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Web Exclusive: Ongoing HRT Research

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Five years after the results of the Women's Health Initiative were announced linking combined hormone replacement therapy (estrogen and progestin) to an increased risk of breast cancer, HRT research continues.

Because estrogen is thought to fuel about 70 percent of all breast cancers (estrogen receptor-positive breast cancer), it came as little surprise to some researchers that combined HRT increased breast cancer risk. But what has puzzled researchers are studies that have shown postmenopausal women receiving estrogen-only HRT have no increased risk—and some studies suggest it may actually decrease risk. The question of why combined HRT increases breast cancer risk while estrogen-only does not is one scientists are trying to answer. And much research points to the effect of synthetic progesterones, or progestin.

One theory being tested is the continuous flood of progestin, in addition with estrogen, increases the risk of breast cancer. The milk-producing cells that line the breast ducts, called epithelial cells, proliferate most during the phase of the menstrual cycle where progesterone production peaks. Researchers are pondering if a continuous dose of progestin somehow speeds up or continues the growth phase of these cells, or if it's something else, such as another form of estrogen called estradiol.

Studies have been contradictory that compare regimens of progestin, taken either continuously or sequentially. A study published in the *Journal of the American Medical Association* in 2003 found that daily progestin compared with sequential progestin (10 days a month) in combined HRT found there was no advantage in reducing breast cancer risk in the sequential regimen. Two later studies examining HRT use in breast cancer survivors found women taking a continuous dose of progestin had a much higher risk of recurrence than the group taking a sequential dose. Both studies were stopped early following an interim combined analysis.

And because the sequential dose has been shown to provide as much protection against endometrial cancer—the reason why progestin was added to estrogen replacement therapy—as a continuous dose, less progestin would be just as effective and possibly lower breast cancer risk.

Another option some doctors use is intrauterine devices, such as Mirena (levonorgestrel) and Progestasert (progesterone), which provide small doses of progestin directly into the uterus, thereby lowering the risk of endometrial cancer while not adding progestin to the bloodstream. Vaginal gels, rings, and sprays are also being explored to provide lower, more direct doses of progestin.

Researchers are also looking into the use of natural progesterone instead of synthetic progestin, which may interact with other hormones and receptors differently than the natural hormone. However, as it stands today, experts believe natural hormones, including estradiol, estriol, and progesterone, as well as bioidentical hormones, carry the same risks as synthetic HRT.