% of them were overweight (BMI 25-29) while 34% were obese (BMI  $\geq$  30). 36% had hypertension. 40% were ex-smokers and 10% were current smokers. Some study participants actually had history of coronary artery bypass surgery and myocardial infarctions.
- In the WHI study, ITT (intention to treat) analysis was used: meaning that if a woman was assigned to HT group, even if she stopped her own study medication at any time in the study, she would have been still analyzed as part of the HT group.
- The validity of the statistical analyses was intensely debated. If one looks at the adjusted odds ratios, then the study findings were no longer significant.
- Only one form of HT (oral conjugated equine estrogens and medroxyprogesterone) was studied in WHI. Effects of other forms of HT including “bioidentical hormones” – estradiol and progesterone, and different routes of administration (eg. transdermal versus oral) were not addressed. There is evidence supporting differential effects of different hormone preparations. The E3N cohort study in France with 80,377 women showed the association of estrogen-progestagen combinations with breast cancer risk varied significantly according to the type of progestagen: the relative risk was 1.00 (0.83–1.22) for estrogen–progesterone and 1.69 (1.50–1.91) for estrogen combined with synthetic progestagens.

After WHI was terminated in 2002, study participants were told to discontinue study medications and those who consented to be in the follow-up study continued to be observed. There were no longer two distinct groups to be compared! Just as in the original WHI, statistical analysis utilized the “intent to treat” method which meant that no matter whether the participants were on hormone therapy or not at the conclusion of the follow-up study, their results were analyzed with the initial groups to which they were assigned. It is also important to remember that the study participants were on average aged 63 in the 1990s when WHI began, in 2009 when the follow up study was concluded these women were in the 70s and 80s. Cancer and mortality are expected to rise as a population advances in age. The study authors indicated the accurate determination of the cause of death after breast cancer diagnosis was problematic given the potential interaction of common comorbidities with breast cancer treatments.

Another important point to consider is the way numbers are presented can drastically affect its impact on the audience. The case in point is the concept of relative risk versus absolute risk. The headlines focused on the relative risk of breast cancer death being double in the HT group as compared to the placebo group. But if you look at the absolute risk, there were actually 2.6 and 1.3 deaths from breast cancer per 10,000 women per year in the HT group and the placebo group respectively. Now you must see the second way of presenting the same data is not quite as fear-generating as the first!

Even the study authors admitted that “for the breast cancer mortality analyses, the wide CIs (confidence intervals) with lower limits close to 1.0 imply caution in interpretation”. The wider confidence intervals mean the less certain one can be about the results. A relative risk of 1.0 means no difference between the treatment group and the placebo group, therefore CIs that approach or include 1.0 would cast serious doubt that any real difference exists between the study groups.

While I would never downplay the seriousness of breast cancer risk, it is not fair for women who need to make informed decisions about whether to take hormone therapy to be bombarded with information based on a study that had serious flaws making its applicability questionable. The skewed presentation of data by the media to create attention-grabbing headlines added insult to injury.

While estrogen is always in the spotlight in discussions about breast cancer risk, it is important to realize that multiple factors affect breast cancer risk. For example, a weight gain of more than 20lbs in adulthood, never having had children, beginning menstrual periods at a younger age or late menopause, and consumption of more than 6oz of wine a day have all been shown to increase breast cancer risk by approximately 30-40%. The process of cancer development can be described by the “multiple-hit theory”, meaning that many different insults (such as environmental toxins, radiation, lifestyle factors, genetic propensity, stress etc) to the body happen before our surveillance and repair mechanisms fail and cancer cells develop and proliferate. Hormone therapy would only be one of the many pieces of the big puzzle in the case of breast cancer pathogenesis.

My recommendation about hormone therapy remains unchanged – each individual woman needs to look at her own symptoms, risk factors and philosophies to make her own decision about menopausal hormone therapy, with input from her trusted personal physician. It is important for women to listen to their own bodies and respect their own unique constitution. There should not be a sweeping statement about HT that all women should follow. Like many other important things in life, the decision about HT is never a black and white one.