Do Women Taking Hormone Replacement Therapy (HRT) Have a Higher Incidence of Breast Cancer Than Women Who Do Not?

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An estimated one third of all American and United Kingdom women take hormone therapy. In sharp contrast to these numbers, as many as one half of women diagnosed with breast cancer have taken hormones. Little additional information is available regarding the risk of breast cancer and even less is known about the association between hormone therapy and fibrocystic (FCD) disease or atypia of the breast. Three hundred women between 30 and 50 years of age were enrolled in this study, including 120 taking hormone replacement (HRT) therapy and 180 women who had never taken hormone therapy. These women were divided into four categories including those with normal breast tissue, those with FCD disease, those with cellular atypia, and those with breast cancer. Another group of women were also identified who had breast implants. Using breast enhanced scintigraphy (BEST) imaging, changes in breast tissue were determined and compared according to the use of HRT. Forty percent (122 of 300) had "normal" breasts, of whom 68.8% (84 of 122) did not take HRT. This accounted for 46.7% (84 of 180) of the women not taking hormone therapy, while only 31.7% (38 of 120) of the women taking HRT had normal breasts. This difference was statistically (p.001) significant. There was a greater incidence of breast abnormality in women taking HRT and a lower incidence in pathology among women not taking HRT when cumulatively analyzed for FCD, cellular atypia, and breast cancer. This difference was statistically significant (p.001) for women with breast cancer where 62.5% (10 of 16) were women taking HRT. Although the study was relatively small, it is the first such study to compare a continuum of changes in breast tissue according to the use of HRT. The study suggests that the initial empirical observations regarding higher incidence of HRT among women with breast cancer, may have a relationship to underlying changes in breast tissue that are associated with differences in mitochondrial content and activity. Further investigation is needed.

Keywords: Hormone replacement therapy (HRT); breast cancer; breast imaging; breast-enhanced scintigraphy test (BEST)

Current estimates suggest that as many as a third of American women may be taking hormone replacement therapy (HRT) for a variety of reasons including osteoporosis, oophorectomy, heart disease, menopause, and so on. These estimates closely match those seen in the United Kingdom,[1] where a third of the women studied took HRT for an average of 5.8 years. It has been estimated that 50% of all women who develop breast cancer have taken HRT, a percentage that appears disproportionately large given the number of women using hormone therapy. Other research[2-4] has raised concerns over women taking HRT and their risk of breast cancer.

In heart disease, individuals do not suddenly go from having a normal healthy heart to needing bypass surgery. Similarly, it seems clear that women do not go from having normal breast tissue to having breast cancer. The transition between normal and pathological begins as cellular atypia occurs and the precancerous cells become more metabolically active with increased numbers of mitochondria and mitochondrial activity. Additionally, increased vascularity (angiogenesis) occurs following the synthesis of vascular endothelial growth factors, which supply nutrients to the highly metabolically active cells. Until recently, it has been difficult to distinguish between these changes in cellular activity. With the advent of breast-enhanced scintigraphy test (BEST)[5,6] imaging, it is possible to further differentiate breast tissue into normal tissue, inflammatory fibrocystic changes of the breast, cellular atypia, and carcinoma of the breast based upon mitochondrial uptake of sestamibi.

In this study, we used BEST imaging to look at 300 women and determined whether they had normal breasts, fibrocystic (FCD) disease, cellular atypia, or breast cancer. These results were then compared with their use of HRT to determine the incidence of disease

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in each category according to their use of hormone therapy.

Methods

Study Population. Three hundred women between the ages of 30 and 50 years were studied using BEST imaging to determine if they had breast cancer, cellular atypia, FCD, or normal breasts. All individuals were pre- or perimenopausal and were either currently taking HRT including both estrogen and progesterone for birth control purposes, oophorectomy, osteoporosis treatment, and/or hot flashes, or had never taken HRT. Participants could not be pregnant. Patients included in the study had not previously been diagnosed with or treated for breast cancer. All individuals signed consent forms approved by the institutional review board prior to participation. Participants completed a medical history form including use of hormone therapy, which was reviewed following completion of the study.

BEST Imaging. Using BEST imaging and sestamibi, mitochondrial activity was determined[5,6] as previously published. Results were matched with tissue pathology specimens.

Statistical Analysis. The results of BEST imaging were used to determine which group a woman belonged to, as correlated with tissue pathology. The incidence of HRT use was then determined and absolute numbers and percentages determined. Chi-square analysis was used to determine statistical differences using a *P* value of .05.[7]

Results

Of the 300 women enrolled in the study, 120 (40%) took HRT on their physicians' recommendations and 180 (60%) did not take HRT. As shown in Table 1, 2.8% of the women studied had breast implants; of these, three quarters did not take HRT. Of the women who did not take HRT, 46.6% (84 of 180) had "normal" breasts without evidence of FCD, cellular atypia, or cancer. This represented 68.8% (84 of 122) of all women with normal breasts. In contrast, only 31.6% (38 of 120) of women taking HRT had normal breasts. This difference was statistically ($P < .001$) significant.

Fibrocystic changes were seen in 41.7% of women taking HRT and made up 43.1% (50 of 116) of the women with FCD. Women who did not take HRT had a 36.7% (66 of 180) incidence of FCD representing 56.9% (66 of 116) of all women with FCD. The difference was not statistically significant.

Table 1. Percentage of Women Using Hormone Replacement Therapy (HRT)

Category (n)	*–HRT (n)*	*+HRT (n)*	*Chi-squared P value*
Breast implants (8)	75% (6)	25% (2)	$P < .001$
Normal (122)	68.8% (84)	31.2% (38)	$P < .001$
Fibrocystic disease (116)	56.9% (66)	43.1% (50)	P = NS
Atypia (38)	47.4% (18)	52.6% (20)	P = NS
Cancer (16)	37.5% (6)	62.5% (10)	$P < .001$
Total women	180	120	

n is the number of women in each category.

Cellular atypia was present in 10% (18 of 180) of the women who did not take HRT. These women represented 47.4% (18 of 38) of all women with cellular atypia. Women who took HRT had a 16.7% (20 of 120) incidence of atypia and accounted for 52.6% (20 of 38) of all instances of cellular atypia. Breast cancer was seen in 5.3% of the women studied, and when added to those with cellular atypia, they represented 8% (24 of 300) of the women in the study.

Women who took HRT had an 8.3% (10 of 120) incidence of breast cancer, which differed significantly ($P < .001$) from the 3.3% (6 of 180) incidence seen in those who did not take HRT. The women who took HRT accounted for 62.5% (10 of 16) of all breast cancers and 55.5% (30 of 54) of all cellular atypia and cancer.

Figure 1 contrasts changes in breast differentiation between women who use HRT and those who do not. The incidences of breast pathology among those who do not use HRT are shown in series 1, whereas those who use HRT are represented by series 2. The proportion of women using HRT becomes larger as the severity of tissue pathology increases. The proportion of women not using HRT becomes smaller as the severity of tissue pathology increases.

Discussion

The use of HRT by women in this group was slightly higher than the national average for both the United States and the United Kingdom; however, these women represent women who actively see physicians and therefore might be expected to have a slightly greater tendency to be taking prescription medications. Of interest was the discovery that most women who had breast implants that were done for cosmetic reasons did not take hormone therapy, perhaps because those who took HRT might have been more satisfied with their physical appearance.

Nonhormone users had a higher incidence of normal breasts than HRT users and accounted for more than two thirds of all women with normal breasts, whereas the women taking HRT accounted for only

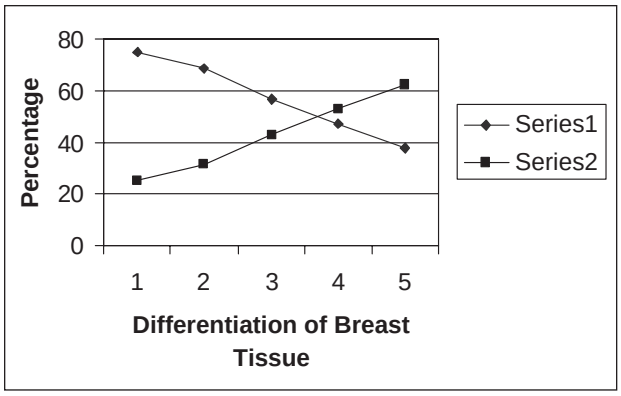

Figure 1 Percentage using or not using hormone replacement therapy (HRT). Three hundred women were studied during a 4-year period. One hundred eighty (series 1) had no history of using HRT, whereas 120 (series 2) were taking HRT. Differentiation of breast tissue is defined as 1 (breast implants), 2 (normal), 3 (fibrocystic disease), 4 (cellular atypia), and 5 (breast cancer). Tissue biopsy and imaging results showed less use of HRT noted in women with normal breast tissue and greater use of HRT among women with breast cancer. The results as shown in Table 1 were statistically significant, with the crossover occurring among women with cellular atypia.

one third. Women who were not taking HRT had a nonsignificantly lower incidence of FCD (36.7%) than women who were taking HRT (41.7%).

More than half of all women with cellular atypia took HRT, even though they represented only 40% of the women in the study. By contrast, only 10% of all women who did not take HRT had cellular atypia. Women who took HRT represented 62.5% of all breast cancers and 55.5% of all women with cellular atypia and breast cancer.

Women who took HRT showed an increased incidence in breast pathology when compared with women who did not take HRT. The incidence of HRT and non-HRT was almost equal for women with FCD, with greater percentages of women taking HRT represented among those with cellular atypia and cancer.

Conclusion

Although considerable debate exists about the potential causative effect of HRT upon breast cancer and the potential for recurrence in breast cancer survivors taking HRT, no data have previously existed regarding FCD and cellular atypia. This study demonstrated higher use of HRT among those with FCD, cellular atypia, and breast cancer. These differences were statistically significant for cellular atypia and breast cancer, with women using HRT significantly more likely than those not using HRT to have breast cancer. These differences in breast differentiation are associated with differences in mitochondrial activity and may provide further insight into changes that occur within breast tissue, which may be influenced by the use of HRT. Although this initial study needs further confirmation and investigation, it provides the first in vivo data about the increased incidence of a continuum of breast disease across women taking HRT and raises questions about the advisability of HRT in pre- and perimenopausal women.

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