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# MAKING THE CASE FOR PROGESTIN TRIALS: Progestins and Breast Cancer Risk

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Roy Scott

**While there is general agreement that up to five years of use of any type of hormone therapy is not associated with a significant increased risk of breast cancer, the epidemiologic evidence about the role of progestins in breast cancer is conflicting. Most studies have examined only one hormone therapy regimen. Further research is needed on the effects of different dosages and types of progestin, and larger randomized trials are urgently needed to compare different estrogen and progestin combinations and doses.**

## Introduction

The use of long-term, combined hormone therapy (HT) is currently controversial. Findings from recent epidemiologic studies have suggested that long-term use of combined HT is associated with a small increased risk of breast cancer.<sup>1,2</sup> Unfortunately, the majority of the clinical trials of HT and breast cancer risk have been performed using either conjugated equine estrogens (CEE) alone or in combination with medroxyprogesterone acetate (MPA). Most of the available evidence would suggest that hormone therapies act as promoters of breast cancer but are not causative agents. To date, the etiology of most human breast cancers remains unknown. Approximately 5-10% of these cancers are probably caused by inherited abnormal genes (such as the BRCA-1 and BRCA-2 genes). Long-term HT has been advocated in the past to lower the risk of cardiovascular disease and osteoporotic fractures. The reality is that most women who take HT take it for the relief of menopausal symptoms.

There is no doubt that the risk of breast cancer does correlate with reproductive markers of ovarian function, such as age at menarche, age at first birth, age at menopause and number of ovulatory cycles. A number of researchers have suggested that unopposed estrogen therapy modestly increases the risk of breast cancer and the addition of progestin further increases this risk. However, I would contend that a broad review of the literature does not uphold these suggestions and that this is an overly simplistic view of a complex issue. This short article will review the current understanding of the role of progesterone and progestins in breast cancer risk. For those interested, a longer review of this subject appeared in a recent issue of the *American Journal of Obstetrics and Gynecology*.<sup>3</sup>

## Cellular Studies of Progesterone

Research at the cellular level has

demonstrated that progesterone can act both as a proliferative and an anti-proliferative agent in breast tissue. For example, breast biopsy studies have shown that the highest mitotic activity is found during the mid-luteal phase.<sup>3</sup> Pregnancy also is associated with marked mitotic activity. On the other hand, clinical trials of progesterone creams applied topically to the breast have shown that percutaneous progesterone seems to behave as an anti-proliferative agent.<sup>3,4</sup> Cell culture studies using human breast cancer cell lines have demonstrated that progesterone and most progestins induce a biphasic response in these cells.<sup>3</sup> Typically, progesterone or progestin induces mild proliferation over the first 24 hours, followed by prolonged inhibition of proliferation.

There also is evidence that different dosages and types of progestin will induce different effects. This scenario is not unique to progestins. Low doses of estradiol stimulate most estrogen-receptor (ER)-positive breast cancer cell lines, yet diethylstilboestrol was used clinically for many decades as a successful treatment for advanced breast cancer, including ER-positive metastatic breast cancer. Many bodily systems behave in the same way. A low, intermittent dose of a particular hormone may induce stimulation, but high, continuous doses of the same hormone may initially induce stimulation but then are often followed by down-regulation of the system. Perhaps progestins work in the same way.

Interestingly, this apparent paradoxical effect is not unique to sex hormones. Kaiser discusses the concept of hormesis in an article that appeared in the journal *Science*.<sup>5</sup> The fascinating concept of hormesis was first described in 1888 by the German pharmacologist Hugo Schultz, who observed that small doses of poisons seem to stimulate the growth of yeast. In more recent times, Edward J. Calabrese, PhD, of the University of Massachusetts has spent over a decade urging toxicologists to recog-

nize that chemicals can have opposite effects at high and low doses. Calabrese and a colleague, Linda Baldwin, reviewed the literature for studies demonstrating hormesis and found thousands of examples. They describe how "plants dosed with herbicides or metals grow lush; bacteria flourish in the presence of tiny amounts of antibiotics; immune cells treated with arsenic proliferate faster..." and point to "insects dosed with pesticides or alcohol living longer and producing more eggs; rats fed a little saccharine developing fewer tumors."<sup>5</sup> We need to move away from the concept that "hormones are bad for the breast" and expect to see paradoxical affects. MPA, in large doses (400-1,000 mg), is an effective treatment for advanced breast cancer, yet when added in small doses to estrogen therapy, it appears to enhance breast cancer risk.

## Progestins and the Synthesis of Estrogen

One of the most important discoveries over the last decade or so has been the realization that the breast not only reacts to estrogen, but also produces it.<sup>3</sup> There appear to be two main biosynthetic pathways in the breast; the best known of these is the aromatase system. Aromatase is the enzyme that converts androgens into estrogens. Aromatase inhibitors have been used for many years to successfully treat breast cancer; however, within the breast a second estrogen biosynthetic pathway known as the sulfatase-sulfotransferase system seems to be more important. Estrone sulfate is the most abundant estrogen in the bloodstream. Many tissues contain the enzyme sulfatase, which can cleave off the sulfur molecule, leaving the active estrogen. Within the breast it would appear that the sulfatase pathway is 50 to 500 times more important than the aromatase pathway.

Another important enzyme within the breast is 17 $\beta$ -hydroxy-steroid dehydrogenase, which catalyzes the bidirectional conversion of inactive estrone to

the biologically active estrogen, estradiol. In broad terms, many progestins, as well as tibolone and its metabolites, promote the production of weak estrogens over strong estrogens and/or act to estrogen-deplete the breast.

### Epidemiologic Evidence

The relationship between HT use and breast cancer risk has been examined in many epidemiologic studies with mixed and inconclusive results. In the past 25 years, there have been more than 50 epidemiologic studies and at least six meta-analyses. It is fair to say that most of these studies contain robust data for unopposed estrogen, with relatively few studies specifically addressing the effect of progestin on breast cancer risk. A few recent studies have received much attention because of the reported modest increase in breast cancer risk in selected sub-populations of HT users. In an analysis of the Breast Cancer Detection Demonstration Project data, Schairer and colleagues<sup>6</sup> concluded that use of combined HT results in a greater risk of breast cancer than unopposed estrogen. This conclusion was based on relatively few subjects and appeared to be limited to a small group of lean women who used progestins for fewer than 15 days. However, the relative risks did not achieve statistical significance.

Similarly, Ross and colleagues<sup>7</sup> reported the results of a

population-based, case-controlled study that also suggested that there was a greater risk of breast cancer with combined HT compared with unopposed estrogen. Again, the number of subjects available was very limited and the comparisons were not statistically significant. On the other hand, there are other studies that have failed to show any significant effect on breast cancer risk.<sup>3</sup> This lack of consistency from a large number of epidemiologic studies suggests that there is either no effect of combined HT on breast cancer risk, or that there is a small risk, perhaps limited to a select population of women.

The preliminary results of the Women's Health Initiative (WHI) study, involving more than 16,000 post-menopausal women, were published in July 2002.<sup>1</sup> The WHI investigators reported a hazard ratio for the risk of invasive breast cancer of 1.26 (95% CI, 1.00 to 1.59). In absolute terms, after 5.2 years they found eight more breast cancers per 10,000 women per year amongst HT users, with an absolute increased risk of breast cancer of 0.4%. Sub-group analysis found that the only group that had a significantly increased risk of breast cancer was the group of women who had been on HT before entering the study. In other words, the results of WHI are consistent with the previously published observational data, suggesting that there may be a slightly increased risk of breast cancer with up to five years' use of combined therapy. The estrogen-only arm of the WHI study is still continuing. Furthermore, two forms of confidence intervals (CIs) are presented in the WHI report, nominal and adjusted. Neither the nominal nor the adjusted CIs were significant.

There have also been several studies looking at the use of combined HT in higher-risk women. For example, one large, prospective cohort study involving more than 41,000 women with a positive family history of breast cancer found that women who were receiving HT did not have a significantly higher risk of breast cancer than those women who never used hormones.<sup>8</sup>

HT is usually withheld from women with a personal history of breast cancer for fear of stimulating a recurrence of the tumor. However, some women have such severe symptoms that they have little choice but to go on some form of hormone therapy. A nested, case-controlled study in Australia examined 1,122 women with surgically proven breast cancer and found that combined HT use after a diagnosis resulted in a significant reduction in risk of recurrence compared with non-use, as well as a significant reduction in all-cause mortality, and death from the primary tumor.<sup>9</sup> It's interesting to note that the majority of the women used a daily dose of progestin equivalent to 50 mg of MPA, a higher dose than commonly given with estrogen, in an attempt to elicit an anti-estrogen effect on the breast. An American study<sup>10</sup> examined 2,755 women diagnosed with breast cancer and observed a significantly lower risk of recurrence for the HT users. In contrast to the Australian study most patients used estrogen without a progestin.

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## Progestins and Breast Cancer Risk

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### Effect of Progestins on Breast Density

Many studies have shown that women on HT appear to have an increase in parenchymal breast density.<sup>3</sup> Most of these studies have suggested that combined HT is associated with a higher rate of breast density than unopposed estrogen use. There are some data suggesting that an increase in breast density is associated with a greater risk of breast cancer.

### Conclusions

In my opinion, there is conflicting epidemiologic evidence about the role of progestins in breast cancer. Most of the studies have examined only one regimen (CEE and low-dose MPA). There is general agreement that up to five years of use of any type of HT is not associated with a significant increased risk of breast cancer. However, it is clear that further large randomized trials are needed. It is entirely possible that low doses of MPA protect the uterus from malignant change, but higher doses of MPA are required to lower the risk of breast cancer. It is also plausible that progestins can be developed (or may already exist) that have a breast-protective effect.

Cellular studies of progesterone and progestins have suggested that low-dose intermittent progesterone appears to stimulate cellular proliferation whereas high-dose continuous progestin may inhibit the breast. There are differences in the laboratory with different progestins. It is clear in the laboratory that some progestins inhibit breast production of potent estrogens and can, in fact, estrogen-deplete the breast.

Ten to twenty percent of women will have significant menopausal symptoms forever. The question then becomes, which therapy should we offer these patients? Further larger randomized trials are urgently needed to compare different estrogen and progestin combinations and doses. In some countries, regulatory authorities are calling for HT to be used only for short-term therapy (i.e., 6-12 months). If this policy were uniformly followed, a large segment of the female population would be doomed to severe, continuing menopausal symptoms forever. As clinicians, we must continue to make the case that this is clearly an unsatisfactory situation, and demand that further clinical trials take place.

For the perimenopausal woman with severe menopausal symptoms, it is my current practice to treat with a cyclical HT for a year or two and then attempt to wean her off therapy, usually during the cooler months, by reducing the dosage slowly over three to six months. If symptoms return, I treat such women for an additional year or two and then attempt to wean them off therapy again. About one in eight women will have flushes forever. I recommend low-dose HT or tibolone for these women. ■

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