

# Hormone replacement therapy and breast cancer: before, after and alternatives

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**This presentation will attempt to bring clinical relevance to the lack of definitive data on whether or not hormone replacement therapy (HRT) causes a significant increase in the risk of breast cancer.**

**With 4000 women going into menopause daily in North America alone, fully 20% of the population will be hormonally estrogenemic by the year 2000 for the remaining one-third of their life. Although purists still await double-blind cross-over long term studies, the existing evidence shows an overall 46% decrease in excessive mortality in HRT users (1). On average there is a 50% decrease in hip and colles fractures plus a 90% decrease in vertebral fractures (2). The rate of coronary heart disease is 40% decreased overall (3), and seven preliminary studies show 50% less senile dementia in those on HRT (4).**

**In contrast with these encouraging studies are those which appear to show an increase in breast cancer risk in users of HRT. However, there is no consistent trend of increase risk in the 63 major published studies on this issue (5). The recent re-analysis of the data from these studies shows that a meta-analysis is required to show a modest 58% increase in breast cancer risk, which becomes significant only with 15 years of use, and was seen in only 337 cases out of the total 52,700 breast cancers (6). The authors calculate that this increase in risk projects to between 7 to 12 excess cases of breast cancer per 1000 women ages 65 to 75 years using long-term HRT.**

Of interest in the Collaborative Group re-analysis is the fact that this excess risk disappears completely after use of HRT is stopped for 5 years. One is left to speculate on how, once HRT use helps to initiate oncogenic transformation in breast epithelium, the cancer is "cured" by the mere cessation of further hormonal use.

Confounding the issue further is the observation that the presence of the P450 aromatase enzyme in breast tissue can convert androgens to endogenous breast estrogen against a serum gradient (7). Breast duct fluid estrogen in postmenopausal women can be 10 to 40 fold higher than that of serum, even in those not on exogenous hormone replacement (8). This observation should be factored into clinical trials seeking the true risk of HRT on breast cancer occurrence. Other confounding variable not generally assessed which could be relevant, are the different nuclear retention times of the variety of estrogen products used in HRT, the bound versus the bioactive fraction of the estrogen, and cofactors such as insulin-like growth factor, plus the presence or absence of oncogens.

It is hoped that the European 1 million-women trial and the multi-center Women's Health Initiative study will shed more light on this issue. Until the data from these two large prospective trials are available, it may be useful to note that there are ten studies which show an apparent 10-40% increase in survival benefit to those women who were using HRT or oral contraceptives when their breast cancer was diagnosed (9, refs 2, 12-20). The proposed reasons upon which this finding is based are observational bias leading to the earlier diagnosis of smaller more receptor positive tumors (10), an increase in humoral B-cell activation by estrogen (11), less DNA hydroxyl-radical damage because of estrogen's anti-oxidative properties (12), upregulation by estrogen of the gap junction connexin gene which controls growth and suppresses cell diversity (13,14), and lastly an upregulation by estrogen of the normal BRCA-1 protein which may prolong tumors in a premalignant state (15). All of these events have the potential for decreasing the risk of metastatic spread which is the ultimate fatal event.

Equally intriguing are the data from 8 preliminary studies where HRT was re-introduced to breast cancer survivors (9, ref 31-34). Although the total number of patients is 545, some follow-up has been as long as 17.5 years. When compared to non-treated matched controls, there was no difference in disease-free interval nor in death rate in the HRT users.

With the discovery of a second (beta) estrogen receptor (16), allowing for three different dimer configurations, plus the discovery that there are different local co-activator and co-suppressor receptor proteins in various tissue such as breast and endometrium (17), alternatives to standard HRT have become available which are seemingly neutral on breast epithelium stimulation.

So called "designer estrogens" or selective estrogen receptor modulators (SERMs) are currently being developed. The first to be FDA approved, Raloxifene is agonistic to bone, both preventing bone resorption (18), and showing a 50% decrease in vertebral fractures (19). It has a positive effect on lipids (18, 20) and is apparently antagonistic in both breast and uterine epithelium (18, 21). However, the currently reported 50% decrease in

estrogen-receptor positive breast cancer seen at 42 months (22, 23) must be viewed somewhat cautiously given the average doubling-time of 7-8 years for the appearance of a mammographically detectable breast cancer (24). Whether or not Raloxifene has any positive effect on the central nervous system has yet to be reported. An increase of up to 34% in vasomotor symptoms is seen (25). No reports have shown it to help with estrogen-deficiency urogenital atrophy. Two other SERMs, Droloxifene and Idoxifene are in phase III trials, and 12 additional analogues are under investigation.

Plant biphenolic isoflavone phyto-estrogens have been long looked upon as potential substitutes for the use of steroidal estrogen. Epidemiologic evidence of low breast, prostate and endometrial cancers in Asia have been attributed to the high dietary consumption of soy-based isoflavones (26, 27). Cardiovascular disease as well as osteoporosis are equally low in Japan and China (28, 29). There is an apparent health advantage seen in the eastern Mediterranean basin where other isoflavonoid rich food such as lentils and garbanzo beans are heavily consumed.

Animal data in the cynomolgous monkey, which undergoes a human-like menopause (30) and shares greater than 90% genetic homologue with the human female (31), shows soy isoflavones to be significantly cardioprotective (32,33). Although bone resorption was not benefitted in the monkey (34), three human studies show an increase in bone density (35) and a decrease in urinary resorption markers(36). There is no proliferative effect on breast epithelium in the monkey model (30), and human studies on soy products show both a premenopausal (37-39) and a postmenopausal (37-40) decrease in breast cancer. Soy acts as an inverse-agonist in monkey endometrium (30). It appears to be agonistic for human vaginal epithelium (41, 42).

Isoflavones are known to have many anti-mitogenic biochemical properties which include inhibiting tyrosine kinase and angiogenesis activity (39). Over 40 studies invitro and in rodents show anti-cancer effects in over 9 different cancers (35, 39, 43). Whether or not this effect will be seen in humans remains a hopeful possibility. A recently released standardized dose isoflavone pill, Promensil (Novogen, Inc. Stamford, CT) extracted via a patented quality-controlled process from red field clover is being tested worldwide as an HRT substitute.

Lastly, targeted tissue-specific estrogens are being developed. An estradiol molecule attached to a quaternary salt, which changes charge when it crosses the blood-brain barrier and locks in brain tissue, but is rapidly cleared from the rest of the body in urine, is being tested in the rodent model (44).

Until a cure for, and better yet a vaccine against breast cancer is developed, HRT will remain strongly associated with the development of this disease in the minds of many. While awaiting these olympian events, the discerning clinician must go beyond p-values and relative risk, and use the known data to make a relatively informed decision on how best to help those menopausal women who need it.

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