

# From the EDITOR



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A pioneer in menopause research, Dr. Utian founded the world's first menopause clinic in Cape Town, South Africa, in 1966, and established the Cleveland Menopause Clinic in 1983.

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## Reconsidering Postmenopausal Estrogen Therapy and Breast Cancer

Yes, I am back on that controversial topic of postmenopausal estrogen therapy (ET) and breast cancer, although the recent news from two major studies makes it a lot less confusing this time.

In 1994 I wrote: "There are data that the relative risk of breast cancer will increase up to 30% in women who have taken high doses of estrogen for more than 10 years. That is, the relative risk might increase from one woman in 1,000 per year to about 1.3 women in 1,000 per year after long-term [estrogen replacement therapy] ERT. This change indicates that—in a low risk population—the potential benefits of ERT outweigh the potential risks."<sup>1</sup> I also noted, "studies suggest that postmenopausal ERT has no negative effect on recurrence of disease or survival in postmenopausal women who develop carcinoma of the breast." Nonetheless, I added, "in all instances where ERT or [hormone replacement therapy] HRT is being prescribed, it is mandatory that the woman be well counseled so that she can make an informed decision and her care can be individualized. In general a conservative approach appears justified because definitive answers are unavailable at this time. Fortunately, studies are beginning that soon may provide solutions to this vexing dilemma."<sup>1</sup>

When that was written, we hardly realized that a part of the dilemma was to differentiate between the effects of estrogens and progestogens, individually or in combination, thinking as we did that risks were probably equally distributed. Now we are acquiring the fruits of long-awaited research, and even as we answer some of the old questions, others arise.

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### Women's Health Initiative

Follow-up results from the Women's Health Initiative (WHI) estrogen-alone trial show that treatment with conjugated equine estrogens (CEE) alone in women 50 to 79 years of age with prior hysterectomy does not increase the risk for breast cancer.<sup>2</sup> CEE treatment alone does increase the incidence of mammography screening requiring short-interval follow-up, and it does show a reduction for ductal carcinomas (HR, 0.71; 95% CI, 0.52-0.99) but not for lobular disease. Of even greater significance, buried in the results is the finding that "in adherence-adjusted analyses that censored follow-up 6 months after a woman became nonadherent, a larger and significant reduction in the incidence of breast cancer was observed in the CEE group compared with the placebo group (HR, 0.67; 95% CI, 0.47-0.97;  $P = 0.03$ )."<sup>2</sup> Indeed, the hazard ratios appeared to indicate, with a divergence of the lines, that this apparent protective effect of CEE might be increasing with time.

To me, comparing the outcomes between groups of study volunteers who are actually taking the active drug and those who are on placebo (adherent-adjusted analysis) makes a lot more sense than some investigators' confusing persistence in comparing outcomes on an "intention-to-treat" basis. In the latter situation, individuals not on active drug in the CEE group (drop-outs) are often compared with individuals in the placebo group who are on active hormone therapy (HT) (drop-ins). Thus, for example, this latest WHI CEE-alone study reports that "54% of participants were no longer adherent to study medication."<sup>2</sup>

### Nurses' Health Study

Subsequently, an analysis of estrogen-only treatment after menopause for up to 20 years of use was reported from the large Nurses' Health Study from Boston.<sup>3</sup> This observational study found a trend to increased risk with time, but risk only became statistically significant after 15 years of current use for estrogen- and progesterone-receptor positive cancers. Overall, among women who used

ET for less than 20 years, an increased risk of breast cancer was not seen.<sup>3</sup>

Thus, the WHI results appear to be indicative of an increased protective effect over time, while the Nurses' Health Study suggests increasing risk beyond 15 or 20 years of estrogen use. Both studies share the problem that their data are weaker the further out the studies are evaluated because of a decrease in statistical power. Even with this proviso, these findings are quite contrary to previous expectations. At the least, these findings are quite reassuring for hysterectomized women taking 10-15 years of CEE alone.

### New Questions

As noted, new data seem always to identify further unanswered questions, and these reports certainly do that. First, the WHI estrogen-plus-progestogen (CEE-medroxyprogesterone acetate [MPA]) group demonstrated a slight increased risk of breast cancer.<sup>4</sup> One question that arises is whether the nonhysterectomized

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women are showing an effect of MPA. Indeed, would any progestin carry the same risk? Another puzzle is whether the difference that exists between combined, continuous use of estrogen plus progestin (EPT) (as in the WHI) and use of estrogen alone is due to the regimen of continuous administration of MPA. If so, would reduction in progestin duration of exposure and/or dose (sequential or long-term sequential administration—say, for 12 days on alternate months) reduce that risk?

The second question that arises is this: Do these results imply that CEE is the effective drug since CEE is a multicomponent biological product? That is, might there be a component in CEE that protects the breast, and

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