What have we learned since the initial results of the WHI study?

The initial results of the WHI study after final adjudication, suggested a 24% increased relative risk of breast cancer in women on estrogen and progestogen therapy (EPT). On further analysis, however, it becomes apparent that a statistically significant effect was not seen until five years into the study, and this effect then began decreasing in year six. When adjusting for analysis not only has raised questions about the WHI study design, but also helped to put the findings in perspective. This brief review will address several key questions:

- What have we learned since the initial results of the WHI study?
- Does HT cause breast cancer?
- Is five years a safe window for HT?
- What about various subpopulations using HT?

What have we learned since the WHI Study?

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Menopause is an inevitable phase for women who live long enough. Despite being a natural event, the cessation of ovarian function has well-documented consequences.

During the four- to five-year transition from perimenopause to postmenopause, for instance, the skeletal system undergoes the greatest accelerated rate of bone loss, which can lead to osteoporosis. Approximately 80% to 90% of menopausal women will experience vasomotor symptoms (hot flashes and night sweats), which in many instances affect the quality of their lives. Furthermore, vaginal atrophy, which can cause dyspareunia, vaginal bleeding and local irritation, is considered an inevitable consequence of hypoestrogenism.

Although hormonal therapy (HT) can relieve or control the symptoms of hypoestrogenism in most patients, the recent scientific findings and controversies surrounding HT risks and benefits have left most patients fearful of using HT. Most women believe breast cancer is the greatest risk to their health and well-being; hence, the potential risk of breast cancer associated with HT drives much of the current concern.

Despite years of observational, case-controlled and cohort studies showing various associations between HT and breast cancer risk (some protective and some detrimental), the Women's Health Initiative (WHI) study, because of its level I evidence, is currently one of the most cited studies when discussing HT risks.

Initial results appeared to show detrimental findings, which led to physicians and female patients becoming concerned about this mode of therapy. More recent results also have suggested that widespread discontinuation of HT has led to lower detection rates of breast cancer, despite stable utilization of mammography. Further...
Does HT cause breast cancer?

An extremely important question in this discussion is, “Does HT actually cause breast cancer?” Unfortunately, we do not have a clear answer. There are, however, several findings that argue against a cause-and-effect relationship. The first finding is that the short time to diagnosis of breast cancer in many of the studies argues for an accelerated growth and earlier detection phenomenon rather than an initiation phenomenon.

Most studies, like the WHI for example, found the increased risk within a five-year period. The Million Women Study (MWS) even recorded a statistically significant detection rate of breast cancer in women on HT with a mean time to diagnosis of 1.2 years after recruitment. It has been argued, however, that based on tumor doubling time, it would take more than five to 10 years for cancer cells to reach a clinically detectable size, suggesting these tumors were present prior to the study commencing.

Many studies have shown that women who develop breast cancer on HT actually have lower grade/stage disease, less metastasis and overall better survival. The WHI study was consistent with this finding and did not show an increased mortality from breast cancer in women on HT. Even the MWS, which initially claimed to show an increased mortality, had a convincing argument by scientists and statisticians to actually show the reverse. These findings argue against an overall detrimental phenomenon from HT. In addition, it has been argued that local production of estrogen in breast tissue, as opposed to exogenous estrogens derived by intracrine aromatase activity converting androgens to estrogens, may be a more reliable marker of breast tumor stimulation. This could explain why exogenous estrogen appears to have a minimal effect in tumor stimulation and conversely why pharmaceuticals that block aromatase activity and block estrogen receptors tend to inhibit breast tumor stimulation.

The EPT arm of the WHI study showed a statistically significant increased risk of breast cancer at year five. However, this risk subsequently began to decrease in year six and immediately lost its significance. This, along with the fact that the effect of HT on breast tumor stimulation is rapidly lost after discontinuing estrogen therapy, both argue for a stimulation of pre-existing tumors and not a causal relationship.

Conversely, the recent finding that widespread discontinuation of HT has led to a lower prevalence of breast cancer, which initially seemed to suggest a cause-and-effect relationship, on further evaluation also seems to argue in favor of a lower detection phenomenon of pre-existing tumors. In other words, the lack of HT may suppress the maturation of pre-existing breast tumors. Whether this will lead to the subsequent development of more aggressive or higher stage breast cancer is not known.

Is 5 years a safe window for HT?

Some data have suggested, and most experts would agree, that up to five years is a safe window for the use of HT in regard to causation of breast cancer. The more challenging question becomes, “Does that mean that HT is unsafe after five years?” Based on the evidence, it is likely that HT is safe in many women for more than five years.

Many studies have shown no increased risk of breast cancer for periods of well over five years. The Nurses Health Study, for instance, did not show an increase until after 20 years. A study by CI Li and colleagues did not show any risk in patients using ET even when used for 25 years or longer. These results highlight the need for consideration of subgroups and the importance of individualizing patient therapy.

What about subpopulations using HT?

Clearly, HT use and prescribing is not a “one size fits all” proposition. In addition, women with a family history may need to see a physician who has expertise and comfort in prescribing and counseling on these more challenging questions. The WHI has acknowledged that these claims are not supported by the medical literature.

We have entered an era where many women who desire HT may need to see a physician who has expertise and comfort in prescribing and counseling on these more difficult and controversial settings. Many women with a family history of breast cancer, similarly, have been directed away from HT use.

The data, on the contrary, have suggested that any underlying risk of breast cancer in women with a family history is not further increased with HT, and the risk of mortality may be decreased for those on HT. Another recent study even showed a small decrease in breast cancer incidence in women on HT vs those not on HT with the BRCA1 mutation. Other subgroup
comparisons have shown that postmenopausal women with increasing BMIs do not have the same degree of potential breast cancer risk with HT, compared to those with lower BMIs.22,29 This lower breast cancer risk also holds true for women who have never previously used HT, compared with women who have.10

There has also been much speculation about the role of progestogens and what effect they may have on breast cancer. While the increased risk of breast cancer in association with HT in the WHI study was only in the EPT arm, it is important to realize that this was not a direct head-to-head comparison of ET vs EPT. In addition, there were differences in the BMIs and prior HT use, along with other differences between the two groups.

Despite this limitation, there is growing evidence that women on ET alone may have a lower detection rate of breast cancer, compared to those on placebo or EPT.24,28,30 To make the topic more controversial, however, there has been a suggestion that the increased detection rate on EPT may actually be a beneficial effect from progestins. In other words, progestins may cause a beneficial effect in the breast, leading to enhanced differentiation of the tissues, which could lead to earlier detection of pre-existing tumors.31

Final note
Clearly we still have a great deal to learn in the area of HT and breast cancer. What initially appeared to be very troubling WHI study results that created panic among patients and many physicians, has since been found to be more reassuring.

It is still not known, for instance, whether there is a direct cause-and-effect phenomenon between HT and breast cancer. Many believe the association is from an accelerated growth effect. In the meantime, patients who have indications for HT use—after a discussion of risks, benefits and exclusion of contraindications—should be encouraged to use HT at a dose and for a period of time appropriate to the indication. □

References


Peter F. Schnatz, DO, is director of the Women’s Ambulatory Center and Generalist Division at The Hospital of Central Connecticut, director of undergraduate education in the Department of Obstetrics and Gynecology at the University of Connecticut (UCO), and an associate professor of obstetrics and gynecology and internal medicine at UConn. He can be reached at pschnat@harthosp.org or pschnatz@thocc.org.
A 52-year-old female is one year postmenopausal. She is suffering from severe vasomotor symptoms and has a family history of breast cancer.

How would you approach the issue of prescribing hormonal therapy (HT) to this patient?

Considering the relatively common occurrence of breast cancer and the very high frequency of vasomotor symptoms, this is a very common scenario—a woman wanting hormonal therapy but having a family history of breast cancer. When approaching this clinical scenario, there are several important points to keep in mind.

First, although there’s a clear association, there’s no clear evidence that hormonal therapy causes breast cancer.

Second, any baseline effect of hormonal therapy and breast cancer is very low. According to the 2008 NAMS position statement on the role of estrogen and progestogen use in postmenopausal women, the absolute risk is classified as “rare.”

Third, and under-recognized, is the fact that women who are on hormones when they develop breast cancer actually have better outcomes, lower-stage disease, fewer metastases and better survival rates.

The fourth point, which is particularly important in this clinical vignette, is that a family history of breast cancer does not further increase the underlying association between hormonal therapy and breast cancer.

Taking the right approach

In counseling this patient, I would first point out that we do not know for sure if hormonal therapy causes breast cancer. While there is an association, we also know that women who are on hormonal therapy actually have better outcomes. I would then say, “Let’s assume for a minute that hormones do cause breast cancer. What’s the worst-case scenario?”

Most experts agree that a relative risk of about 1.25 is a good estimate of the association between hormonal therapy and breast cancer. Our patients, however, greatly misunderstand relative risk. When they hear 25% risk, what they hear is, “If I’m on hormonal therapy and three of my friends are on hormonal therapy, one of the four of us, or 25% of us, are going to get breast cancer.” Yet physicians know that is not the case. That is why it is so important that we talk about absolute risk.

To talk about absolute risk in this scenario, we need to know the underlying rate of the disease. In the average 50-year-old woman—the women that we’re frequently talking to about starting hormonal therapy—the baseline risk of breast cancer is about one in 50, which would be 2%.

Taking a more positive approach, the physician can say, “You have a 98% chance of not developing breast cancer.” Now if we take the relative risk of 1.25, and as a worst-case scenario assume a cause-and-effect relationship, there would be a 2.5% risk (1.25 times 2%) or a 97.5% chance of not getting breast cancer. Hearing these figures and realizing that we do not know for sure if there is a cause-and-effect relationship, and that those in the 2.5% group actually had better outcomes, helps put in balance the actual risks with the well-known benefits.

Case study reference


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