

MENOPAUSE

CONFIDENT COUNSELING How to explain HT and breast cancer risk ... What if hot flashes reheat?

The pendulum set in motion during the summer of 2002 continues its return swing toward a balanced perspective on hormone therapy.^{1,2} Now we have the opportunity to help our menopausal patients make decisions in a less emotional environment. Nonetheless, explaining the findings of the initial Women's Health Initiative report—added to the findings of many subsequent WHI reports—is tricky even for the statistics experts.

How can we confidently counsel our patients?

American women fear breast cancer more than any other disease.³ That is understandable. Recent large studies, including WHI and the British Million Women Study, have been remarkably consistent in finding that combination hormone therapy (HT) modestly elevates the risk of being diagnosed with invasive breast cancer (relative risks or hazard ratios >1.0 and <2.0).^{2,4,5}

Our challenge is to understand what the relative risk (RR) and hazard ratios mean as we guide our patients in making decisions about HT. To place these risks in a meaningful context, let's compare them with risk factors for other cancers, other risk factors for breast cancer, and translate these relative risks into absolute risks, which patients understand much better.

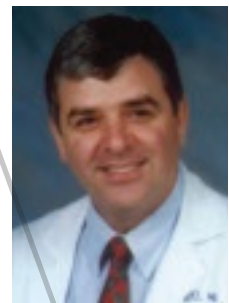
We might start with lung cancer as a comparison. While the relative risk for breast cancer is less than 2 for menopausal women using combination HT, the relative risk of lung cancer is 15 to 30 for cigarette smokers.⁶

Other breast cancer risk factors of magnitudes similar to that of combination HT (RR <2.0) include menarche prior to age 12, high socioeconomic status, nulliparity, never having nursed an infant, first full-term pregnancy after age 30, and alcohol consumption.⁷

Relative risk vs attributable risk

If our patients understand how the relative risks used in clinical trials translate into absolute or attributable risks, they will be better prepared to make sound choices regarding HT. Too often, however, relative risks are confused with attributable risk, which in this context is the incidence of an outcome (breast cancer) in women exposed to HT, minus the incidence in those not exposed.

The WHI trial of combination HT found an RR of 1.26 for breast cancer, meaning that HT users were 26% more likely to be diagnosed with this disease



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than were participants randomized to the placebo arm. Applying this RR to the absolute incidence of breast cancer observed in participants, the study's authors noted that the attributable risk associated with use of combination HT was "low": 8 additional breast tumors were diagnosed annually per 10,000 women (0.08% or ~0.1%) in the combination HT arm compared with the placebo arm.² The annual breast cancer incidence in the HT arm (38 of 10,000 participants) is indeed some 26% higher than in the

placebo arm (30 of 10,000 participants).

Keep in mind that WHI participants' mean age at screening was 63 years and mean duration of HT use was 5.2 years. Because the incidence of breast cancer rises with age, and risk at baseline relates to attributable risk, the attributable risk associated with use of HT by younger menopausal women (those most likely to be seeking treatment for bothersome vasomotor symptoms) would be substantially lower than the 0.08% additional risk noted by the WHI investigators.

Most physicians misinterpret WHI —except ObGyns

IThe findings of the Women's Health Initiative are misunderstood by most primary care specialists, although ObGyns have a better understanding of the risks and benefits compared to other specialties.⁸

IWe hypothesize that physicians who overestimated the increase or decrease in risk were making the error of confusing relative risk with absolute risk difference. There is a great need for physician education about the attributable risks and benefits of HRT.⁸

A survey of physicians underscored the difficulty of trying to translate relative risks into attributable risks, and thereby helps us understand how readily our patients may overestimate their own risk. In Williams and colleagues' survey⁸ of Florida physicians, conducted in 2004, prior to publication of the results of the WHI estrogen-only trial, all respondents correctly indicated that HT was associated with an elevated risk of breast cancer.

When asked to characterize the attributable risk of breast cancer associated with HT (the choices were 0.1%, 3%, 10%, and 30%), fewer than half of physicians answered correctly that the attributable risk is 0.1%. More than half of physicians picked one of the wrong choices—all of which were higher than the correct attributable risk of breast cancer associated with HT.

Breast cancer risk: Estrogen-only vs combined HT

In 2004, results of the WHI clinical trial of

women with hysterectomy indicated that estrogen was not associated with an increased risk of breast cancer,⁹ consistent with a number of large observational studies conducted in the United States^{10,11} and Sweden.¹² Although the British Million Women study found a minimally elevated risk of breast cancer with use of estrogen alone, this risk (RR 1.3) was substantially lower than the risk associated with combination HT (RR 2.0).⁵ Other studies have also found that estrogen-only therapy, compared with combination HT, is associated with either less increased risk or no increased risk.¹³

Confident counseling

Overall, this body of evidence allows us to confidently counsel menopausal patients who have had a hysterectomy and are contemplating use of HT that use of estrogen-only HT is associated with no increased risk or a minimally increased risk of breast cancer.⁴

FAST TRACK

We can advise women who have had a hysterectomy that estrogen-only HT carries no increased risk or minimally increased risk of breast cancer

CONTINUED

How does HT affect mammograms?

- Seven statistical models showed that both screening mammography and treatment have helped reduce the rate of death from breast cancer in the United States.¹⁴
- The overall diagnostic accuracy of digital and film mammography as a means of screening for breast cancer is similar, but digital mammography is more accurate in women younger than 50 years, women with radiographically dense breasts, and premenopausal or perimenopausal women.¹⁵
- Use of estrogen plus progestin is associated with increases in mammographic density.¹⁷

Mammography has contributed much to the detection and treatment of breast cancer, as well as its decline in mortality in the United States since the mid-1970s,¹⁴ reminding us of the importance of this screening test. Increased breast density reduces the sensitivity of mammograms,¹⁵ however, and use of HT (particularly combination HT) increases mammographic breast density.^{16,17} In the WHI trial of combination HT, women assigned to HT were more likely to have abnormal mammograms requiring recall.¹⁸

HT may become an indication for digital mammographic technique

In contrast with the findings of many observational studies, the breast tumors found in combination-HT users in the WHI trial were also larger, and disease stage was more advanced at diagnosis.¹⁸ As the WHI authors speculated, these sobering observations suggest that combination HT may have the dual impact of stimulating growth in existing tumors and delaying mammographic diagnosis.¹⁸ Speroff has suggested that the differences between findings of observational studies and the WHI reflect that the WHI participants were older postmenopausal women,

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who were more likely to have preexisting tumors, and therefore the results may be of less relevance to younger postmenopausal women using HT.¹⁶

For women with dense breast tissue, use of digital as opposed to film mammography enhances accuracy.¹⁵ Accordingly, as digital mammography becomes more available, use of HT may

become an indication for use of digital mammographic technique among postmenopausal women.

Use digital if it's available

In practice settings where digital mammography is available, its use should be considered in preference to film mammography for women using menopausal HT.

Evidence-based answers to 3 top concerns of patients

Armed with a balanced perspective based on evidence rather than fear, our patients can make sound decisions on use of menopausal HT. We can advise our patients to consider the following evidence-based lines of reasoning:

How does HT affect risk of breast cancer?

- **Combination hormone therapy vs estrogen only.** Women considering whether to start HT, as well as those deciding whether to continue, need to understand the small but real risk of breast cancer attributable to combination HT, and that this risk is lower (if present at all) with estrogen-only therapy if they have had a hysterectomy.
- **It may help** to place the risks associated with combination HT in perspective with other breast cancer risk factors and risk factors for other cancers.
- **Symptomatic women in their 50s** contemplating initiation or ongoing use of HT should also recognize that any increased relative risk of breast cancer associated with use of combination HT translates into an attributable risk substantially lower than that faced by older menopausal women (the WHI population).
- **Risk increases with longer duration of combination HT.** A consistent finding of recent large studies is that the risk of breast cancer increased with longer durations of combination HT use.⁴ This observation supports clinical strategies

that attempt to minimize the duration of combination HT use.

Does HT affect coronary risk?

- **Timing of HT initiation** in relation to menopause onset or to age might influence coronary risk, with users under age 60 possibly experiencing cardioprotection, concluded a Nurses Health Study report. This study provides reassurance for younger menopausal women (in their 50s) with respect to coronary artery disease risk associated with HT use.¹⁹

What is the right duration?

- **Not indefinitely.** Consistent with the guidelines of The North American Menopause Society and the American College of Obstetricians and Gynecologists,^{20,21} HT should not be prescribed indefinitely, but should be tailored to a woman's need for treatment of bothersome menopausal symptoms.⁴

FAST TRACK

For women in their 50s, the attributable risk of breast cancer associated with combination HT is much lower than in older women

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What if hot flashes reheat?

More than half of the women with vasomotor symptoms at randomization to active conjugated equine estrogen + medroxyprogesterone acetate also reported these symptoms after discontinuing use of the study pills, concluded a study of symptom experience after stopping HT.²²

Because we cannot predict in an individual woman how long menopausal symptoms will persist, and such symptoms often return after HT is discontinued,²² women with bothersome menopausal symptoms and their clinicians should collaboratively decide on use of HT based on an understanding of all the risks and benefits of this therapy.²¹ ■

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EXAMINING THE EVIDENCE

CLINICAL IMPLICATIONS OF KEY TRIALS

Q How common is
hypoactive sexual desire
disorder?

A Turn to page 14

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