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Postmenopausal Hormone Therapy and Breast Cancer

A Clinician's Message for Patients

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The Women's Health Initiative agrees with some but not all case-control and cohort studies that current use of postmenopausal estrogen–progestin therapy is associated with a small increase in the risk of breast cancer. It is not known whether this is because of new tumor growth or an effect of hormonal therapy on preexisting tumors. Many studies indicate that women who develop breast cancer while using postmenopausal hormone therapy have a reduced risk of dying from breast cancer; this is consistent with an effect on preexisting tumors so that tumors appear at a less virulent and aggressive stage.

Key Words: Risk of breast cancer; estrogen–progestin therapy; Women's Health Initiative.

Introduction

Women and clinicians are regularly reminded about the threat of breast cancer, in the media, by advertisements, and by the experience of a friend or family member fighting this disease. There is good reason why this medical condition is prominent in our consciousness. The breast is the leading site of cancer in US women (32% of all cancers) and is now, unfortunately (because smoking is obviously the reason), exceeded by lung and bronchus cancer as the leading cause of death from cancer in women *(1)*. Currently, female American newborns have a lifetime probability of developing breast cancer of 12.5%, about 1 in 8, double the risk in 1940 *(1)*. There are about 212,000 new cases of invasive breast cancer and 56,000 new cases of *in situ* breast cancer per year. However, there is also good news. Since 1990, breast cancer incidence has plateaued, increasing only in women over age 50 at a rate of about 0.4% per year and limited to localized disease. Mortality rates began a decline in the 1990s. The 5-yr survival rate for localized breast cancer (about 60% of breast cancers) has risen from 72% in the 1940s to 97% *(1)*. This is attributed to earlier diagnosis because of the greater utilization of screening mammography and increased use of chemotherapy, and a continuing decline in mortality should be observed. Breast cancer is a major focus in the health concerns and care for postmenopausal women because it has an increasing frequency with age. About 94% of all breast cancers occur in women over age 40; only 6.5% of all cases occur under age 40, 15% under age 50 *(2)*.

For these reasons, it is entirely appropriate that the association between postmenopausal hormone therapy and the risk of breast cancer receives major attention by clinicians and patients. The long-term use of hormone therapy has been challenged by clinical trial data that were interpreted to indicate that the risk of breast cancer is increased in hormone users. The debate over this issue, as well as others, has made decision-making very difficult. This review concentrates on the clinical trial data regarding hormone therapy and breast cancer and offers an interpretation as a guide for the clinical use of postmenopausal hormone therapy.

The Women's Health Initiative

The Women's Health Initiative (WHI) was organized by the US National Institutes of Health in 1992 to study the health of postmenopausal women and was scheduled to be completed in 2007 *(3)*. From 1993 to 1998, the WHI enrolled 161,809 women aged 50–79 in 40 clinical centers. The major components of the WHI are (1) two randomized trials of postmenopausal hormone therapy that were scheduled to conclude in 2005, (2) a dietary modification trial that randomizes 48,000 women to either a sustained low-fat or a self-determined diet, (3) a calcium/vitamin D supplementation trial, and (4) an observational study. One of the randomized trials of postmenopausal hormone therapy, the combined estrogen–progestin arm (daily 0.625 mg conjugated estrogens and 2.5 mg medroxyprogesterone acetate), randomized 16,608 women to either treatment or placebo. The other hormone trial, an estrogen-only arm (daily 0.625 mg conjugated estrogens), randomized 10,739 hysterectomized women to treatment or placebo.

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. The DMSB made two recommendations that were announced on July 9, 2002: (1) to discontinue the trial arm administering daily estrogen–progestin and (2) to continue the trial arm comparing daily

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unopposed estrogen in hysterectomized women. The combined estrogen–progestin arm was discontinued after about 5 yr of follow-up because of a statistically significant increase in invasive breast cancer and an increase in cardiovascular events *(4)*. 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.

On March 2, 2004, the National Heart, Lung, and Blood Institute of the US National Institutes of Health canceled the estrogen-only (0.625 mg conjugated estrogens daily) arm of the Women's Health Initiative (WHI). This arm of the WHI included 10,739 hysterectomized, postmenopausal women who had completed an average of 6.8 yr of follow-up. The WHI Data and Safety Monitoring Board made their last periodic review of the study data in December 2003. The DSMB was not unanimous in their decision; some wanted to stop the study and others wanted the study to continue after sending a letter to the participants describing the findings. Even though none of the findings had crossed the predefined boundaries, the NIH made the decision to stop the study on February 2, 2004. The decision was based on the following results *(5)*:

- An increased risk of stroke similar to that reported in the canceled estrogen–progestin arm of the WHI.
- No increase or decrease in coronary heart disease.
- A trend toward an increased risk of probable dementia and/or mild cognitive impairment.
- A reduction in hip fractures.
- No increase in breast cancer.

A Clinician's Interpretation

For nearly a decade, we have been teaching that the lack of a uniform, consistent conclusion in more than 60 case-control and cohort studies on breast cancer and postmenopausal hormone therapy means that any effect has to be a small one. The WHI results do not change that teaching. *The most important unanswered question is whether postmenopausal hormone therapy initiates the growth of new breast cancers or whether the epidemiologic results reflect an impact on preexisting tumors.* Observations that favor an impact on preexisting tumors include: (1) in the studies reporting an increase in risk, the evidence is apparent relatively rapidly, within a few years; (2) the return of the hazard risk in the WHI estrogen–progestin arm almost to 1.0 in yr 6, and in the observational data, a return to baseline immediately after discontinuing therapy; (3) no difference in noninvasive breast cancers in the treatment and placebo arms of the WHI; and (4) the large body of literature documenting lower grade and stage disease in hormone users, resulting in better survival rates. The WHI agreed with convincing evidence in the literature that postmenopausal hormone therapy does not increase the risk of breast cancer beyond that already associated with recognized risk factors, such as a positive family history *(6)*.

Table 1
WHI—Invasive Breast Cancer *(7)*

Years	Estrogen–progestin	Placebo	Hazard Ratio
1	12 cases	19 cases	0.60 (0.29–1.23)
2	26	32	0.77 (0.46–1.30)
3	29	22	1.26 (0.73–2.20)
4	44	27	1.54 (0.95–2.49)
5	43	21	1.99 (1.18–3.35)
6 or more	45	29	1.35 (0.85–2.16)
Overall	199	150	1.24 (1.01–1.54)
Deaths	4	4	

Table 2
WHI—Characteristics of the Invasive Breast Cancers *(7)*

	Estrogen–progestin	Placebo
Average tumor size	1.7 ± 1.1 cm	1.5 ± 0.9 cm
Positive lymph nodes	45 (25.9%)	21 (15.8%)
Localized disease	144 (74.6%)	124 (82.7%)
Non-localized disease	49 (25.4%)	24 (16.0%)

The updated WHI report on breast cancer in the estrogen–progestin arm resulted in little change in the hazard ratios published a year earlier in the initial report (Table 1) *(7)*. Invasive breast cancer was increased, 199 cases in the treated group and 150 in the placebo group (1.24; CI=1.01–1.54) *(7)*. However, *in situ* cancer was only slightly increased, 47 cases in the treated group and 37 in the placebo group, a difference that did not achieve statistical significance! Analysis of the invasive breast cancers only in adherent participants, acknowledging the high drop-out rate in the study, did not change the results. The breast cancers in the treated group were slightly larger with more positive nodes and less localized disease (Table 2). There were no differences in distribution of estrogen-receptor and progesterone-receptor cancers or tumor grade. The WHI detected no differences in the histologic types of breast cancer, disagreeing with case-control studies that estrogen-progestin therapy is associated with mainly an increase in invasive lobular tumors *(8,9)*. How does this correlate with national statistics that indicate a rise in lobular tumors and an unchanging incidence of ductal cancers *(10)*?

Abnormal mammograms were reported by the WHI at a greater rate in the estrogen–progestin treated group in the first year of the study, and this difference was maintained each year (Table 3). The mammography findings are very important, suggesting that the greater rate of abnormal mammograms in women treated with estrogen–progestin represents an unwanted and expensive effect of hormone therapy. Nearly 5000 of the 8506 women in the treated group were unblinded because of vaginal bleeding. Is it possible that this

Table 3
WHI—Abnormal Mammography Findings *(7)*

Year	Estrogen–progestin	Placebo
1	716 (9.4%)	398 (5.4%)
2	651 (8.7%)	386 (5.5%)
3	650 (8.9%)	405 (5.8%)
4	661 (9.5%)	432 (6.5%)
5	478 (9.6%)	269 (5.8%)
6 or more	371 (9.1%)	224 (6.7%)
Overall	2601 (31.5%)	1677 (21.2%)

unblinding introduced diagnostic bias into the mammography findings? The WHI believes this is unlikely because mammography findings were managed by the participants' local clinicians, separately from the WHI study reports. However, the most important individual unblinded was the patient. What influence was there on that management when the patient reported to her clinician that she was experiencing vaginal bleeding? Surely the clinician, knowing the patient is a WHI participant, would conclude that she was receiving hormonal treatment.

Women with a greater mammographic breast density have a higher risk of breast cancer *(11–13)*, and about 25% of women on estrogen–progestin therapy have an increase in their breast density. In contrast, raloxifene and tibolone have no impact on breast density *(14)*. However, it is not certain that the short-term increase in density with hormone therapy changes an individual's risk of breast cancer. More current users of hormone therapy have dense breasts than nonusers *(15–18)*. In the Seattle area, 49% of current users had dense breasts compared with 33% of nonusers, and the effect was greater with increasing age *(19)*. Indeed, in women younger than age 55, it is difficult to find any differences between hormone users and nonusers *(20)*. But how large is the impact in women older than 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 *(20)*.

The effect of hormone therapy on breast density occurs rapidly; thus, duration of use has no effect *(20)*. In the PEPI 3-year randomized trial, almost all increases occurred within the first year, with an increase in breast density observed in 8% of estrogen users and 19–24% of estrogen–progestin users and only 2% in the placebo group *(21)*. The users of estrogen–progestin combined regimens had a greater risk of developing denser breasts compared with estrogen-alone treatment (7- to 13-fold greater in the PEPI trial with no differences observed comparing medroxyprogesterone acetate to micronized progesterone) *(21)*. 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 *(22–26)*. *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.* However, this effect is only seen in at most about 25% more users compared with nonusers; indeed, not all women respond in this fashion (in fact, most do not). And most importantly, in those women who respond with an increase in breast density, discontinuation of treatment is followed by a decrease in density *(18,27,28)*.

The increase in breast density associated with postmenopausal hormone therapy appears to be a transient, reversible change, a change not consistent with a persistent effect on cellular proliferation. After discontinuing hormone therapy, breast density rapidly decreases *(18,27,28)*. In a retrospective analysis, regression of hormone-induced abnormalities was found to occur within 2 wk of cessation of treatment *(28)*. In the 12 patients who exhibited no change after discontinuing therapy, 8 were biopsied after ultrasonography, revealing one cancer and one case of atypical hyperplasia. Similar results were observed in a prospective study observing a reduction in density 3 wk after stopping treatment *(29)*. Bigger and better studies of this approach are needed, but it suggests the following clinical recommendation. The older a postmenopausal patient is, the greater the risk of developing an increase in breast density with hormone therapy. Therefore, there is a good reason to recommend the discontinuation of hormone therapy for 2 wk 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 2 wk prior to the repeat evaluation.

Does hormone therapy impair mammographic screening? The literature is mixed on this question. A review of seven studies concluded that six of the seven studies indicated decreased mammographic sensitivity in hormone users, with a slight increase in false-positive recalls *(30)*. A French study found a lower incidence of interval cancers in nonusers, but a prospective American study concluded that recall rates were essentially the same comparing hormone users and nonusers and that hormone therapy rarely causes a diagnostic dilemma *(31,32)*. However, overall, studies have suggested a decrease in mammographic sensitivity with little impact on specificity (false-recall rates). The studies are based on small numbers of interval cancers, and it is uncertain how real or how large this effect is because of the difficulty in controlling for confounding factors (for example, age, age at menopause, and time since menopause). 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 *(26)*, and 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 *(33–43)*. Evidence indicates that hormone users develop smaller, better-differentiated (lower grade) tumors, evidence that is consistent with effects on preexisting tumors and that surveillance/detection bias is not the only explanation for better survival *(44–55)*. 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 *(40,42,50)*. More tumors in hormone users are detected by screening mammography, but when assessing outcomes in all cancers detected by mammography, hormone users have more ductal *in situ* tumors, more node-negative cancers, smaller tumors, and less invasive disease and, thus, better survival rates *(56)*.

In contrast, the WHI results in the estrogen–progestin arm indicated an earlier appearance of worse tumors than previously reported in case-control and cohort studies. The WHI pointed out that the results (both the invasive breast cancers and the mammography findings) are consistent with stimulation of growth in established breast cancers (supported by no statistical difference in *in situ* tumors) but at the same time a delay in diagnosis. This certainly challenges the idea that hormone users have better outcomes because of earlier detection. The WHI suggests that this disagreement could be because of a difference of mammography use in the observational studies. However, even studies that examine tumor characteristics and outcome in users and nonusers who have equally used mammography, lower grade and stage disease with a better outcome is identified in the users *(40,42,56)*. In addition, a prospective cohort study found little impact of hormone use on mammography specificity *(57)*. In contrast to many reports in the literature, the WHI concluded that their results suggested that invasive breast cancers diagnosed in women who use hormone therapy may have a worse prognosis, basing this conclusion on the differences observed in tumor size and spread of disease. By now, it is well-recognized that the participants in the WHI represent an older postmenopausal population (average age 63 and an average of 18 yr since menopause). This older population is more likely to have preexisting occult tumors that would become detectable quickly after hormonal stimulation. In addition, breast tissue in older postmenopausal women may respond differently to hormone stimulation than breast tissue in women close to their menopause. Is it possible that the WHI results reflect this older population that might have occult tumors that are in fact larger and more prone to respond to hormonal stimulation than tumors in younger women? Other problems include lack of true adjudication of histologic diagnoses that were established by hundreds of pathologists and variations in treatment among the scattered participants (e.g., the introduction of sentinal node assessment midway through the study in an uncontrolled fashion).

Table 4
WHI—Invasive Breast Cancer *(5)*

	Estrogen-only	Placebo	Hazard Ratio
Invasive breast cancer	94 cases	124 cases	0.77 (0.59–1.01)

The estrogen-only arm of the WHI failed to observe an increase in breast cancer; indeed, the risk of breast cancer was reduced in the treatment group, although it just failed to reach statistical significance (Table 4) *(5)*.

It is important to keep in mind that the participants in the two arms of the WHI were not identical *(58)*. The estrogen-only arm had 5859 fewer participants, making it more susceptible to a loss of statistical power with the increasing dropout rate that reached 53.8% over time. In regard to risk factors for breast cancer: the women in the estrogen-only arm experienced more early births, bilateral oophorectomy, and more and longer duration of previous hormone therapy. Thus the risks of breast cancer in the two arms would not be identical, and it is possible that earlier and greater use of hormone therapy before participation in the study identified those individuals with preexisting tumors who were then excluded from participation, accounting for the lower incidence of breast cancer in the treated group. Also keep in mind, that the increase in breast cancer in the estrogen–progestin arm was a small one and that the statistical power of the estrogen-only arm is not as great (5869 fewer participants). Although it is tempting to compare the results in the two trial arms of the WHI, these were two different trials with two different populations and treatments, making direct comparisons inappropriate.

Summary: Postmenopausal Hormone Therapy and Breast Cancer

- The WHI agrees with some case-control and cohort studies indicating that current use of combined estrogen and progestin has a slightly increased risk of breast cancer. It is still not known whether this finding is due to an effect of hormonal therapy on preexisting tumors.
- 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) increased surveillance and early detection; and (2) an effect on preexisting tumors so that tumors appear at a less virulent and aggressive stage.

Table 5
Risk Factors for Breast Cancer *(2)*

Relative risk greater than 4.0:	Over age 65
	Inherited mutations
	Two or more first-degree relatives with early disease
	Dense postmenopausal breasts
Relative risk 2.1–4.0:	One first-degree relative with breast cancer
	Atypical hyperplasia on breast biopsy
	High-dose radiation to the chest
	High postmenopausal bone density
Relative risk 1.1–2.0:	First full-term pregnancy after age 30
	Menarche before age 12
	Menopause after age 55
	Nulliparity
	Never breastfed
	Postmenopausal obesity
	Previous cancer of endometrium, ovary, or colon
	Daily alcohol consumption

A Message for Patients

Postmenopausal hormone therapy is either associated with a small increase in the risk of breast cancer or it affects preexisting tumors. Of course, even a small increase in risk for breast cancer is frightening for patients to contemplate. It is helpful to remind patients of the risk of lung cancer associated with smoking (a relative risk of 10–20), a risk magnitude that provides perspective on the possible risk associated with hormone therapy. It is also worth pointing out that the reported risk with hormone therapy is even smaller than that associated with recognized risk factors such as a positive family history, being overweight after menopause, and alcohol intake (Table 5).

In my view, because the literature is sufficiently strong, it is appropriate to share with patients an alternative explanation for the epidemiologic reports regarding breast cancer and postmenopausal hormone therapy. It is helpful to emphasize the possibility that the studies reflect an effect of hormone therapy on preexisting tumors and that hormone users who develop breast cancer have a reduced risk of dying of breast cancer because their tumors are better differentiated, more localized, and smaller. The different results reported by the WHI in regard to tumor characteristics are a puzzle and may reflect the older age of the participants or variations in diagnosis and management.

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