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Discussing breast cancer and hormone replacement therapy with women

ABSTRACT

Although the results of the Women's Health Initiative showed an increased risk of breast cancer in women taking hormone replacement therapy (HRT), the absolute risk is very low. We discuss limitations of the study, questions that remain, and how to discuss the study with women at average risk and high risk for breast cancer.

KEY POINTS

The Women's Health Initiative evaluated only one HRT regimen and did not study lower-dose estrogens or newer progestins.

Clinicians must be able to summarize the cumulative body of evidence—not just the results of one trial—when talking to patients about the effects of HRT.

Misinterpreting or magnifying the already well-established risks of HRT may deprive women of an improved quality of life and potential long-term health benefits.

Individualized risk assessment puts breast cancer risk into a more personal perspective for the individual woman.

This paper discusses therapies that are not approved by the US Food and Drug Administration for some of the uses under discussion.

WHAT DO YOU TELL a woman who asks if hormone replacement therapy (HRT) will give her breast cancer?

Until recently, no randomized controlled trials had addressed this question. Thus, women often found themselves overwhelmed with conflicting information.

Now, the Women's Health Initiative[1] has found an estrogen-progestin regimen to be associated with an increased risk of breast cancer (and heart disease and thromboembolism), leading many clinicians to discourage patients from taking HRT, and causing widespread distress among patients.

Actually, we should be telling patients that, for an individual patient taking HRT, the risk of breast cancer remains low, and we need to relay the true magnitude of the risks and the benefits of HRT in simple language.

In this article, we discuss the findings of the Women's Health Initiative in the context of current clinical practice and 60 years of epidemiologic data on exogenous hormone therapy.

THE WOMEN'S HEALTH INITIATIVE

The Women's Health Initiative[1] is a large, multicenter trial evaluating the effects of HRT on the cardiovascular system, breast, bones, and other organ systems.

Women with an intact uterus were randomly assigned to receive either combined HRT (Prempro—conjugated equine estrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg) or placebo; women without a uterus were assigned to receive either conjugated equine estrogens alone or placebo.

The study began in 1991, with results expected by 2006. However, the combination HRT arm was stopped early, after a mean fol-

TABLE 1

Quantitative reviews of hormone replacement therapy and risk of breast cancer

AUTHORS	YEAR	NO. OF STUDIES	CONCLUSIONS
Dupont et al[8]	1991	28	No increased risk
Steinberg et al[4]	1991	16	No increased risk until 5 years; 30% increase after 15 years
Sillero-Arenas et al[5]	1992	37	6% increased risk
Colditz et al[6]	1993	31	23% increased risk after 10 years
Collaborative Group[3]	1997	51	35% increased risk after 5 years
Bush et al[7]	2001	65	No increased risk

low-up of 5.2 years because the "global index" (the combination of the total increased rates of harm compared with the combination of the benefits) exceeded a predetermined cut-point. On the harm side, the HRT group had higher rates of:

- Coronary artery disease (hazard ratio 1.29, 95% CI 1.02–1.63)
- Breast cancer (hazard ratio 1.26, 95% CI 1.00–1.59)
- Stroke (hazard ratio 1.41, 95% CI 1.07–1.85)
- Pulmonary embolism (hazard ratio 2.13, 95% CI 1.39–3.25).

On the other hand, the risks of colorectal cancer and hip fracture were significantly lower in the HRT group than in the placebo group. Overall, there was no increase in cancer deaths or total mortality in the HRT group compared with the placebo group.

Further, in absolute numbers, the risks were small—there were 38 cases of invasive breast cancer per 10,000 woman-years in the HRT group vs 30 in the placebo group.

We should not overstate the risks of HRT

LIMITATIONS OF THE STUDY

The Women's Health Initiative was the first randomized controlled trial to evaluate the effect of combined HRT on multiple disease outcomes, but it had several limitations:

- During the trial, physicians were allowed to adjust the doses of both the estrogen and progestin to manage symptoms.
- The analysis was by "intention to treat"; women who had a hysterectomy during the trial and thus changed from combined HRT to estrogen replacement alone or stopped HRT were still included in the combined HRT group for analysis.
- About 40% of patients in the combined HRT group did not adhere to the regimen, and 10% of the women in the placebo group started HRT through their own clinicians.
- The median age was 63, which is about 10 years older than the average menopausal woman considering HRT. Since age is the greatest risk factor for breast cancer in women, the population studied may have been at greater risk than the average woman considering HRT.
- Although the women in the study were considered at low risk for breast cancer, more than 20% had a 5-year risk greater than 2%, as estimated by the Gail model (see below). This is the level at which women are considered at high risk and tamoxifen chemoprophylaxis is considered.
- One of the criteria for diagnosis of silent myocardial infarction was evaluation by serial electrocardiography, but the diagnosis of heart disease on the basis of electrocardiograms has been shown to be inaccurate in women.[2]
- Women in the study were not at high risk for osteoporosis, although the greatest expected benefit of estrogen in this group would be the prevention of osteoporosis. Baseline radiographs were not obtained to look for subclin-

ical vertebral fractures, even though about two thirds of vertebral fractures are asymptomatic and are diagnosed as an incidental finding on a chest or abdominal radiograph. Despite this, all types of fractures were reduced, including hip fractures.

- The trial did not study the newer low-dose estrogen (0.45-mg, 0.3-mg) or alternate progestin regimens. Furthermore, the arm of the Women's Health Initiative that is studying the net risks and benefits of unopposed estrogen replacement is still under way; these findings will be of significance to women with a hysterectomy.

DIVERGENT FINDINGS IN EPIDEMIOLOGIC STUDIES

The results of the Women's Health Initiative are consistent with the findings of several epidemiologic studies, in which the overall relative risk of breast cancer in HRT users was variously estimated at between 1.06 and 1.40 (TABLE 1).[3–8] The magnitude of risk was similar to other risk factors discussed below.

On the other hand, other epidemiologic studies found no increased risk with HRT. These data are not false but rather are part of the greater picture.

Bush et al[7] reviewed 65 epidemiologic studies performed between 1975 and 2000, including 45 studies of estrogen-only HRT and 20 studies of combined HRT. In about 80% of the studies the relative risk of breast cancer in HRT users was 1.0, ie, HRT was not associated with breast cancer. The authors concluded that there was no consensus in the literature regarding breast cancer risk from HRT use, and that the variability in results could be due to sampling error from multiple repeated studies.

As for mortality, the Nurse's Health Study[9] followed 91,523 women for 17 years and found that current HRT users had a 37% lower risk of death than women who had never taken HRT. The risk was still 20% lower even in those using HRT for more than 10 years. Among women with a first-degree relative with breast cancer (a group that tends to be concerned about their cancer risk), the risk of death was 35% lower in HRT users than in nonusers.

ALL HORMONES MAY NOT BE THE SAME

One explanation for the discrepancies may that the various endogenous and exogenous hormones differ in their effects.

Estrogens vary

Conjugated estrogen is made up of different estrogens, all with varying degrees of potency, making their interplay and the effect of each component estrogen at the tissue level very complex.[10]

To answer the question of whether HRT increases breast cancer risk, it would seem intuitive to measure estrogen levels in women and to compare the incidence of breast cancer in women who have low vs high estrogen levels. Unfortunately, this is difficult, given the variety of endogenous estrogens, the variability in levels among individuals, and the great variability in the assays used. Furthermore, the protein-bound serum hormone levels measured in standard assays reflect neither the activity of estrogen at the receptor level nor estrogen's intracellular genomic effects.

Nevertheless, a review of six prospective studies evaluating estrogen concentrations and breast cancer risk[11] showed that women who developed breast cancer had 15% higher estradiol concentrations in their blood compared with women who did not develop cancer. Subsequently, a similar association between breast cancer and higher levels of estrone, estrone sulfate, and dehydroepiandrosterone sulfate was shown.[12] We do not yet know, however, which of these hormones, if any, has the greatest effect on breast cancer risk.

A woman's menstrual history, such as the age at menarche and menopause, is an indirect measure of her lifetime exposure to endogenous estrogen (early menses and late menopause denote longer estrogen exposure). These factors and their relation to breast cancer diagnosis were evaluated in a case-control study of 16,417 women by Titus-Ernstoff et al[13]: they showed that early menopause, whether surgical or natural, was associated with a lower risk of breast cancer, with the greatest protection when menopause occurred before age 40. Breast cancer incidence was also lower in premenopausal women who underwent menarche at age 15 compared with age 13 (odds ratio 0.72).[13]

Discuss the issues in terms patients can understand

TABLE 2

Factors affecting risk of breast cancer: The Gail model risk-assessment tool

Race
Age
Age at menarche
Age at first live birth
Number of first-degree relatives (mother, sisters, daughters) with breast cancer
Number and findings of previous breast biopsies

Average 5-year risk of breast cancer:
• No HRT – 1.1%
• With HRT – 1.4%

Do progestins matter?

The effect of progestins on the breast and other organ systems is even less certain.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial,[14] which evaluated the effects of hormones on breast density on mammography, revealed that patients on combined HRT regimens were seven to 13 times more likely to have increased density on screening mammography compared with those taking estrogen alone.

Increased breast density is not necessarily an independent risk factor for breast cancer, but it may make mammograms more difficult to interpret, potentially limiting their diagnostic sensitivity. Other studies found no significant difference in the risk of cancer between women taking estrogen-only and combined HRT.[3]

This is an area of ongoing research, so final conclusions cannot yet be drawn. With the expanding use of newer progestins, more information will be needed about the various combinations now available to patients and how they differ from the traditional combinations that contain medroxyprogesterone acetate.

SUMMARIZING THE RESULTS OF THESE STUDIES FOR PATIENTS

How can we put all of these findings into perspective for our patients? When discussing HRT with patients, we recommend the following:

- Admit to patients that there is controversy and concern, especially since many women come to the physician's office with their own opinions on this issue, often sculpted by media coverage, the Internet, and the experience of family or friends.
- Discuss with them the results of the recent comprehensive review by Bush et al,[7] pointing out that some well-designed reviews do not show an association between HRT and breast cancer, which patients may find reassuring.
- Point out that, despite the uncertainties, we cannot disregard the modest increase in breast cancer risk with long-term use of standard-dose combination HRT, as observed in the Women's Health Initiative.
- Make sure patients understand that, despite a possible increase in the risk of breast cancer, we have no evidence that HRT increases mortality.
- Calculate your patient's actual risk (see below).

EXPLAINING BREAST CANCER RISK TO PATIENTS

The Gail model risk-assessment tool[15] (TABLE 2) can be used to predict the 5-year and lifetime percent likelihood that a woman will develop breast cancer, taking into account family history and several external risk factors. This instrument can be used online at the National Cancer Institute web site (**http://bcra.nci.nih.gov/brc**). Versions that can be downloaded to Palm handheld organizer devices can be found at **http://www.pdacortex.com/BreastCa_Download.htm** and **http://www.stanford.edu/~pmcheng/breastca**.

Calculating the individual 5-year risk

After you calculate your patient's risk of breast cancer, multiply by 1.26 to find her risk with HRT.

For example, using the Gail risk-assessment tool, an average menopausal woman has an approximately 1.1% 5-year risk of developing cancer, with average defined as follows: age 51, white, menarche at age 12, first live birth at age 26, no family history of breast cancer, no breast biopsies.

Using the Women's Health Initiative data, such a patient has a 26% relative increase in risk if she takes HRT. Thus, this

woman's 5-year risk of breast cancer diagnosis increases from 1.1% to approximately 1.4% (1.1% × 1.26). Conversely, without HRT, she has a 98.9% chance of *not* being diagnosed with breast cancer in 5 years, compared with a 98.6% chance of not being diagnosed with breast cancer if she takes HRT.

Other, less-appreciated risk factors for breast cancer include first pregnancy after age 30 (relative risk 1.48), body mass index greater than 29 (relative risk 1.48), alcohol use more than 5 g/day (relative risk 1.16), and, oddly, a college degree (relative risk 1.36).[3]

Many patients overestimate their risk

The Gail model helps women to estimate their personal risk of breast cancer more realistically. If a patient has an estimate of her baseline breast cancer risk and understands the potential contribution of HRT to this calculated risk, she may be able to make a more educated decision about whether HRT is right for her.

This is important, since women overestimate their risk of breast cancer morbidity and mortality. In fact, in both Europe and the United States, women rank breast cancer as the leading cause of death among women, although cardiovascular disease is the most common cause of death and disability on both continents. After age 65, one out of three women develops symptoms of cardiovascular disease.

The Gail model helps put risk in a personal perspective

We have found that our patients are often relieved to hear about the low 5-year and lifetime risks of breast cancer, compared with what they would have predicted.

Conversely, women at higher risk of breast cancer may underestimate their actual risk. The Gail model can help select the women who may benefit from genetic testing, intensive screening with ductal lavage, or chemoprevention with tamoxifen.

Limitations of the Gail model

It is crucial, however, to ensure that women are aware of the limitations of this model and that they understand that this is a mathematical model designed for assessments of population risk in women undergoing annual mammography. In women with a family history of breast cancer in a second-degree or third-degree relative (such as the father's side of the family) or early-onset breast cancer in family members, the Gail model may underestimate the risk because it does not include these factors in its calculations.

Despite its limitations, however, the Gail model can be useful when discussing the complex subject of risk with patients, and it should be part of an annual risk reevaluation, since both risk factors and indications for HRT may change.

Discussing absolute risk with patients

Patients often find estimates of absolute risk more useful and easier to understand than relative risk. Recall that in the Women's Health Initiative, there were 38 cases of breast cancer per 10,000 HRT users per year, compared with 30 cases without HRT—an absolute difference of 8 cases.[1] Many patients find the risk associated with HRT much more acceptable when put in these terms instead of a "26% increased risk of developing breast cancer."

Prognosis, duration of therapy

Other issues to discuss with patients include the prognosis of breast cancer that occurs with HRT use and the optimal length of therapy.

Interestingly, the Iowa Women's Health Study[16] showed that cancers diagnosed in women who had used HRT were less advanced. Exposure to HRT was associated most strongly with breast cancer that had a favorable histology and prognosis.

Furthermore, short-term treatment for menopausal symptoms has not been shown to significantly increase breast cancer risk. Women who wish to start HRT for menopausal symptoms such as vasomotor instability, urogenital atrophy, and mood or sleep changes can begin treatment and decide later if they want to take HRT long-term to protect against osteoporosis, colon cancer, and other conditions.[17,18]

Finally, the data regarding breast cancer risk beyond 10 years of HRT are insufficient to draw absolute conclusions at this time.

HRT IN HIGH-RISK PATIENTS

Women who have previously been diagnosed with breast cancer are at highest risk of new or recurrent breast cancer with HRT use.

The number of breast cancer survivors in the United States now approaches 2.5 million and is on the rise. In view of their numbers, their nononcologic health problems become a prominent health concern.

A major side effect of current chemotherapy regimens is menopausal symptoms due to premature ovarian failure. These symptoms can be so bothersome that some breast cancer survivors are willing to accept a modest increase in the risk of breast cancer recurrence to alleviate their symptoms and thus improve their quality of life. HRT is sometimes offered to breast cancer survivors to relieve these symptoms, with the patient's informed consent.

Although women with a history of breast cancer are at higher risk for new breast cancer, a greater concern is the possibility of developing distant breast cancer metastasis, which is incurable. A recent controlled cohort study of 174 women with breast cancer[19] who were subsequently treated with HRT showed that there was actually a lower risk of cancer recurrence and mortality in the group on HRT compared with those not on HRT.

In another recent study,[20] Cheek et al showed that women on HRT at the time of diagnosis with breast cancer had a much more favorable outcome than postmenopausal women diagnosed with breast cancer who were not on HRT. A history of HRT use in this retrospective case series of 292 women did not show any discernible adverse effects on either breast cancer detection or outcomes.

While potential bias in cohort studies must be acknowledged, it is now clear that more research is needed in this area. Thus far, no study has shown an increased recurrence rate or increased mortality in women with a history of breast cancer who choose to take hormones after their diagnosis.

FINAL RECOMMENDATIONS

We should avoid overemphasizing the risks from HRT, as this may deprive women of its benefits. These include improved quality of life and beneficial effects on the bones, genitourinary tract, skin, colon (cancer prevention), and, possibly, cognitive function.

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