

Clinicians' FORUM

From time to time, the editors of *Menopause Management* field interesting clinical questions and dilemmas. In this forum, our Editorial Advisory Board members, and guest commentators,* experts in a range of fields related to midlife women's health, tell readers how they handle these situations.

The viewpoints expressed in "Clinicians' Forum" are those of the contributors, and not necessarily those of *Menopause Management* or The North American Menopause Society (NAMS).

Question: Recently, two studies have reported conflicting findings. From Texas, Ravdin and colleagues (2007) reported a steep decline in breast cancer incidence after 2002. They reported that this was, at least theoretically, attributable to the July 2002 termination of the EPT arm of the WHI, and 56% of women immediately discontinuing postmenopausal hormone use. More recently, the WHI observational follow-up of 5 years from the termination of the EPT arm (Heiss et al, 2008) reported HT users to be at higher risk for breast cancer than women who were on placebo. How are practitioners meant to digest this conflicting information? What should they believe and should it influence their patterns of practice?

Answers:

This is an excellent question, and brings out the important point that a reported study is not necessarily a "truth." It is obvious, and an astute observation, that both papers cannot be

correct. Neither paper gives an answer to the important clinical question: Does treating a patient with estrogen and progesterone (EPT) increase the risk of breast cancer after discontinuing therapy?

First, the Ravdin paper¹ was not reporting on a controlled study; it was, in fact, not a study at all but rather an hypothesis. In a letter to the editor of the *New England Journal of Medicine*, which was acknowledged but never published, James Simon, Richard Nachtigall and I wrote the following: "The recent publication in the Journal indicating a decrease in breast cancer rates from 2002-2003, and suggesting a link to a decrease in hormone therapy use, deserves discussion. We are concerned first and foremost that the [Surveillance, Epidemiology, and End Results] SEER data and other epidemiological information cannot and should not be used to indicate causality."

In the American Cancer Society's publication of the 2003 USA SEER breast cancer data, they clearly state: "It is very important to note that the incidence in mortality data in the

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2003 report will be age adjusted to the 2000 population standard of the United States. This change in method will affect the comparability of the new reports with that of previous years. The new approach will result in some dramatic changes in the rates of cancer incidence and mortality rates at different ages, magnitude of improvement of cancer, and racial and ethnic differences.²²

In addition, since clinical use of hormone therapy (HT) is most likely in symptomatic



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women ages 45-55, and these are the women most likely to have been on HT and to have discontinued therapy, the fact that breast cancer incidence did not decrease in the under-50 age group opposes the hypothesis. To emphasize this further, the best evidence comes from the Women's Health

Initiative (WHI) itself. That study showed no statistically significant increase in breast cancer risk with 5.3 years of HT (E+P arm),³ or 7.2 years of estrogen therapy (E-only arm)⁴ in those individuals who had not previously used hormones.

Ravdin et al further showed an 11% decrease in the 2003 USA SEER cancer incidence for women over age 70.¹ The very small numbers of women on HT in this advanced age group could not have accounted for such a large decline in breast cancer incidence, even if they all stopped their HT.

The authors found a sharp decline in USA SEER breast cancer incidence from 2001-2003 which, they reported, levels off in 2004. This "leveling off" occurred despite a 17% continued reduction in the number of HT prescriptions (2004 vs. 2003), which continued significantly into 2005. If the 31% decreased estrogen or estrogen/progestogen use (2002 vs. 2003) was responsible for the 7% decline in USA SEER breast cancer statistics, why did we not see a continuation of the decline in 2004? Shouldn't there have been another 3.8% (estimated) decline in that year?

With all these factors considered, this implied statistical possibility does not prove causality. As to the WHI 3-year follow-up after the placebo-controlled trial of EPT was ended,⁵ the authors themselves warned that "the juxtaposition of a randomized controlled trial with an observational post intervention phase warrants caution in the interpretation of results." However, the most important point in this follow-up is that the slight increase in breast cancer in treated women versus those receiving placebo (HR 1.27; CI, 0.91-1.78) was not statistically significant. There are other factors as well: perhaps as density decreased post-treatment with EPT, mammograms showed previously undetected cancers rather than new findings.

In any case, the bottom line and the important issue here is that although practitioners need to read and digest all the new information they can, they cannot—and should not—respond to and change patient care with each new study.

—Lila E. Nachtigall, MD

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Due to space considerations, the entire Clinicians' Forum article, which also contains replies to the Forum question submitted by Robert R. Shenk, MD, FACS, Leon Speroff, MD, Ian H. Thorneycroft, PhD, MD, PC, and Robert A. Wild, MD, PhD, MPH, can be accessed online at the *Menopause Management* website:

www.menopausegmt.com/Forum_JA08_Web.pdf

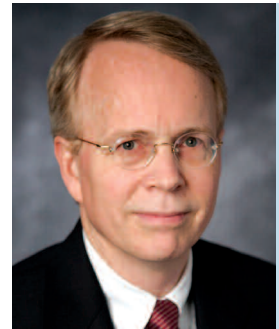
The incidence of breast cancer showed a marked decrease in 2003. That should be cause for celebration. But why did it decrease? Ravdin and colleagues attributed the 6.7% decline to the decreased use of HT—a decrease that accelerated in mid-2002.¹ At that time, the WHI randomized controlled trial of HT was unblinded because of data showing an increased risk of cardiac events, pulmonary embolism, stroke and breast cancer.² Prescriptions for HT fell by more than 20 million over the next year. Since the decreased incidence of breast cancer was seen in women over age 50 and mainly in estrogen-receptor (ER)-positive tumors, the decrease in HT use was felt to be the explanation for the drop. Although decreased mammography rates were considered, this decrease was not felt to be large enough to account for the 6.7% decrease in breast cancer incidence. The recent WHI follow-up study does not support the HT explanation of the drop;³ the magnitude and timing of the decrease argues against HT as well. The stabilization of mammogram rates followed by a decline appears to be a more likely cause of the decrease in breast cancer incidence. That would be cause for concern.

In the follow-up of the WHI study, both the placebo and HT groups stopped their medications but not their mammograms in 2002.³ There was no change in breast cancer incidence 3 years later (HT group: 0.43% incidence in 2002, 0.42% in 2005; placebo group: 0.34% in 2002, 0.33% in 2005). This argues against HT cessation as causing the decline in breast cancer.

Earlier data suggest that it takes 5 years after stopping HT to return to baseline risk,⁴ so a large drop in incidence would not be expected within 1-2 years of stopping HT. The increased risk of breast cancer with HT use varied with length of use and age, but was a 1-2% absolute increase.⁴ Stopping HT, therefore, should not result in a 6.7% decrease in breast cancer over any time period. The fact that most of the decline was in ER-positive tumors is consistent with the decline in mammography rates for postmenopausal women, who have a high percentage of ER-positive

tumors. There was no decline in mammography rates for premenopausal women, who have a lower percentage of ER-positive cancers.⁵

Breast cancer rates should start to decline a few years after mammogram rates stabilize because mammograms detect cancer a few years before clinical detection. As long as mammogram rates are increasing, the incidence of breast cancer will increase, as we have seen in the 1980s and 1990s. Once they stabilize, as they did in 2000,⁵ breast cancer incidence should start to drop a few years later. When mammography rates decrease, there should be an immediate decrease in breast cancer detection. Every 1% decline in mammograms would yield a 1% decline in breast cancer detection. Ravdin and colleagues cited data showing a 3.2% decline in mammographies from 2000 to 2003. This decline, combined with the delayed decrease from stable rates, could explain the 6.7% drop. But what is the true decrease in mammography rates? Breen et al found a 6.8% decline in



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women ages 50-65 and a 4.1% decline in women over age 65 from 2000-2005.⁵ This is much closer to the 6.7% breast cancer decline. Stopping HT should result in a decline in breast cancer rates, but the sudden large drop is better explained by the stabilization and subsequent decline in mammography rates.

While the decrease in breast cancer incidence is welcome, we shouldn't celebrate if it is due to declining mammography rates. While we await more incidence data, we need to examine the reasons for the decline in mammography and reverse the trend. Mammography has significantly contributed to the increase in breast cancer survival rates, accounting for almost 50% of the improvement.⁶ If the drop in incidence is due to declining mammography rates, we will just see more cancers later with poorer prognoses—certainly a cause for concern.

—Robert R. Shenk, MD, FACS

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Multiple reports have documented a decline in breast cancer incidence in the US that parallels the decrease in the use of postmenopausal HT that followed the publications from the WHI.¹⁻⁴ The decline was partially influenced by a decrease in screening mammography in the US, but the correlation with hormone use exists even when the examined population includes only women screened with mammography. The 3-year follow-up from the WHI reported 79 cases of invasive breast cancer in the treated group in the follow-up period compared with 60 in the placebo group, and the authors puzzled over why these numbers didn't jibe with the national decline.⁵

There are two important points to be made. First, the 3-year follow-up breast cancer data may not conflict with the national observations. In the most recent previous WHI report on breast

cancer, another WHI puzzle was apparent.⁶ The hazard ratio of 1.20 for breast cancer was no longer statistically significant after multiple adjustments were performed—adjustments that were necessary because, despite the size and randomized design of the trial, important

differences existed in comparing the treated and placebo groups. A closer look at the data

reveals an expected age-related increase in breast cancer in the treated group, but there is no age-related increase in the placebo group—an increase that *should* be there. There is no reason that these differences are still not present

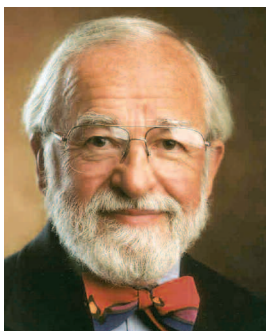
I have repeatedly argued that the epidemiologic data on breast cancer reflect an impact of HT on preexisting tumors. The national decline in prevalence and the WHI results are both consistent with such an effect.

—Leon Speroff, MD

in the 3-year follow-up report, responsible for a lower prevalence in the placebo group and masking a true decline in the treated group. Indeed, the WHI authors conclude that the trend of increasing breast cancer during the trial period did not extend into the follow-up period. Thus, it is very likely that the WHI results agree with the national data.

The second point to be made is even more important. I have repeatedly argued that the epidemiologic data on breast cancer reflect an impact of HT on preexisting tumors. The national decline in prevalence and the WHI results are both consistent with such an effect. If HT is affecting preexisting tumors, one would expect small, undetectable tumors to stop changing (at least temporarily) when women discontinue HT. This response would be consistent with the effects being reported; namely, a decrease in ER-positive tumors in younger postmenopausal women. Now a new worry must be addressed. Will tumors that stopped growing or changing (thus, escaping detection) emerge later and be of greater stage and grade of disease with poorer outcomes? The answer should become available in both the national data and the WHI follow-up over the next few years.

—Leon Speroff, MD



Leon Speroff, MD

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In 2007 Ravdin et al¹ reported a sharp 6.7% decline in the age-adjusted incidence rate of breast cancer in women in the US in 2003, and they related that decline to the decreased prescribing of estrogens after publication of the WHI results in 2002. They utilized the SEER database. This was interpreted as proof of the relationship of estrogens to breast cancer.

In another study, published this year from the WHI postintervention phase, Heiss et al² showed an almost identical hazards ratio to

that seen in the intervention phase of the trial, therefore not showing any decrease in breast cancer after discontinuation of drug. In fact, the annualized rate of breast cancer in those assigned to Prempro 2.5 was 4.3 cases per 10,000 during the clinical trial and 4.4 cases per 10,000 during the post-

intervention phase; for those assigned to placebo the rates were and 3.4 per 10,000 (clinical trial) and 3.3 per 10,000 (postintervention). These reports appear to be at odds with each other: one study showing a decrease in the diagnosis of breast cancer correlated with a decrease in usage in the population,¹ and the other showing no decrease after discontinuance of therapy in a clinical trial.² What might explain the apparent differences between the findings?

The publication by Ravdin et al uses data from the SEER database, a program of the

National Cancer Institute collecting data from nine cancer registries and reporting on 26% of the US population. There were many published criticisms of the Ravdin study:

1. There was no control for a probable decrease in mammography in those discontinuing HT. In the WHI postintervention phase study, subjects who discontinued therapy continued with regular mammography.
2. The findings reported in the SEER database by Ravdin et al are not present in another database from Scandinavia.³
3. Inspection of the graph from the SEER data would indicate a small decrease prior to the publication of the WHI study with a greater decrease after the WHI. If true, the decrease was occurring before the WHI.
4. It had been expected that there would be an eventual decline in breast cancer due to the introduction of wide-scale mammography. The decline could explain this phenomenon.
5. Biologically, the decrease in breast cancer rate is too much, too soon. A decrease is apparent in the fourth quarter of 2002, after the original WHI data were reported in mid-2002. This is too early for a biological effect of estrogen/progestin withdrawal. Ten to 15 percent of women use hormones and two-thirds of those patients use estrogen alone, which was demonstrated to have a statistically insignificant decrease in breast cancer rates. Indeed, the 24% reduction was statistically significant in compliant patients. Patients discontinuing therapy in the general population would be compliant users. These patients could not affect the rate of breast cancer as they, unlike the combined hormone users, had no increase in breast cancer rate. Furthermore, only 38% stopped using hormones in 2002, with further reductions in 2003. With only about 1 extra case of breast cancer per 1,000 women per year from combined HT, a 6% drop from discontinuance of therapy is too large. Furthermore, if estrogens cause cancer a drop in the cancer rates would occur many years after discontinuance of therapy.



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Heiss et al concluded that their information was insufficient to support or refute any hypothesis regarding the reported temporal decrease in breast cancer incidence after discontinuance of HT.² I disagree. Their data show that those who previously used hormones and presumably are no longer using hormones continued to have a numerically increased rate of breast cancer, although it was statistically insignificant. The WHI data would more closely agree with the Scandinavian data.

In conclusion, the impact of discontinuation of HT cannot be addressed by either of these studies, and may once again have to be addressed by observational studies, some of which have shown a disappearance of an increased risk within 6 months after discontinuance of therapy. These studies also are plagued

Heiss et al concluded that their information was insufficient to support or refute any hypothesis regarding the reported temporal decrease in breast cancer incidence after discontinuance of HT.² I disagree.

—Ian H. Thorneycroft, PhD, MD, PC

by the question of mammographic frequency. For the time being, I believe it better to use the WHI postintervention-phase data and inform patients that no early decrease in breast cancer risk has been noted in past users.

—Ian H. Thorneycroft, PhD, MD, PC

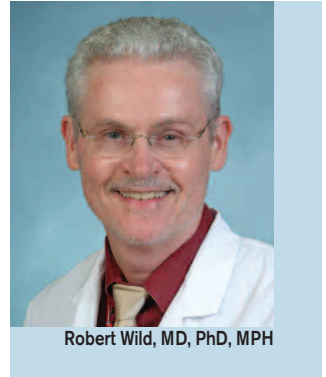
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Using the SEER registry, Ravdin et al¹ point out that there was a decrease in breast cancer incidence in 2003. This decrease seems to be temporally related to the first report of the WHI and the ensuing drop in the use of HT among postmenopausal women in the US. The paper describes an association and, because of its design, cannot prove causality. There are a number of possible alternative explanations for the findings. The authors point out that changes in breast cancer screening may be an alternative explanation. The authors favor a direct effect of HT on preclinical disease as the best such explanation. The paper caused quite a stir and a lot of concern amongst patients and doctors because many were sensitized to what happened when the original WHI trial results were publicized (pointing out that the incidence of breast cancer, although infrequent, was higher in women using EPT).

The paper basically strengthens the perception that HT use has significant public health implications. It provides the basis for an excellent discussion and underscores the importance of breast screening for women before they are started on HT, since such treatment is likely to stimulate preexisting tumors. As Ravdin and colleagues argue, the decline in numbers can be just as attributable to women not initiating HT as to women actually stopping it.

Previous meta-analysis of available HT studies provided fairly strong estimates of continuing breast cancer risk following HT cessation, with a model of steadily declining risk until it normalizes 5 years after stopping HT.² The WHI findings, as reported by Heiss et al, are in keeping with this, although the authors acknowledge that there were insufficient numbers to assess trends.³ The two studies are not mutually contradictory; a combination of declining risk after stopping HT and fewer women starting HT could, at least



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partly, explain the drop in breast cancer incidence seen following the first WHI report.

I think advice to women over age 50 stays the same—to start HT for symptomatic relief, to stay on it as long as it is needed, and, in general, that the benefits outweigh the risks. In addition, patients should be encouraged to have a mammogram if they haven't had one in the past year before starting HT, and to continue with regular breast screening. Women should be cautioned that more false-positives are likely because of associated breast density.

Advice to women with premature menopause regarding initiating and continuing HT may, of course, be different. The WHI does not address these patients, and because of the absence of randomized prospective studies in this group, questions of overall risk/benefit remain unresolved.

—Robert Wild, MD, PhD, MPH

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