

Hormone Replacement Therapy and Breast Cancer Risk

As with other mammals the purpose of the human breast is to produce milk for newborns. It does this in response to a complex pattern of chemical messages called hormones that are produced in the brain, thyroid and ovary. Two of these hormones, *estrogen* and *progesterone*, control a woman's fertility during the reproductive years and the loss of estrogen as the ovaries age creates the symptoms and physical changes of menopause. These include hot flashes, mood instability, sleep disruption, rapid decline in bone density, decrease in skin elasticity, and vaginal thinning and dryness. The average age of menopause is fifty-one.

The breast is primarily fatty tissue that contains multiple pockets of milk producing glands feeding into collecting ducts that exit at the nipple. Because these glands and ducts grow and recede each month in response to the ovaries cyclic production of estrogen and progesterone, they have the potential of developing cancer.

A variety of studies suggest that a woman's risk of developing breast cancer depends in part on her total lifetime exposure to estrogen. This exposure varies with age of first menses, age of menopause, age of first childbirth and number of children. Certain lifestyle features such as alcohol use and postmenopausal obesity may increase breast cancer risk.

While some women pass through menopause with minimal symptoms, the large majority suffer a significant decline in quality of life. While the better known symptoms of hot flashes, sleep disturbance and mood instability resolve with time as the brain adjusts to lower estrogen levels, the impact on structures such as bone, pelvic support and the vagina is progressive.

Several studies have investigated the safety of hormone replacement therapy (HRT). However, the design and quality of most of these studies limit their use only to indicating whether or not a large, expensive, well designed study to determine safety is warranted. One of these, the *Collaborative Study*, was a grouping and reanalysis of 51 smaller studies. It did indicate the need for a large, well designed study when it suggested a small possible increase in breast cancer risk with HRT.

The *Women's Health Initiative* (WHI) study was a series of well designed studies of healthy postmenopausal women aged 50-79 years asking questions about the impact of multiple items on women's health. Two of the WHI studies looked at HRT and were designed primarily to determine if HRT reduced heart disease risk but also examined breast cancer risk with HRT.

One studied women with prior hysterectomies (removal of the uterus) taking *Premarin* and the other studied women without hysterectomies taking *Premarin* plus *Provera*. *Premarin* is a mixture of estrogens derived from horse urine and *Provera* is synthetic progesterone. When a postmenopausal woman with a uterus takes estrogen she must also take progesterone to prevent the estrogen from causing uterine cancer.

The **Premarin-Provera** study found that after five years of use breast cancer risk increased in the HRT group with 4 additional cases of breast cancer per 1000 women. Neither Race nor family history had any impact. Importantly, women taking HRT for less than four to five years had no increased risk. Benefits included 3 fewer cases of colon cancer and 2-3 fewer hip fractures.

The **Premarin-only** study actually trended toward decreased risk. This suggested that Provera (progesterone) may have been responsible for the greater risk in the Premarin-Provera group.

The Nurses Health Study also examined estrogen-only HRT and found a small increase in breast cancer risk but only after 15-20 years of use. Again, the design of this study limited its use to raising but not answering questions about HRT safety.

The overall impact of HRT on lifespan is far from clear and any woman considering HRT should have a thorough discussion with her physician about risks and benefits before making her own decision. Naturally most women fear anything that may increase their breast cancer risk however the loss of estrogen with menopause can have a tremendous impact on quality of life.

As this brief review shows, raising questions about the safety of HRT is easier than finding absolute answers. However, several statements can be made with some degree of comfort.

- Combined estrogen-progesterone use for less than four years does not seem to increase breast cancer risk and allows improved quality of life during the transition through menopause.
- Estrogen-only use appears to be safe for at least 15-20 years of use in women without a uterus.
- Alcohol use should be limited.
- Weight control is important.
- The lowest effective HRT dose should be used.
- The WHI studied only Premarin and Provera. While we may speculate, no accurate statements can be made about other estrogen or progesterone compounds, estrogen-like chemicals in soy and legumes or herbal medicines.