Weighing HRT use after breast cancer

HRT has long been contraindicated in women who have—or have had—breast cancer. Here, the author examines the effects estrogen has on the breast and reviews several studies that suggest HRT actually may be of benefit to these women.

By WILLIAM CREASMAN, MD

This year, almost 50,000 women under the age of 50 will develop breast cancer. Most will undergo chemotherapy and become amennorhic. It is well known that premature surgical menopause usually results in more significant vasomotor symptoms than a natural menopause. It certainly follows that women who have had a chemotherapeutically-induced menopause will have a similar experience.

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Hormone replacement therapy (HRT) has proven efficient in the treatment of vasomotor symptoms. Many women also take HRT for good urogenital health, primary cardiac protection, and to assist in the prevention of osteoporosis, colon cancer, and possibly Alzheimer's disease. In some studies HRT has been linked to an increased risk of breast cancer due to prolonged estrogen exposure; however, the data are inconclusive.

Thankfully, 80% of the approximately 205,000 women expected to develop breast cancer this year will be successfully treated. As a result, more and more breast cancer survivors will present to their Ob/Gyns for the treatment of vasomotor symptoms or other benefits that HRT offers. For this reason, it is important to examine fully the effects of estrogen on the breast and the potential use of HRT in the breast cancer patient.

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Sorting the data

Laboratory data. Volumes of research have been conducted on the association between estrogen use and breast cancer. Laboratory data have shown increased cellular activity of estrogen-receptor mammary cancer cells when estradiol is applied and decreased activity when estradiol is withdrawn or a progestin added.[1] Apparently, this is not the case with estrogen-receptor-negative tumor cells. Elevated estrogen serum levels also have suggested a direct relationship to breast cancer.[2] In some of these studies, only a one-time sample was available for evaluation, estradiol levels were determined only when breast cancer had been diagnosed, and the highest quintile was compared with the lowest quintile—not the mean or median levels. There have been no studies indicating whether serial serum levels are associated with breast cancer. Apparently, in the premenopausal patient, the correlation between serum estradiol levels and breast cancer has produced conflicting results.

While the actions of estrogen in established breast cancers are not entirely understood, they appear to be very complex. Estrogen appears to stimulate the growth of breast cancer cells in tissue cultures at low doses, but inhibits growth at high doses.[3] Evidence also suggests that, in breast

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Key points

- Eighty percent of the approximately 205,000 women expected to develop breast cancer this year will be succesfully treated.
- The data to date suggest that HRT in the patient who has had breast cancer is not detrimental. Some larger studies note fewer recurrences and breast cancer deaths, and less total mortality in HRT users.
- The absolute risk of breast cancer in a 10-year HRT user is 0.6%.
- Fifty-nine percent of premenopausal breast cancer patients are willing to consider eventually taking HRT.

tumors, internal levels of estradiol can be maintained independent of levels outside the tumor. Therefore, endogenous and exogenous estrogens may have relatively little effect on tumor growth.[4]

Clinical data. These are mainly epidemiologic studies suggesting that risk factors are increased when prolonged estrogen exposure is present, i.e., early menarche, late menopause, obesity, unopposed endogenous estrogen. Late first-term pregnancy also has been suggested as a risk factor because final differentiation of the terminal duct epithelium—induced by pregnancy and lactation—was postponed by about a decade. In the last quarter-century, more than 50 epidemiological studies have investigated the effect of HRT in the breast cancer patient. These studies have produced mixed results. The Collaborative Group's breast cancer study, which reanalyzed most of the world's data, suggests a slightly increased risk of breast cancer in HRT users.[5] Although the risk ratio (RR) is said to be 1.35 in women who take HRT for 5 years or more, the absolute risk notes an increase of 45 to 51 per 1,000 women, or 0.6% in a 10-year user. The greatest risk appears to be in thin women.

Several studies—including the Nurses' Health Study[6] and the Iowa Women's Health Study[7]—have established an association between the use of postmenopausal HRT and reduced mortality. The Iowa study evaluated the association between HRT and mortality in women with and without a family history of breast cancer. The adjusted RR for total mortality in women with a family history of breast cancer currently using HRT for more than 5 years was 0.55 (CI 0.28–1.07), which was lower than the estimated RR for women without a family history of breast cancer. Cobleigh and associates summarized data from 5 studies and found that the prognosis was better for women with breast cancer who took HRT before diagnosis than those who never took HRT. Those patients who took HRT before diagnosis had smaller tumors, with better differentiation and less cellular proliferation than women who developed breast cancer and had not taken HRT.

The post-breast cancer patient

Since most breast cancers are estrogen-receptor positive, laboratory data suggest that cancer cells may be influenced by estradiol; epidemiologic studies note a slightly increased risk of breast cancer in HRT users, what rationale is there for giving a woman HRT after the diagnosis of breast cancer? The *Physicians' Desk Reference* (PDR) notes that breast cancer is a contraindication to HRT. While this is the recognized dictum, there are no data to substantiate it. In the PDR, the contraindications listed do not include a *history* of breast cancer. Nor does the bibliography contain any references addressing the post-breast cancer patient.

If there are no data to support the non-use of HRT in the breast cancer patient, are there data to support its use? Indeed, studies do exist. But before reviewing these important research findings, consider a parallel scenario. For many years, a woman who was diagnosed with breast cancer during pregnancy was thought to have an extremely poor prognosis due to the high level of hormones produced. More than 50 years ago, Haagerson, the recognized surgical breast authority in the United States, suggested that the combination of breast cancer and pregnancy had such a poor outcome that surgical therapy was not indicated.[8] Ten years later, more than 50 "recognized breast authorities"

restated the recommendation against surgical therapy, noting the high levels of hormones from pregnancy (gas-on-the-fire theory).[9] We now know that, when corrected for age and stage, survival in the pregnant and nonpregnant breast cancer patient is similar.[10,11] Carrying the pregnancy to term is not detrimental, nor is terminating the pregnancy beneficial.

Similarly, subsequent pregnancies after breast cancer were thought to be contraindicated because of the fear that the hormones elevated during pregnancy would reactivate dormant cancer cells. Data would suggest just the opposite. Subsequent pregnancies do not increase recurrences. Nor does the time of pregnancy (less than or greater than 2 years) after breast cancer appear to be a factor.[12]

For many years, part of the primary treatment for the premenopausal patient with breast cancer was bilateral salpingo-oophorectomy. Prospective randomized studies have shown that this was not beneficial with respect to survival and is no longer done.[13] Endogenous estrogen appears to be acceptable in the premenopausal breast cancer patient, but exogenous estrogen in the postmenopausal patient is not. It is interesting to note that tamoxifen given to the premenopausal patient with breast cancer increases estradiol levels way beyond peak levels during the menstrual cycle. Still, it is indicated because of decreased breast cancer recurrence when compared to patients not taking tamoxifen. Thus, there is little rationale for denying the benefits of exogenous estrogen to the postmenopausal woman with breast cancer.

There have been several retrospective as well as case-controlled and cohort studies demonstrating that HRT can be given to the post-breast cancer patient without a negative impact on survival. The retrospective studies note very low recurrence and death rates (*Table 1*).[14-19]

Results from the case-controlled and cohort studies demonstrate no difference in the prognosis of patients who did or did not receive HRT post-cancer. Recently, in a cohort study, DiSaia and associates examined 125 breast cancer patients who received HRT after diagnosis,[20] along with 362 controls from the same geographic region. The risk of death was considerably lower in the HRT users compared to non-HRT users, with an odds ratio (OR) of 0.28 (CI 0.11–0.71).

The largest study to date evaluated 2,755 women with breast cancer who were enrolled in a large health maintenance organization (HMO).[21] Medical and pharmacy records were reviewed and patients with breast cancer taking HRT were identified. Of these, 174 eligible HRT users were available for analysis. Four matched controls were identified for each of the breast cancer patients. Estrogen, as well as estrogen plus progesterone, was administered. Breast cancer recurrence was diagnosed in 16 hormone users (9%) compared with 101 (15%) non-users. The rate of recurrence was 17 per 1,000 person-years in HRT users and 30 per 1,000 person-years in non-users. Comparison of rates adjusted for multiple factors noted an

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HRT in women with breast cancer — TABLE 1

Author	Cancer recurrence	Deaths
Stoll	0/65 (0%)	0
Powles	2/35 (8%)	0
Sellin	1/49 (2%)	0
Bluming	12/189 (6%)	1 (1%)
Brewster	13/145 (9%)	3 (2%)
Natrajan	2/50 (4%)	3 (6%)
Total	**30/533 (6%)**	**7 (1%)**

Pending evidence

While gold-standard clinical trials (double-blinded, prospective, randomized studies) on HRT use after breast cancer have not been completed, 2 such studies are presently ongoing in Europe, including the HABITS Trial in Sweden and a similar study in the United Kingdom. In addition, a prospective trial is underway at the M.D. Anderson Hospital in Houston, Tex. The Gynecologic Oncology Group also has approved a prospective, randomized, double-blind study comparing estrogen with a placebo in women who have had breast cancer. And the Eastern Cooperative Oncology Group (ECOG) recently completed a feasibility study of HRT in patients who have had breast cancer. Unfortunately, it will be several years before these trials yield definitive answers.

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RR of 0.50 (CI 0.30–0.85). Five users (3%) and 59 non-users (8%) died of breast cancer (5 per 1,000 person-years versus 15 per 1,000 person-years). The adjusted RR was 0.34 (CI =0.13–0.91). Total mortality noted an RR (adjusted) of 0.48 (CI 0.29–0.78).

Conclusion

The American College of Obstetricians and Gynecologists (ACOG) states in a committee opinion that "there is no conclusive data to indicate an increased risk of recurrent breast cancer in postmenopausal women taking HRT. No woman can be guaranteed protection from recurrence. Late manifestations of recurrent disease and an apparent predisposition to recur (as shown by a selected subgroup of women) cannot be ignored; however, the benefits of HRT are well recognized and contribute to the quality and length of life in postmenopausal women."[22]

The data to date suggest that HRT in the

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patient who has had breast cancer is not detrimental. In fact, some of the larger studies note significantly fewer recurrences and breast cancer deaths, and less total mortality in HRT users, compared with matched controls.

Many women who have had breast cancer express an interest in HRT. A recent study of 224 women with breast cancer reported that 34% of the menopausal patients wanted to consider HRT as an option. Among women treated for breast cancer with surgery only, 71% also would consider its use.[23] In addition, 59% of the premenopausal patients expressed interest in eventual HRT treatment. Therefore, to reject HRT out of hand for a patient who may be having significant vasomotor symptoms, or one who is several years beyond breast cancer therapy and may want preventive measures for cardiovascular disease and osteoporosis, is not in the patient's best interest. Women want information so they can make an appropriate choice. As health-care providers, we need to be sensitive to their desires and supportive of their decisions.■

ACOG states in a committee opinion that "there is no conclusive data to indicate an increased risk of recurrent breast cancer in postmenopausal women taking HRT."

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