

American Society for Reproductive Medicine Menopausal MEDICINE

Volume 11, Number 1, Spring 2003

FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

WHI Response to Goodman, Goldzieher and Ayala's Critique of the Women's Health Initiative Report on the Risks and Benefits of Estrogen Plus Progestin



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Editor's Note: The following is a rebuttal to "Critique of the Report from the Writing Group of the WHI," which appeared in the previous issue of Menopausal Medicine.

We appreciate the interest and scrutiny that our report¹ on the benefits and risks of combined conjugated equine estrogen (0.625 mg/day) plus medroxyprogesterone acetate (2.5 mg/day), hereafter referred to as E+P, is receiving from clini-

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icians, scientists, and the public. The quality of the debate has made clear that each of these communities appreciates the critical role of well-conducted randomized controlled trials for reliably addressing questions having such major clinical and public health implications. In fact, one could argue that it is unfortunate that data from large randomized, controlled trials are only recently coming available for postmenopausal hormone therapy (HT), when some such preparations have been widely used for decades.

We also appreciate Drs. Goodman, Goldzieher, and Ayala's (hereafter the authors) effort² to "publicly set the record straight" concerning the overall risks and benefits of E+P. However, their commentary is inaccurate in its characterization of the WHI randomized controlled trial of E+P and of the findings over an average of 5.2 years of follow-up as reported last July.¹

We begin by noting some points of agreement with the authors. First, we agree that a follow-up period of 5.2 years, on average, leaves important questions open concerning the longer term risks and benefits of a few years of E+P use. In fact, we will continue to follow the E+P cohort with quality-controlled outcome ascertainment at least through 2005, the conclusion of the initial phase of WHI. A proposal for an additional five years of follow-up has been developed by study investigators. We also agree that no single

FROM THE EDITOR

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The results of the Women's Health Initiative reported in 2002 have led to a major discussion regarding the counseling of postmenopausal women. This prospective, randomized clinical trial has evoked a significant reaction in the medical/scientific community. In our last issue, Drs. Goodman and Goldzieher addressed concerns regarding the validity of the data based on the statistical analysis of the data.

Susan L. Hendrix, D.O., and Ross L. Prentice, Ph.D., discuss the design, statistical analysis, and outcomes of the WHI trial in terms of clinical decision-making. It is apparent that there are several points that are debatable. Physicians should understand that often we require more than one study to confirm the findings. It is important that the reader carefully review this article and the Goodman and Goldzieher article in order to comprehend that no trial is completely accurate and without problems.

Leon Speroff, M.D., rejoins us to present his views on the issue of hormone therapy and breast cancer based on the results of the WHI. Dr. Speroff, in his usual well-organized, thoughtful manner, discusses the clinical implications of the WHI data and how it is applicable to the patient across the desk.

Noel S. Weiss, M.D., Dr.Ph.H., offers commentary on the findings of endometrial cancer from the WHI data. He points out that there is a weak negative association between continuous combined hormone therapy and endometrial cancer. At issue is whether these data are applicable to other estrogen and progestin regimens used in postmenopausal women.

There will probably be no further large randomized clinical trials of hormone therapy in postmenopausal women. We anticipate the publication of further data from the WHI trial over the next several years. It is important that the physician be cognizant of these results. A critical reading of all of the articles is recommended in order to be able to adequately counsel your patients who are seeking answers to their questions.

Menopausal Medicine

A Newsletter of the
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*The ASRM is pleased to acknowledge the generous
contribution of Wyeth-Ayerst Laboratories toward
the publication of this newsletter.*



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index, such as our global index (defined by the occurrence of coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer, hip fracture, or death from other causes during trial follow-up) is fully adequate to summarize the health risks and benefits of E+P treatment. Reports on quality of life, hormone-related symptoms, dementia, and diabetes, among others, can be expected from the E+P trial in upcoming months and will help to provide a more comprehensive view of the risks and benefits of five years of E+P use. We also agree that a woman's choice concerning E+P use, and the dosage and duration of any such use, should be fully informed by her personal physician. We hope that our data on the effects of the particular E+P preparation for an average five-year period will be helpful in this dialogue. As we have discussed,¹ the effects we have reported on cardiovascular disease, cancer, fracture, and mortality are fairly modest in terms of absolute risk, but the population implications for several million users, and potential users, are substantial.

Now we will address points of lesser agreement. First, we should note that there are quite a few instances where the authors have not accurately described the WHI design or protocol. These begin in the second sentence where it is asserted that the planned E+P sample size was 19,000, whereas the actual projected sample size was 15,125 (55% of the 27,500 in the overall HT trial) as compared to 16,608 actually enrolled. The same sentence states that women with severe menopausal symptoms were excluded from the E+P trial. In fact, menopausal symptoms per se were not an exclusionary criterion. However, women using HT at screening for the WHI trial were only eligible if they chose to discontinue this treatment and to undertake a three-month "washout" period. Hence, women having severe hot flashes at screening were presumably less likely to make themselves available for randomization. Note that 75% of the women had never been on any hormones prior to WHI, and the results apply to this group as well.

Such inaccuracies continue throughout the authors' commentary. For example, the E+P trial did not "focus on" the 60 or older age group. Rather, age-specific target sample sizes were specified toward assuring an informative benefit versus risk statement over the 50 to 79 age range, leading to the enrollment of 5,521

women (33% of total) who were 50 to 59 at baseline. Additionally, unblinding of study medication for women experiencing excessive bleeding was a fundamental safety element of the WHI protocol rather than a "departure from the study treatment protocol" as the authors suggest. Similarly, the external Data and Safety Monitoring Board's (DSMB) recommendation to stop active intervention in the E+P trial is not adequately described as a "statistical decision" since the statistical procedures were adopted by the DSMB as guidelines rather than rules, and since the Board reviewed data on a broad range of clinical outcomes and symptoms as well as pertinent external data in reaching their recommendation. We recommend that readers rely on WHI publications on design and monitoring^{1,3,4} for points of detail concerning the E+P trial.

Now we would like to address the issues of reporting and interpreting E+P trial results over an average of 5.2 years of follow-up. Here we will provide our perspective on the validity of results from E+P trials, on the statistical significance of findings to date, and on the extent to which our E+P trial provides primary prevention information, since those appear to be the authors' most substantial concerns.

The authors state that because treatment was discontinued prior to planned study termination, study power is reduced and "...the study is flawed and may be invalid." Such early termination, of course, impacts the potential for longer term benefits versus risks assessment, but it does not affect the validity of comparisons over the reported average 5.2 years of follow-up. The authors also assert that "WHI may be flawed" because the study included some women who were not "healthy" at baseline. The characteristics of the study cohort do affect the study implications but not the validity of study comparisons for the population of women similar to those enrolled in the E+P trial. Importantly, 93% of the women had no history of cardiovascular disease. In fact, WHI women are very healthy with a markedly lower risk for heart disease than HERS women. The annualized rate of myocardial infarction/coronary heart disease (MI/CHD) death in the placebo group was 0.3% in WHI¹ and 3.1% in HERS.⁵

The authors note that we did not have recent clinical outcome data on 3.5% of trial women, and they suggest that differential disease occurrence in such women

could “have a major impact on conclusions.” However, the fact that the fraction of women without recent outcome data was similar by treatment arm (3.6% in active and 3.4% in placebo), that most such women remain blinded to their treatment, and that only a small fraction of such women can be expected to have experienced any important disease diagnosis since their last contact with WHI argues against any major impact. Similarly, the authors note that about 40% of participating women had stopped taking their assigned pills, at least temporarily, prior to the termination of treatment in the E+P trial, and they raise related questions about bias and confounding. The results presented in our *JAMA* paper were based on comparisons between the active and placebo group. Drop-out from intervention in one or both randomization groups reduces power but does not affect the validity of tests to compare disease occurrence between groups. Relative risk estimates will typically be affected by lack of intervention adherence and, for this reason, we presented sensitivity analyses^{1*} indicating that hazard ratios were more extreme when the analyses were conducted with women who took their pills. The similarity of intervention adherence rates in the active and placebo group attests to well implemented procedures for managing “adverse phenomena,” with or without protocol-consistent unblinding, in both treatment arms.

The authors also note that unblinding rates were noticeably higher in the active versus the placebo arms, primarily in response to persistent vaginal bleeding, and they assert that “the clinical staff obtaining follow-up data was no longer blinded and bias could have been introduced.” In fact, even though study gynecologists were unblinded as necessary for management of bleeding, outcomes staff and physician adjudicators remained blinded to treatment assignment and generally were not involved in participant management.

Now we would like to discuss the statistical significance of the study findings. The nominal 95% confidence intervals reproduced by the authors in their Table 1 provide evidence of risk for total CHD (and non-fatal CHD), total stroke (and non-fatal stroke), pulmonary embolism, deep vein thrombosis, and, marginally, breast cancer. These are the traditional types of confidence intervals typically reported in clinical trials and observational studies. We also included a less tradi-

tional adjusted confidence interval to help readers understand that these confidence intervals, as well as the nominal 95% confidence intervals providing evidence of benefit for hip, vertebral, and other fractures and for colorectal cancer reproduced by the authors in their Table 4, do not acknowledge all sources of random variation in the data. For the indices featured in the trial monitoring guidelines (coronary heart disease, breast cancer, global index), these wider intervals acknowledge the fact that data are examined biannually by the DSMB and that an adjustment is needed if one wishes to assure that there is less than a 5% probability that any such confidence interval will exclude 1.00 under the null hypothesis. For the other outcomes that contribute to our global index, this same source of variation is acknowledged. An additional adjustment is made to ensure that there is less than a 5% probability that any such confidence interval across the multiple time points, and across the various outcomes, excludes 1.00 under the null hypothesis. Hence these adjusted intervals present a very conservative view of the data, and it is not accurate to assert for a given outcome that evidence for an effect is lacking because the corresponding adjusted confidence interval includes 1.00.

Incidentally, the authors’ statement that significance is routinely reported when hazard ratios exceed 1.5 has no basis, known to us, in statistical theory or application, nor does their apparent assertion that significance would not be claimed if the confidence interval came close to excluding 1.00. It can also be commented that even though the hazard ratios presented were developed under proportional hazards assumptions, these ratios can be regarded as estimates of an average hazard ratio over the study follow-up period.

Finally, we will touch on the issue of the extent to which the E+P trial can be regarded as a primary or secondary prevention trial, especially regarding coronary heart disease. This question is primarily of etiologic interest, since for clinical and public health purposes, trial results are relevant to the population of postmenopausal women, similar to those studied in WHI, regardless of whether or not the observed effects are affected by the presence of clinical or preclinical disease. The etiologic question cannot be very fully addressed with available data since measures of coronary atherosclerosis were

generally not available for participating women. However, atherosclerosis begins in childhood, and thus many peri- or immediately postmenopausal women would be expected to have significant atherosclerosis. The fact that we did not observe a difference in CHD hazard ratios according to whether or not participating women had a coronary event prior to enrollment in the WHI, or according to their age strata (50s, 60s, or 70s) at the time of enrollment, suggests that the state of coronary arteries at the time of initiation of E+P therapy may not relate strongly to the E+P hazard ratio. We are not able to rule out, however, that results following a five-year intervention period may differ from those we reported¹ if a large trial were conducted in recently postmenopausal women known to have excellent cardiovascular health at enrollment.

From my view, WHI makes the “practice of menopausal medicine” much more straightforward. The WHI randomized trial of estrogen plus progestin provides the strongest data available to date and guides practice by giving us real risk: benefit estimates to be used to counsel our patients before we make treatment decisions. The FDA estimates there are 6 million users of PremPro^{®6} in the United States. This would potentially translate into an additional 4,200 heart attacks, 4,800 strokes, 4,800 pulmonary emboli, and 4,800 invasive breast cancers more per year in our patients over 50 years old. Although the risk is small for any one woman, these risks are serious and we have to ask under what circumstances a woman should accept any risk. WHI tells us there is no role for hormone therapy in women without menopausal symptoms. For the individual woman with menopausal symptoms, the decision to use combined hormones for hot flash relief must be weighed against these small but real risks.

We thank Drs. Goodman, Goldzieher, and Ayala for their interest in the WHI trial and their efforts to grapple with these complex issues, and we thank *Menopausal Medicine* for the opportunity to provide this response.

* Follow-up time was censored six months after a woman stopped taking at least 80% of her study pills.

REFERENCES

1. Writing Group for the Women’s Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative ran

domized controlled trial. *JAMA*. 2002;288:321-333 (Reprinted)

- Goodman D, Goldzieher J, Ayala C. Critique of the Report from the Writing Group of the WHI. *Menopausal Medicine*. 2003;10:1-4.
- The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19:61-109.
- Freedman LS, Anderson G, Kipnis V, et al. Approaches to monitoring the results of long-term disease prevention trials: examples from the Women's Health Initiative. *Control Clin Trials*. 1996;17:509-525.
- Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998;280:605-613.
- Wyeth-Ayerst, St. Davids, PA.

Susan Hendrix, D.O., has revealed the following potential conflicts of interest: Grant/Research support from Bristol Meyer Squibb, 3M, Organon, Merck & Co., TAP, Wyeth-Ayerst, GlaxoSmithKline; Consultant for Lilly, Merck, Organon, Proctor & Gamble, GlaxoSmithKline; and Speaker's Bureau for Lilly, Merck, 3M, and Pfizer.

The WHI and Breast Cancer: What Does It Mean?



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On May 31, 2002, the Data and Safety Monitoring Board (DMSB) made its periodic review of the data accumulated by the Women's Health Initiative (WHI). The DMSB made two recommendations that were made public on July 9, 2002:

- To discontinue the trial arm administering daily 0.625 mg conjugated estrogens combined with 2.5 mg medroxyprogesterone acetate or placebo.
- To continue the trial arm comparing daily unopposed estrogen (0.625 mg conjugated estrogens) with placebo in women with hysterectomies.

The combined estrogen/progestin arm was discontinued after an average of 5.2 years of follow-up because of an increase

in invasive breast cancer that approached, but did not reach, statistical significance. The WHI enrolled participants between 1993 and 1998 at over 40 sites and was scheduled to end in 2005. The statistical parameters for benefit or harm were established in 1997 early in the study. When the increase in breast cancer exceeded the predetermined boundary, the DMSB was obligated to recommend discontinuation of this arm of the trial. The released results are in Table 1.¹

For several years, I have argued that the lack of agreement, uniformity, and consistency among more than 60 case-control and cohort studies is a strong reason that the risk of breast cancer associated with hormone therapy has to be a small one. The WHI results support that conclusion, amounting to a 26% increase, an attributable risk of eight additional cases per 10,000 women per year, a result that trended toward statistical significance. I have further argued that those studies reporting an increase in risk could be reflecting hormonal effects on pre-existing tumors. Is that a possibility in the WHI results? An analysis year-by-year (Table 2) is helpful.

It is apparent that the breast cancer results are heavily influenced by years four and five. Remember that the growth of breast tumors is slow (it takes 10 years for a malignant cell to become clinically detectable at 1 cm diameter). The WHI breast cancer results are consistent with hormonal stimulation of pre-existing tumors. Notice that the hazard risk returned almost to 1.0 in year six!

Prior to the WHI publication, the reference most cited on this subject was the reanalysis of the world's data in 1997. A team of epidemiologists invited all investigators who had previously studied the association of postmenopausal hormone use and the risk of breast cancer (51 studies) to submit their original data for a collaborative combined reanalysis, an undertaking more rigorous than a standard meta-analysis. This analysis reached the following conclusions:²

- Ever users of postmenopausal hormones had an overall increased relative risk of breast cancer of 1.14.

- Current users for five or more years had a relative risk of 1.35 (C.I. = 1.21-1.49), and the risk increased with increasing duration of use.
- Current and recent users had evidence of having only localized disease (no metastatic disease), and ever users had less metastatic disease.
- There was no effect of a family history of breast cancer.
- There was no increase in relative risk in past users.

The most compelling reason to believe that long-term use of postmenopausal estrogen increases the risk of breast cancer is the inherent biologic plausibility. Factors known to increase a woman's exposure to estrogen are known to increase the risk of breast cancer; e.g., age of menarche and age of menopause. Indeed, in the 1997 reanalysis, the authors make a point of demonstrating that the quantitative effect of their conclusion is similar to extending the age of menopause. Many clinicians are attracted by the logic in this comparison; however, the steady exposure to postmenopausal estrogen is not exactly the same as extended exposure to cyclic ovarian function.

The most recent report on this subject is a large population-based, case-control study funded by the NIH.³ This study found a statistically significant increased risk of breast cancer associated with five or more years use of continuous combined estrogen-progestin therapy (1.54; CI=1.10-2.17) and further concluded that there was a statistically significant trend for increasing risk with longer duration of treatment. However, inexplicably the investigators failed to adjust for important differences between the hormone users and the controls, specifically a greater prevalence of a family history of breast cancer and alcohol consumption among the hormone users and more pregnancies before the age of 25 among the controls. In addition, corrections were not made for the use of oral contraceptives and recent mammography. There was a surprising reduction of breast cancer risk (statistically significant) associated with less than six

Table 1: Overall WHI Results with Risk of Breast Cancer

	E/P Treatment	Placebo	Hazard Risk
Total number of women	8,506	8,102	
Invasive breast cancer	166	124	1.26 (1.00-1.59)
Noninvasive breast cancer	40	33	1.13 (NS)

months use of hormone therapy. When this six-month period was removed from the calculation, the test for trend was no longer significant. Thus, this study, while seeming to add to the conclusion of the WHI, does not further clarify or strengthen the current state of knowledge.

BREAST CANCER SURVIVAL IN POSTMENOPAUSAL HORMONE USERS

Most of the studies that have examined the breast cancer mortality rates of women who had used postmenopausal hormone therapy have documented improved survival rates.⁴ Even studies that detect an increased risk of breast cancer in hormone users indicate a paradoxical better outcome. This is believed to partly reflect earlier diagnosis because increased utilization of mammography by hormone users is a well-recognized phenomenon.⁵

The better outcomes in hormone users who develop breast cancer, however, are not only due to a greater use of mammography; the tumors themselves represent lower stage and grade disease, a finding that is consistent with effects on pre-existing tumors. These biologic differences imply that hormone treatment promotes the growth of a malignant locus already in place, and it presents clinically with a more favorable biology. This conclusion is consistent with the fact that virtually all the positive studies find that any increase in risk disappears within five years of discontinuing hormone therapy, and tumors occur at an earlier stage and a younger age in women using hormone therapy.

The WHI could make no statement regarding breast cancer survival. In the WHI results, there were only three deaths due to breast cancer in the treated group and two in the placebo group. The follow-up was not long enough to provide the outcome of the breast cancers in the participants. The health of the participants in the WHI is supposed to be monitored until 2005, so hopefully we will learn more about this important outcome, breast cancer mortality.

Lower grade tumors are present even when there is no difference in the prevalence of mammography comparing hormone users and nonusers or when the data

are adjusted for the method of detection.⁶⁻⁸ In the Breast Cancer Detection Project, current hormone use was associated with a 40% to 60% reduction in breast cancer mortality for 12 years after diagnosis.⁶ This effect remained after correcting for cases detected at the first screening visit and when in situ data were excluded, indicating that the results were not due to detection/surveillance bias. In this report, the protection against breast cancer mortality associated with hormone use could

less aggressive tumors, and this appears to be more important than screening mammography in producing better outcomes in hormone users.

My concept of the effect of hormone therapy on pre-existing tumors led me to the conclusion that hormonal stimulation accelerated the growth and clinical appearance of the tumor. However, there is another possibility. In the WHI, the increase in breast cancer did achieve statistical significance only in the group of

women who had been on hormone therapy prior to entry into the study. In the Oregon experience that indicated the presence of less aggressive tumors in hormone users, the average duration of hormone use was an impressively long 16 years.¹⁰ Rather than accelerating growth, the major impact of hormone therapy may be on differentiation. A better differentiated tumor actually grows

Table 2: Year-by-Year Results with Risk of Breast Cancer

	E/P Treatment	Placebo	Ratio	Participants
Year 1	11	17	0.62	8,435/8,050
Year 2	26	30	0.83	8,353/7,980
Year 3	28	23	1.16	8,268/7,888
Year 4	40	22	1.73	7,926/7,652
Year 5	34	12	2.64	5,864/5,566
Year 6	27	20	1.12	5,129/4,243

not be attributed to tumor size, age at diagnosis, BMI, tumor histology, or node status. Thus, an important effect is on grade of disease (tumor differentiation and aneuploidy). An excess of Grade I tumors has been documented equally in users of estrogen alone and in users of combined estrogen and progestin.⁹

An analysis of breast cancer cases at my own medical center has yielded some striking conclusions.¹⁰ Comparing breast cancer patients who were users of hormone therapy with nonusers, the users had the following characteristics:

1. More tumors in hormone users were detected by screening mammography.
2. Hormone users had more ductal in situ tumors, more node-negative cancers, smaller tumors, and less invasive disease.
3. There were no differences in histological types or in estrogen receptor status.

The difference in survival rates was especially remarkable. The five-year survival rate in the nonusers was 87%; the eight-year survival rate in the hormone users was 100%! The frequency of mammography screening was identical in both groups; therefore, the better outcome in the hormone users was not due just to earlier detection. Hormone users develop

slower, allowing time for a stromal reaction to the tumor, a reaction that can then be detected by screening mammography at a less aggressive stage of development.

The WHI has indicated that an increase in breast cancer has not been observed in the arm of the study in which women are administered only estrogen (without the concomitant use of a progestin). This is consistent with the failure to observe an increase in relative risk in the estrogen only groups analyzed by recent case-control studies in contrast to the results observed with the use of combined estrogen and progestin.^{3,11,12} There are several possible explanations. The response to estrogen-progestin may be more rapid, and with time, similar results may appear in the estrogen-only arm of the WHI. The effect of estrogen-progestin on the histology of a breast tumor may be more profound allowing earlier detection. Finally, it is possible that only estrogen-progestin therapy is associated with an increased risk of breast cancer.

MAMMOGRAPHIC BREAST DENSITY

Mammographically dense breasts reflect a high proportion of stromal, ductal, and glandular tissue. The likelihood of dense breasts decreases with advancing age and increasing body weight as glandular tissue

is replaced by fat.¹³ High breast density on mammography is associated with a four- to six-fold increased risk of breast cancer.¹⁴ Increased density is also a worry because it might impair the detection of breast masses. A failure to detect masses because of high density would cause an increase in interval cancers (cancers that present between mammographic screenings). Difficulties in reading high-density mammograms could also produce false positive recalls (patients who are recalled for assessment and found not to have cancer). Factors that are associated with greater breast density are nulliparity, older age at first birth, and current use of postmenopausal hormone therapy.¹³

More current users of hormone therapy have dense breasts than nonusers.^{15,16} In the Seattle area, 49% of current users had dense breasts compared with 33% of nonusers, and the effect was greater with increasing age.¹³ Indeed, in women under age 55, it is difficult to find any differences between hormone users and nonusers.¹⁷ But how large is the impact over age 55? In one study, breast density increased in only 8% of hormone users over age 55 (two-thirds of the patients used estrogen alone, one-third used estrogen and progestin); in the large majority of the patients, the breasts remained the same.¹⁷

The effect of hormone therapy occurs rapidly; thus, duration of use has no effect.¹⁷ In the PEPI three-year randomized trial, almost all increases occurred within the first year, with an increase in breast density observed in 8% of estrogen users, 19% to 24% of estrogen-progestin users, and only 2% in the placebo group.¹⁸ The users of estrogen-progestin combined regimens had a greater risk of developing denser breasts compared with estrogen alone treatment (seven- to 13-fold greater in the PEPI trial with no differences observed comparing medroxyprogesterone acetate to micronized progesterone).¹⁸ In careful studies, the daily, continuous combined estrogen-progestin regimens have been reported to have a greater effect than sequential regimens, with an increase in density occurring within the first months of treatment and then maintained with no change. Therefore, hormone therapy increases breast density mainly in older postmenopausal women, more women respond to combined estrogen-progestin regimens (especially the daily, continuous programs), and the effect occurs within the first

months of use and remains stable with no changes with increasing duration of use. But this effect is only seen in, at most, about 20% more users compared to nonusers; indeed, not all women respond in this fashion (in fact, most do not). Most importantly, in those women who respond with an increase in breast density, discontinuation of treatment is followed by a decrease in density.^{16,19,20}

It seems to me that there are good reasons to suspect that the increase in breast density reported with postmenopausal hormone therapy may not be identical to the high breast density associated with an increased risk of breast cancer. If the effectiveness of breast cancer screening is reduced by postmenopausal hormone therapy, one would expect an adverse impact on breast cancer mortality. Instead, a study that indicated a reduction in mammographic sensitivity also reported smaller, more differentiated (Grade I) tumors among the users compared with the nonusers.²¹

Another reason to believe that the increase in breast density associated with postmenopausal hormone therapy is different than that associated with an increased risk of breast cancer is that it is a transient, reversible change. After discontinuing hormone therapy, breast density rapidly decreases.^{16,19,20} Rather than epithelial proliferation, this change in response to hormone therapy could be a combination of edema and vasodilatation. In a retrospective analysis, regression of hormone-induced abnormalities was found to occur within two weeks of cessation of treatment.²⁰ The older a postmenopausal patient, the greater the risk of developing an increase in breast density with hormone therapy. Therefore, it is reasonable to recommend the discontinuation of hormone therapy for two weeks prior to mammography in women older than age 65 who have dense breasts. In younger women who are recalled for a suspicious or difficult-to-read mammogram, it would be worthwhile to discontinue hormone treatment for two weeks prior to the repeat evaluation.

SUMMARY: Postmenopausal Hormone Therapy and Breast Cancer

- The WHI agrees with some case-control and cohort studies indicating that long-term (about five years) current use of combined estrogen and progestin has a slightly increased risk of breast cancer. It is possible that this finding is due to

an effect of hormonal therapy on pre-existing tumors. The evidence certainly does not indicate a major impact on the risk of breast cancer.

- The epidemiologic data indicate that a positive family history of breast cancer should not be a contraindication to the use of postmenopausal hormone therapy.
- Women who develop breast cancer while using postmenopausal hormone therapy have a reduced risk of dying from breast cancer. This is probably because of two factors: 1) development of a more differentiated tumor so that tumors appear at a less virulent and aggressive stage; 2) increased surveillance and early detection by screening mammography.

I find it helpful to offer patients contrasting examples. Patients and clinicians alike believe without question that smoking causes lung cancer. It is helpful to remind patients that there is no disagreement here; every study says the same thing, and the relative risks are in the range of 10 to 20, not like the small risk reported by the WHI.

Another contrast is at the other end of the spectrum. The risk of breast cancer published by the WHI is smaller than that with other risk factors known to be associated with breast cancer. For example, the increased risk of breast cancer attributed to being overweight after menopause is in the range of 1.8 to 2.0.

Finally, it is time to bring a new important message to our patients. With confidence, we can say that hormone users who develop breast cancer have better outcomes and this is consistent with hormonal effects on pre-existing tumors.

REFERENCES

1. Writing Group For The Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health initiative randomized controlled trial. *JAMA*. 2002;288: 321-333.
2. Collaborative Group On Hormonal Factors In Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet*. 1997;350:1047-59.
3. Weiss LK, Burkman RT, Cushing-Haugen KL, et al. Hormone replacement therapy regimens and breast cancer risk. *Obstet Gynecol*. 2002;100.
4. Nanda K, Bastian LA, Schulz K. Hormone replacement therapy and the risk of death from breast cancer: a systematic review. *Am J Obstet Gynecol*. 2002;186:325-334.
5. Magnusson C, Holmberg L, Norden T, Lindgren

A, Persson I. Prognostic characteristics in breast cancers after hormone replacement therapy. *Breast Cancer Res Treat.* 1996;38:325-34.

6. Schairer C, Gail M, Byrne C, et al. Estrogen replacement therapy and breast cancer survival in a large screening study. *J Natl Cancer Inst.* 1999;91:264-70.

7. Jernström H, Frenander J, Fernö M, Olsson H. Hormone replacement therapy before breast cancer diagnosis significantly reduces the overall death rate compared with never-use among 984 breast cancer patients. *Br J Cancer.* 1999;80:1453-58.

8. Bilimoria MM, Winchester DJ, Sener SF, Motykie G, Sehgal UL, Winchester DP. Estrogen replacement therapy and breast cancer: analysis of age of onset and tumor characteristics. *Ann Surg Oncol.* 1999;6:200-07.

9. Harding C, Knox WF, Faragher EB, Baildam A, Bundred NJ. Hormone replacement therapy and tumour grade in breast cancer: prospective study in screening unit. *Br Med J.* 1996;312:1646-47.

10. Cheek J, Lacy J, Toth-Fejel S, Morris K, Calhoun K, Pommier RF. The impact of hormone replacement therapy on the detection and stage of breast cancer. *Arch Surg.* 2002;137:1015-1019.

11. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA.* 2000;283:485-91.

12. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst.* 2000;92:328-32.

13. El-Bastawissi AY, White E, Mandelson MT, Taplin SH. Reproductive and hormonal factors associated with mammographic breast density by age (United States). *Cancer Causes and Control.* 2000;11:955-963.

14. Byng JW, Yaffe MJ, Jong RA, et al. Analysis of mammographic density and breast cancer risk from digitized mammograms. *Radiographics.* 1998;18:1587-1598.

15. Sala E, Warren R, McCann J, Duffy S, Luben R, Day N. High-risk mammographic parenchymal patterns, hormone replacement therapy and other risk factors: a case-control study. *Int J Epidemiol.* 2000;29:629-636.

16. Rutter CM, Mandelson MT, Laya MB, Seger DJ, Taplin S. Changes in breast density associated with initiation, discontinuation, and continuing use of hormone replacement therapy. *JAMA.* 2001;285:171-176.

17. Sterns EE, Zee B. Mammographic density changes in perimenopausal and postmenopausal women: is effect of hormone replacement therapy predictable? *Breast Cancer Res Treat* 2000;59:125-132.

18. Greendale GA, Reboussin BA, Sie A, et al. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. *Ann Intern Med.* 1999;130:262-269.

19. Berkowitz JE, Gatewood OMB, Goldblum LE, Gayler BW. Hormonal replacement therapy: mammographic manifestations. *Radiol.* 1990;174:199-201.

20. Harvey JA, Pinkerton JV, Herman CR. Short-term cessation of hormone replacement therapy and improvement of mammographic specificity. *J Natl Cancer Inst.* 1997;89:1623-1625.

21. Sendag F, Terek MC, Özener S, et al. Mammographic density changes during different postmenopausal hormone replacement therapies. *Fertil Steril.* 2001;76:445-450.

The author has revealed the following potential conflicts of interest: Consultant and research grants from Pfizer, Wyeth, Ortho, Organon, and WomenFirst.

Endometrial Cancer in Relation to Combined-Continuous Postmenopausal Hormone Therapy: Status of Knowledge After the WHI



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THE DESIGN OF THE HORMONE COMPONENT OF THE WOMEN'S HEALTH INITIATIVE (WHI)¹

One component of the WHI specifically addressed the safety and efficacy of continuous-combined hormone therapy, a regimen of conjugated equine estrogens, 0.625 mg/day, plus medroxyprogesterone acetate, 2.5 mg/day. During 1993 to 1998, 50- to 79-year-old American postmenopausal women with an intact uterus who were recruited at 40 centers to take part in the study were randomly assigned to receive this regimen (n = 8,506) or a placebo (n = 8,102). Some participants had previously taken postmenopausal hormone therapy, but none had done so within three months of entry into the trial.

During a 5.2-year follow-up period, participants were contacted by phone every six months and attended a study clinic every year. If vaginal bleeding occurred, it was managed initially by means of a treatment plan that did not necessitate revealing whether or not the patient had been assigned hormone therapy or placebo. When clinically mandated, a study clinic physician not involved in the assessment of outcome events was unblinded so that appropriate care could be provided. Every six months, participants were asked about the occurrence of endometrial cancer and

other conditions. Reports of endometrial cancer were followed up by examination of medical records. The presence of endometrial cancer was judged by a study clinic physician who had no knowledge of any woman's treatment status.

Only 3.5% of women dropped out of the study. However, about 40% of participants were at least somewhat noncompliant in taking their assigned study medication. Also, by the end of follow-up, 6.2% of women in the hormone group and 10.7% of women in the placebo group had begun to take a hormone preparation on their own. During follow-up, 248 women given hormone therapy and 183 women given placebo underwent a hysterectomy.

ENDOMETRIAL CANCER INCIDENCE IN THE WHI

In all, endometrial cancer was diagnosed in 22 women assigned to receive continuous-combined hormone therapy (five per 10,000 per year), and 25 women assigned to placebo (six per 10,000 per year). The relative risk of endometrial cancer associated with continuous-combined hormone use was 0.83 (95% confidence limits = 0.47 – 1.47). A year-by-year analysis did not reveal any clear trend over time in the size of this weak negative association. No data were provided by which to judge whether the risk of endometrial cancer in certain subgroups of women with other risk factors for the disease (e.g., former hormone users, heavy women) was affected in an atypical way by the hormone regimen administered.

OTHER RELEVANT DATA

That the WHI found no evidence of any increased risk of endometrial cancer among women taking continuous combined hormone therapy is not surprising. Randomized trials have not observed the incidence of endometrial hyperplasia, a precursor condition, to be elevated during several years of treatment.^{2,3} None of the three principal case-control studies of continuous-combined HRT and endometrial cancer risk observed an increased risk,⁴⁻⁶ and in two of them there was a suggestion of a lower risk compared to women who had never taken hormones.^{5,6}

STRENGTHS AND LIMITATIONS OF THE WHI

The WHI has some distinct strengths as compared to non-randomized study designs, in particular the comparability of

women in the two arms of the trial with regard to the underlying risk of endometrial cancer. However, a limitation is the relatively small number of cases observed, resulting in a statistically imprecise result. Based on the confidence limits, the data are compatible with as much as a true 53% reduction in the incidence of endometrial cancer associated with use of continuous-combined hormone therapy, or alternatively as much as a 47% increase. A second limitation (common to virtually all randomized trials) is the non-adherence of some participants to the assigned regimen, producing a diluted estimate of the true benefit that might be expected with full compliance.

In addition, it must be kept in mind that the WHI addressed the consequences of using one particular postmenopausal hormone regimen for a particular duration. There is no certainty that the results will apply to regimens that include agents other than 0.625 mg/day of conjugated estrogens or 2.5 mg/day of medroxyprogesterone acetate, or to durations of use of more than five years. To date, non-randomized studies have not seen substantial

differences of risk of endometrial cancer in relation to type or dose of unopposed estrogen therapy.^{5,7} There is a suggestion⁵ (though no more than this) that progestogens that are testosterone-derived (e.g., norethisterone, levonorgestrel) are more protective of the endometrium than medroxyprogesterone acetate.

SUMMARY

The results of the WHI provide strong evidence that the form of continuous-combined hormone therapy used in that trial has no strong bearing on the incidence of endometrial cancer. Whether that or other regimens of postmenopausal hormone therapy produce small-to-moderate changes in risk, especially when taken for extended periods of time, remains an open question. This question likely will be answered only after the conduct of well-done cohort and case-control studies in populations in which long-term use of these regimens is relatively common.

The author thanks Jennifer Doherty, Ph.D., and Susan Reed, M.D., M.P.H., for their suggestions.

REFERENCES

1. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of Estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. *JAMA*. 2002;288:321-333
2. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The postmenopausal estrogen/progestin interventions (PEPI) Trial. *JAMA*. 1995;273:199-208.
3. Woodruff JD, Pickar JH for The Menopause Study Group. Incidence of endometrial hyperplasia in postmenopausal women taking conjugated estrogens (Premarin) with medroxyprogesterone acetate or conjugated estrogens alone. *Am J Obstet Gynecol*. 1994;170:1213-23.
4. Pike MC, Peters RK, Cozen W, et al. Estrogen-progestin replacement therapy and endometrial cancer. *J Natl Cancer Inst*. 1997;89:1110-6.
5. Weiderpass E, Adami H-O, Baron JA, et al. Risk of endometrial cancer following estrogen replacement with and without progestins. *J Natl Cancer Inst*. 1999;91:1131-37.
6. Hill DA, Weiss NS, Beresford SAA, et al. Continuous combined hormone replacement therapy and risk of endometrial cancer. *Am J Obstet Gynecol*. 2000;183:1456-61.
7. Herrinton LJ, Weiss NS. Postmenopausal unopposed estrogens. Characteristics of use in relation to the risk of endometrial carcinoma. *Ann Epidemiology*. 1993;3:308-18.

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MEDICINE



Volume 11, Number 1, Spring 2003

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