

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).

Editor's note: The first two responses to the question below (by Steven R. Goldstein, MD and JoAnn V. Pinkerton, MD) appear in the March/April 2007 issue of Menopause Management (page 26).

Question: Given your review of The North American Menopause Society's March 2007 Position Statement on estrogen and progestogen use in peri- and postmenopausal women, together with recent epidemiologic data suggesting a reduction in the incidence of breast cancer since the termination of the Women's Health Initiative, what might you consider as changes in your clinical practice with regard to hormone usage after menopause?

Answers:

In preparing to answer this query, I carefully reviewed the recent NAMS position statement¹ and reviewed the Surveillance, Epidemiology, and End Results (SEER) data summary² and Geneva registry data.³ The NAMS Position

Statement is quite up-to-date and balanced in its approach to the use of hormone therapy (HT) or estrogen therapy (ET). It summarizes the thought process of a group of erudite individuals who certainly know the current evidence-based data regarding menopause therapies. It also gives a balanced view and allows the provider to make a judgment regarding the use of hormones on an individual, case-by-case basis. Although these recent articles suggest that there is a decline in breast cancer rates in women because of the decrease in the nationwide use of hormones, I do not believe the data are conclusive. At this point I would not change the NAMS position on this since it is balanced. I will also continue to administer hormones after careful discussion about their benefits and risks with the individual patient. It is also my practice to prescribe the lowest effective dose; currently, I do minimize the exposure to progestins.

The cancer data in the SEER study shows a steep decline in the number of breast cancer cases in 2003.² This is obviously excellent news. The SEER investigators suggest that breast cancer rates have declined due to the "sharp discontinuation of HT" following the Women's Health Initiative (WHI) report of 2002. The question is: Will stopping HT or ET have a significant impact on future rates of breast cancer?

Needless to say, since 2002 we have also learned from the WHI population that ET

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does not increase breast cancer rates (at least during a study duration of about 7 years). We are left with the fact that HT does slightly increase the rates of invasive breast cancer (but not in situ), albeit also with a shorter duration

Are we finally seeing some effect from early screening or is it the discontinuation of HT or the focus on using progestins differently that will make the difference?

—Veronica A. Ravnikar, MD

of use. If we take these assumptions literally, we would have to say that the terminology distinguishing HT and ET should be clarified. The suggestion is that progestins may be the culprit in increasing the rate of breast cancer, along with a critical duration of use of ET and HT. The summary of this data is clearly defined in the NAMS Position Statement.

Another point to consider is that the SEER database is not the same as the WHI database. The SEER database follows all ethnic groups, features the Hispanic/Latino populations, and reports only invasive breast cancer. For breast cancer, death rates declined from 1995 through 2003 in Latinas, non-Latinas, white and black women, with a steep decline in 2003. This decline was seen most dramatically in women between the ages of 50 and 69, who had estrogen-positive tumors.

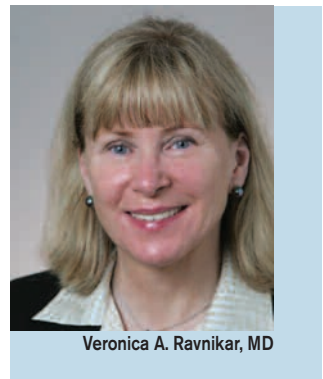
The entry and follow-up into this SEER database is somewhat less consistent in Latinas due to immigration issues and the fact that Latinas tend to travel back to their countries when they have a cancer diagnosis. Latinas also represent a population of women who generally do not use HT. It is not appropriate to assume that the WHI study population is the same. In fact, the authors of the SEER database comment that, “Most registries in the SEER regions, upon which trends statistics are based, reported a steep decline in the number of 2003 breast cancer cases...The factors that influence breast can-

cer incidence are complex, including reproductive risks, obesity, age-cohort effects, and the prevalence of mammography screening, among others.”²

In contrast, a study published from a Geneva cancer registry previously suggested a correlation between discontinuation of hormones and lowering rates of breast cancer, leading to this notion of cause and effect.³ However, in this database a different trend was appreciated. Instead of breast cancer continuously rising after age 65, the highest breast cancer risk was associated with 60- to 64-year-old women who had early-stage disease and estrogen-positive tumors. In the subgroup of women for whom the investigators had information on HT use, the peak breast cancer incidence occurred only in these women. Trends for breast cancer after age 65 sharply declined overall. Again, good news, but this does not necessarily imply a direct cause-and-effect relationship. It may imply, as the authors also suggest, that breast cancer is revealed at an earlier age in HT users, and therefore may also be responsible for the decline in breast cancer after age 65.

Nevertheless, I feel it is premature to make overreaching assumptions that declining rates of breast cancer are due to the declining use of HT, especially ET. There is no way to make head-to-head comparisons with the SEER data, the Geneva cancer registry, and the WHI. Needless to say, following these trends further is still of vital interest since the rates of breast cancer have been declining over this decade. If we put all this disparate information together, we must ask: Are we finally seeing some effect from early screening or is it the discontinuation of HT or the focus on using progestins differently that will make the difference? Can we safely say to a patient that estrogen uncovers preexisting lesions? Time will tell.

As the final pages of the NAMS Position Statement suggest, there are still areas that



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preclude consensus and areas that need further research. The NAMS guidelines sufficiently justify the use of HT or ET in various clinical settings, and I do not feel that they need to be changed on the basis of the above database results. However, the issue of type and use of

To me, a fundamental problem with large studies and derivative guidelines is that what may be right for a population is difficult to apply to the individual.

—Marcie K. Richardson, MD

progestins and duration of therapy is still not practically defined. Furthermore, age-stratified recommendations as to how to treat new-start patients peri- and postmenopausally are needed—that is, which type of therapy to use; oral contraceptives or sequential HT. The guidelines should also address patients who want to restart therapy for various reasons beyond the 6th and 7th decades, short of stipulating that this should never occur since such a statement is impractical. Finally, addressing the risk of a genetic cause for thrombophilia is also important since this condition is common and the data show a distinct risk-benefit ratio with different routes of HT.

—Veronica A. Ravnikar, MD

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This commentary reflects the opinion of an Ob-Gyn who thinks of herself as supportive of evidence-based medicine, and as a feminist. Identifying the appropriate role for estrogen in my menopause practice has been an ongoing challenge. Just the way it still bothers me to hear

obstetricians talk as if no woman is capable of having a healthy baby without obstetric intervention, I was always uncomfortable with the notion promoted by many of my colleagues in the 90s; specifically, that all postmenopausal women should be on estrogen. But by the same token, I find the assertion of activist and scholar on aging Margaret Morganroth Gullette that “it is time for estrogen nostalgia to go the way of whalebone corsets and bound feet” over the top. She might find it enlightening to sit in my office and hear from the women who have tried to go off estrogen and endured many ongoing miserable months.

But what about the 2007 NAMS Position Statement? What distinguishes it from the one published in 2004? What does that tell us about progress in woman’s health research? Can it help us with our patients?

Some notable differences in the new statement include:

- the assertion that progestogen is not generally indicated when low-dose estrogen is administered locally for vaginal atrophy. This is a reassuring opinion for those of us who like to limit our patients’ exposure to progestogens, although it is just that—opinion;
- the concept of age-related vulnerability to the effects of HT, especially in relationship to cardiovascular disease. This was only hinted at in the previous statement. No therapeutic recommendations can be made on this basis, however, because there are no randomized clinical trial data to investigate this notion;
- mention of a few very small studies on estrogen and depression—certainly an area that needs more study; and
- the statement that breast cancer risk increases with use of HT beyond 5 years, whereas previously it was suggested this was only probable.

An additional interesting point of comparison is that in 2004 there were 25 “areas for future research,” and now there are 32.

There are some ways in which the current document leaves one with the sense that its authors are holding out hope that there is a pro-

phylactic role for estrogen in managing the postmenopausal woman, perhaps the sense that Ms. Gullete was trying to capture and repudiate. The repetition that estrogen cannot be recommended for prevention of coronary heart disease, stroke, and diabetes seems off the mark. Was estrogen ever being used or advocated to prevent diabetes or stroke?

The 2007 Position Statement both cautions against extrapolation from one kind and dose of HT to another, yet suggests we have to use

the data we have—mostly on one kind and dose of HT—to estimate risk. To me, a fundamental problem with large studies and derivative guidelines is that what may be right for a population is difficult to apply to the individual. But, this is what we have. So, I appreciate the effort of Dr. Utian and his team

in attempting to summarize what that is, and especially in identifying that there are more and more areas that need future research.

I will continue to try to sort out the best approach for the woman in my exam room by trying to hone in on where the benefit and harm equation really lies for her within the limited framework provided by the science, such as it is.

—*Marcie K. Richardson, MD*

My clinical practice with respect to prescribing HT has not changed despite the recent report of a 7% decrease in the incidence of breast cancer in the year 2003. This apparently good news has led the media to erroneously conclude that the finding is solely related to women stopping HT after the July 2002 early ending of the estrogen plus progestogen therapy (EPT) arm of the WHI.¹ There are a number of factors that may account for this news: better breast health and awareness, decreased use of hormone disruptors present in pesticides and preservatives, increased use of agents known to reduce breast cancer di-

agnosis (tamoxifen and raloxifene), as well as the real concern about decreases in breast cancer diagnoses due simply to decreases in access to screening mammography. Malpractice, governmental regulation, and a shortage of breast imagers have led to wait times to up to 6 months for screening mammography in many areas of the country. Furthermore, recent reports have noted that up to 33% of breast cancer survivors, known to be at the highest risk for breast cancer, do not even return for annual mammography.²

It is important to note that decreases in breast cancer mortality rates predated the premature stoppage of the EPT arm of the WHI. During the so-called heyday of HT, age-adjusted breast cancer mortality in white females in the US dropped by 6.8% from 1989 to 1993.³ During this timeframe, decreases in breast cancer mortality dropped too rapidly to be explained solely by either use of screening mammography or increases in survival due to breast cancer therapy

alone. It has been estimated that the number of prescriptions for HT in the year 2003 was similar to the prescription rate in 1995.⁴

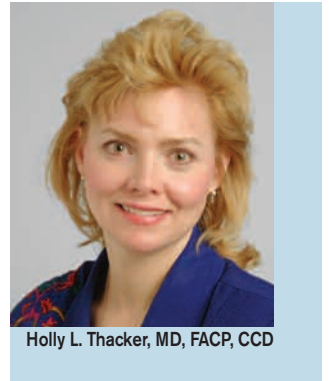
Nevertheless, women are acutely concerned about breast cancer risk, and many women and clinicians associate any hormone use with an increased risk of breast cancer. I routinely assess breast cancer risk in peri- and postmenopausal women and, in the absence of other known high-risk situations (such as prior breast cancer, known BRACA mutation, LCIS or atypical hyperplasia), I calculate a woman's baseline 5-year risk of being diagnosed with breast cancer using the Gail model (www.cancer.gov/bcrisktool/).

I explain to patients that using EPT for over 5 years has been associated with a relative risk of 1.24 for breast cancer diagnosis.⁵ If, for example, a woman's 5-year risk for breast cancer diagnosis is calculated at 1.0%, then 5 or more

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years of EPT would increase that risk by 24% (1.0% multiplied by 24% = 0.24 and 1.0 + 0.24 = a 1.24% 5-year risk of being diagnosed with breast cancer; a woman with a baseline 5-year risk of 2.0% would have a 2.48% risk of breast cancer diagnosis if on long-term EPT). Women who have been hysterectomized and are on ET, specifically 0.625 mg of conjugated equine estrogens as used in the ET arm of the WHI, are informed that studies showed no increase in breast cancer diagnosis for up to 7.1 years, with an actual decreased risk of breast cancer diagnosis in women adherent to treatment.⁶

In women at high risk for breast cancer, I consult the BRCA mutation prevalence tables for risks of carrying the BRCA gene mutation (www.myriadtests.com/provider/brca-mutation-prevalence.htm), and if there is a 10% or greater chance of carrying a BRCA mutation I refer the patient for formal genetic counseling. Women with a 5-year risk for breast cancer diagnosis of 3% or more and/or a lifetime risk of breast cancer diagnosis of 30% or more are referred for more intensive follow-up and/or are given more intensive risk assessment and risk reduction information, including tamoxifen chemoprevention or raloxifene therapy. I also assess these women for any nipple aspirate because any woman with nipple discharge may be a candidate for breast ductal lavage (an FDA-approved procedure, but not a diagnostic procedure), which can be done for further risk assessment. I also consider referral for more intensive evaluation, such as adjunctive breast magnetic resonance imaging, and/or participation in chemoprevention trials. If a woman has a sister with breast cancer, I refer her to the Sister Study (www.sisterstudy.org), a National Institutes of Health-sponsored study looking into breast cancer causes.

Finally, the recently released NAMS 2007 Estrogen and Progestogen Position Statement⁷ provides very helpful information for the clinician in communicating benefits and risks of HT in terms of classifying the increased

risk of breast cancer as “rare” (less than 1 per 1,000 woman years, or 4-6 additional invasive breast cancers per 10,000 women per year who use EPT for 5 or more years). This new position statement also notes that extended use of HT is acceptable as long as the woman is aware of the risks and benefits and is under clinical supervision, something that should be true of any prescription therapy.

—Holly L. Thacker, MD, FACP, CCD

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