Hormone replacement therapy in breast cancer survivors: A cohort study

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OBJECTIVE: Our purpose was to measure any adverse effect (if one exists) of hormone replacement therapy administered to breast cancer survivors.

STUDY DESIGN: Forty-one patients from a group of 77 patients who received hormone replacement therapy after therapy for breast cancer were matched with 82 comparison patients not receiving hormone replacement therapy. Both groups were taken from the same population on the basis of cancer registry of the Cancer Surveillance Program of Orange County and were compared with regard to survival results.

RESULTS: An analysis of survival time and disease-free time revealed no statistically significant difference between the two groups.

CONCLUSIONS: No obvious adverse effect of hormone replacement therapy could be shown in this pilot study. A case is made for a prospective randomized trial. (Am J Obstet Gynecol 1996;174:1494-8.)

Key words: Breast cancer, hormone replacement therapy

The majority of medical literature on hormone replacement therapy and breast cancer has focused on the risk for development of the disease with and without the use of hormone replacement therapy. The practice of withholding this therapy from women with a history of breast cancer because of the theoretic risk of activating quiescent disease and inducing tumor regrowth ("fuel-on-the-fire" theory) has only recently come under scrutiny. In 1989 Wile and DiSaia[1] suggested that in the absence of a prospective study of hormone replacement therapy in the breast cancer patient, patients exposed to high levels of ovarian hormones at times when they may have been harboring breast cancer cells could be analyzed. These situations were defined as pregnancy coincident with breast cancer, pregnancy subsequent to breast cancer, breast cancer in both previous and current users of oral contraceptives, and breast cancer in postmenopausal women receiving hormone replacement therapy. They pointed out that approximately 185,000 cases of breast cancer occur in the United States annually and as many as 67% of these patients survive this devastating disease and live to an old age. The benefits of hormone replacement therapy in preventing osteoporosis, postponing the onset of ischemic heart disease, maintaining a favorable lipid profile, and improving quality of life are well documented.[2-12] Because all medical practice involves a risk-benefit analysis of a given therapy, a reappraisal needed to be made of these issues. Such a reappraisal was reported in a review article by DiSaia[13] in 1993. DiSaia et al.[14] briefly reported their experience with 77 breast cancer survivors taking hormone replacement therapy in 1994. No support for the so-called "fuel-on-the-fire" theory could be found in their data.

This report analyzes 41 of those 77 patients receiving hormone replacement therapy who were matched to 82 comparison patients not receiving hormone replacement therapy taken from the population-based cancer registry of the Cancer Surveillance Program of Orange County. The 41 patients were selected because their diagnosis occurred during a time when the registry was operational.

Material and methods

Patients who had been diagnosed with breast cancer and who subsequently received hormone replacement therapy ($n = 41$) were identified through patient records. The population-based cancer registry of the Cancer Surveillance Program of Orange County was used to select two comparison patients with breast cancer (International Classification of Diseases for Oncology codes C50.0 to C50.9)[15] for each patient in the study. The description of the Cancer Surveillance Program of Orange County and the details of data collection methods have been reported previously.[16] The 1990 population of Orange County reported by the United States census included 1,196,496 women with a median age of 31.5 years. The

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population includes 64% non-Hispanic whites, 23% Hispanics, and 10% Asians or Pacific Islanders. The median household income was $45,922.

The Cancer Surveillance Program of Orange County maintains a cancer information reporting system that includes case reports for all cancer patients seen in every hospital in Orange County and case reports for Orange County resident patients diagnosed or treated for active cancer at hospitals outside the county. Also included are case reports from physicians' offices and other facilities in Orange County, such as clinics where cancer may be diagnosed and treated without hospitalization. To ensure that all cases of cancer in Orange County residents are included, death certificates of county residents with cancer reported as a cause of death are matched to case reports on file. Where no case report exists, the source of certifying the death is contacted for more information, and a case report is generated for the patient. Those who are not Orange County residents with diagnosis and treatment in Orange County referral facilities are not included in the patient pool for this study. There were about 11,000 patients available for selection as comparison study subjects.

Female breast cancer patients were selected for the comparison group on the basis of three matching factors: (1) age at diagnosis, (2) stage of disease (American Joint Commission on Cancer), and (3) year of diagnosis (1984 to 1992). The samples of patients studied included 41 patients receiving hormone replacement therapy and 82 matched comparison patients.

The distributions of age, stage of disease, first course of treatment, and year of diagnosis of the hormone replacement therapy and comparison patients are shown in Table I. With respect to these factors, the two groups are similar. Mean age at diagnosis in the patients receiving hormone replacement therapy is 52.0 years and in the comparison patients 52.2 years. For 16 study patients, both comparison patients are the same age as the study patient with whom they are matched. For 23 study patients, both comparison patients are +1 year compared with the age at diagnosis of the study patient with whom they are matched. For the remaining 2 study patients, 1 of the comparison patients is 3 years younger than the study patient. Exact matching by American Joint Commission on Cancer stage of disease is accomplished for 40 of the 41 study patients. In one patient with stage IIA disease receiving hormone replacement therapy one of the comparison patients had stage IIB breast cancer. Although there are fewer cases in the study group who are treated with surgery alone (26.8% hormone replacement therapy vs 32.1% comparison), this difference between the groups is not statistically significant. Year of diagnosis is within +1 year in 39 of 41 patients receiving hormone replacement therapy. The year of diagnosis for two study patients differs by 2 to 5 years from the year of diagnosis of the matched comparison patients. The earliest diagnosis of study patients was 1984, the reference date of the Cancer Surveillance Program of Orange County.

In the 41 study subjects, information on history of cancer before the diagnosis of breast cancer, type and duration of hormone replacement therapy, and follow-up information including recurrent disease and multiple primary cancer were determined through the records of the referring physicians. In the 82 comparison subjects information on history of cancer before diagnosis of breast cancer was determined through the population-based cancer registry. Information on subsequent disease (recurrent breast cancer and multiple primary cancers) was determined through the population-based cancer registry and by calling treating or follow-up physicians. The cause and date of death for both groups of patients were determined through records of the Orange County Health Care Agency. The follow-up period was defined to end on June 1, 1993.

Receptor status was not available from the registry for most of the patients studied before 1990, so a comparison of this parameter was not made. Patients were not excluded from the estrogen replacement therapy series if they had estrogen receptor–positive lesions. Most patients received 0.625 mg of conjugated estrogens or its equivalent with medroxyprogesterone 2.5 mg daily.

Data were processed and analyzed with the SAS software package (SAS Institute, Cary, N.C.).[17] Rates and proportions were compared by standard χ^2 methods. Survival curves were compared by the log-rank test.[18] Survival data were also analyzed by regression analysis to adjust for effects of possible confounding factors.[19]

Results

Cancer before diagnosis of breast cancer. As shown in Table II, there are four patients receiving hormone replacement therapy and four comparison patients who had cancer diagnoses before the diagnosis of breast cancer. Among study patients three were diagnosed with cancer of the endometrium and one with leukemia. Among comparison patients prior cancer diagnoses were two breast cancer, one colon cancer, and one malignant melanoma. The rate of cancer before the diagnosis of breast cancer (4/41 in patients receiving hormone replacement therapy and 4/82 in comparison patients) is not significantly different.

Recurrent disease or multiple primary cancer after the diagnosis of breast cancer. In the hormone replacement therapy group there were six patients who had recurrent breast cancer during the follow-up period through June 1, 1993, with two of these patients dying of breast cancer (see Table II). Among comparison group patients, there are six cases who had recurrence and who died of recurrent breast cancer and one patient who had another primary cancer of the ovary and died within 2 years of her

Table I. Distributions of age at diagnosis, American Joint Commission on Cancer stage of disease, treatment modality, year of diagnosis in hormone replacement therapy and comparison breast cancer patients

	HRT patients (n = 41)	*Comparison patients (n = 82)*
Age at diagnosis		
30-39 yr	2 (4.9%)	4 (4.9%)
40-49 yr	18 (43.9%)	36 (43.9%)
50-59 yr	13 (31.7%)	26 (31.7%)
60-69 yr	6 (14.6%)	12 (14.6%)
≥70 yr	2 (4.9%)	4 (4.9%)
AJC stage of disease		
In situ	4 (9.8%)	8 (9.8%)
Stage I	23 (56.1%)	46 (56.1%)
Stage IIA	9 (22.0%)	17 (20.7%)
Stage IIB	4 (9.8%)	9 (11.0%)
Stage IIIA	1 (2.4%)	2 (2.4%)
Treatment modality*		
Surgery only	11 (26.8%)	26 (32.1%)
Surgery + radiation	19 (46.3%)	35 (43.2%)
Surgery + chemotherapy	6 (14.6%)	11 (13.6%)
Surgery + radiation + chemotherapy	5 (12.2%)	9 (11.1%)
Year of diagnosis		
1984-1985	2 (4.9%)	4 (4.9%)
1986-1987	8 (19.5%)	16 (19.5%)
1988-1989	13 (31.7%)	28 (34.1%)
1990-1991	13 (31.7%)	27 (32.9%)
1992	5 (12.2%)	7 (8.5%)

HRT, Hormone replacement therapy; *AJC,* American Joint Commission on Cancer.
*One comparison patient with type of treatment unknown.

Table II. Cancer before diagnosis of breast cancer and recurrent disease or multiple primaries after diagnosis of breast cancer in study and comparison patients

	HRT	*Comparison*
Total	41	82
Cancer before breast cancer diagnosis	4*	4†
No cancer before breast cancer diagnosis	37	78
Rate of cancer before breast cancer (HRT 4/41, comparison 4/82; NS)		
Recurrence or multiple primaries after diagnosis of breast cancer	6‡	7§
No recurrence or multiple primaries after diagnosis of breast cancer	35	75
Rate of recurrent disease or multiple primary cancer after diagnosis of breast cancer (HRT 6/41, comparison 7/82; NS)		

HRT, Hormone replacement therapy; *NS,* not significant.
*Three endometrium, one leukemia.
†Two breast, one colon, one malignant melanoma.
‡Six recurrent breast cancer (two of whom died of breast cancer).
§Six deaths from recurrent breast cancer, one primary cancer of ovary.

breast cancer diagnosis with what appeared to be disease from both primary cancers. The rate of recurrent disease or multiple primary cancer after the diagnosis of breast cancer (6/41 in patients receiving hormone replacement therapy and 7/82 in comparison patients) is not significantly different.

Analysis of survival time. Survival curves are generated for patients receiving hormone replacement therapy and comparison patients and comparisons are made by the log-rank test. As seen in Table IIIA, there were two breast cancer deaths among study patients and six breast cancer deaths among comparison patients. The survival curves were not significantly different. The 4-year survival rate was 86% and 87%, respectively. By use of Cox regression analysis to adjust for age and stage of disease, the effect due to hormone replacement therapy versus no hormone replacement therapy group is not statistically significant.

Analysis of disease-free time. Disease-free time is computed where the outcome during the follow-up period subsequent to the diagnosis of breast cancer was defined as recurrent disease or multiple primary cancer or death from breast cancer. Summary data are shown in Table IIIB. Six patients with recurrent breast disease received hormone replacement therapy (two whom died of breast cancer). Seven comparison patients had an outcome of

Table IIIA. Analysis of survival time (in months)* in study and comparison breast cancer cases

Survival	*HRT patients*	*Comparison patients*
No.	41	82
No. of patients dead from breast cancer	2	6
4 yr survival rate ± SE (mo)	68.9 ± 1.9	46.2 ± 0.6
Comparison of survival curves	NS, $p < 0.5415$	
Cox regression	Age: NS	
	Stage of disease: NS	
	HRT vs comparison: NS	

HRT, Hormone replacement therapy; *NS*, not significant.
*Outcome: death from breast cancer. In all eight deaths cause of death was breast cancer.

Table IIIB. Analysis of disease-free time (months)* in study and comparison breast cancer cases

Survival	*Patients*	*Comparison patients*
No.	41	82
No. of patients with subsequent disease	6	7
Mean disease-free time ± SE (mo)	50.6 ± 1.9	45.5 ± 0.9
Comparison of disease-free curves	NS, $p < 0.3212$	
Cox regression	Age: NS	
	Stage of disease: NS	
	HRT vs comparison: NS	

NS, Not significant; *HRT*, hormone replacement therapy.
*Outcome: recurrent disease or multiple primary.

recurrent disease or multiple primary cancer or death from breast cancer (six patients died of recurrent breast cancer, one patient with multiple cancer of the ovary). The difference in the proportion of patients not disease free in the follow-up period (6/41 hormone replacement therapy and 7/82 comparison) is not statistically significant. The log-rank test result to compare the disease-free curves is not statistically significant. The 4-year disease-free rate is 74% in the hormone replacement therapy group and 86% in the comparison group. By use of Cox regression analysis to adjust for the effects of age and stage of disease, the effect on the disease-free curves resulting from the hormone replacement therapy group versus the comparison group is not statistically significant.

Comment

No prospective study has ever tested the impact of posttreatment hormone replacement therapy on breast cancer survivors. The number of patients who become candidates for hormone replacement therapy appears to be increasing with rising cure rates and more liberal use of adjuvant chemotherapy. Premenopausal patients given adjuvant chemotherapy lose ovarian function at least 80% of the time. This leaves the patient in her 30s or 40s with a premature menopausal state and at high risk for early onset of osteoporosis or ischemic heart disease. Freedom from recurrent breast cancer can never be guaranteed and some women will have recurrence coincident with renewed hormone exposure; patients must understand this possibility. However, when women who have had breast cancer request information on hormone replacement therapy for the relief of menopausal symptoms and the prevention of osteoporosis, etc., they deserve a comprehensive explanation.

In this climate of medical litigation there is an understandable reluctance to offer exogenous estrogen to women with a history of breast cancer. Patient and physician education will be necessary to change these patterns. The benefits of hormone replacement therapy in preventing some degenerating processes in postmenopausal women cannot be denied. Patients must be informed so that they can make their own decisions regarding this important therapeutic tool.

Reports such as this will hopefully lead to a prospective randomized trial studying this important issue. Many colleagues in medical oncology have suggested that such a study should have tamoxifen in both arms along with progestin. Our experience with this group of patients suggests that tamoxifen can be used with hormone replacement therapy with no obvious loss of biologic effect. To our knowledge, this observation has not been previously reported. Long-term studies will be necessary to measure the impact of estrogen replacement therapy plus tamoxifen on disorders such as ischemic heart disease, osteoporosis, etc.

A third of our patients from this series receiving hormone replacement therapy used tamoxifen for some period during the replacement therapy. Their symptoms and the clinical manifestations usually seen with hormone replacement therapy were seemingly unaffected by the use of tamoxifen. We would be in favor of a prospec-

tive study that included tamoxifen if its inclusion would promote the commencement of this necessary trial.

Sample size requirements were calculated for such a prospective randomized trial to evaluate the rate of recurrent disease and to compare disease-free time. If the difference in rates of recurrent disease were approximately 6%, as observed in this report, between 425 and 560 individuals would be required in each of two treatment groups. By use of the differences in disease-free time observed in this report, approximately 580 to 920 individuals would be needed in each of two treatment groups. All sample size calculations were made for two-sided tests, significance level of 0.05, and statistical power of 0.80.

The number of patients reported here is small, but many more will be available for analysis in the future from our population-based tumor registry. Hopefully, this report will stimulate other investigators to pursue this important question.

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