Clinical and Biologic Prognostic Factors in Breast Cancer Diagnosed During Postmenopausal Hormone Replacement Therapy

P. BONNIER, MD, S. ROMAIN, PharmD, P. L. GIACALONE, MD, F. LAFFARGUE, MD, P. M. MARTIN, PhD, MD, AND L. PIANA, MD

Objective: **To ascertain the influence of hormone replacement therapy on clinical and biologic prognostic factors of breast cancer.**

Methods: **Between 1976–1992, we treated 1081 postmenopausal women for breast cancer at our institution. Of these, 68 were undergoing postmenopausal hormone replacement therapy at the time of diagnosis. These patients were compared with a matched control group of 272 breast cancer patients who had not undergone prior hormone replacement therapy.**

Results: **Patients who developed breast cancer during hormone replacement therapy had fewer locally advanced cancers (large tumors and extensive lymph node involvement) and more well-differentiated cancers (infiltrating lobular cancers and grade 1 cancer). The number of patients with estradiol or progesterone receptors was lower in the hormone-treated group. Metastasis-free survival curves showed a tendency (P = .05) for better prognosis in hormone-treated patients both overall and in stage T2.**

Conclusions: **Hormone replacement therapy per se does not affect the prognosis of breast cancer. Regular surveillance during hormone replacement therapy reduces the number of locally advanced cancers and thus improves the survival rate. The higher number of well-differentiated cancers and the distribution of hormone receptivity may reflect interaction between neoplastic tissue and exogenous hormones.** *(Obstet Gynecol 1995;85:11–7)*

Hormone replacement therapy is widely used by postmenopausal women. Numerous epidemiologic surveys have studied the risk of breast cancer associated with the use of estrogen replacement therapy.[1–7] Although this treatment has little or no effect on the incidence of breast cancer, more and more cases are diagnosed concurrent with hormone use. Few data are available concerning the characteristics and outcome in this subgroup of hormone-treated breast cancer patients. Some evidence suggests that the characteristics of endometrial cancer are different in patients after hormone replacement therapy.[6–8]

The purpose of this study was to determine if previous postmenopausal hormone replacement therapy changes the prognosis and survival rate of patients. To answer this question, we compared the clinical features, biologic factors, and survival rates of 68 patients who developed breast cancer during hormone replacement therapy with 272 matched breast cancer patients who did not undergo hormone replacement therapy. Mean follow-up time was 49.5 months.

Materials and Methods

During the period 1976–1992, 1081 postmenopausal women were treated for breast cancer at our institution by the same team using similar strategies. Patients presenting with metastases at the time of diagnosis, in situ lobular cancer, or inflammatory cancers, patients for whom the conditions of hormone therapy were not known, and patients for whom hormone therapy had been discontinued in the months before diagnosis were not included. Based on these criteria, we obtained a cohort of 794 patients with a median age of 62.1 years (range 34.7–90.2).

Hormone replacement therapy is usually initiated after only a few months of amenorrhea, especially in patients complaining of hot flashes. For this reason, we considered patients as menopausal after a 6-month period of amenorrhea. This contrasts with the classic definition of menopause, which requires a 1–2-year

From the Service de Gynécologie et Obstétrique A, Hôpital de la Conception, Marseille; Laboratoire d'Oncologie et Biopathologie Tissulaire, Assistance publique à Marseille; and Service de Gynécologie et Obstétrique, Hôpital A. de Villeneuve, Montpellier, France.

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period of amenorrhea, unless the ovaries were surgically removed.

The cohort of 794 patients was divided into three groups of patients as follows:

Group 1 comprised 68 patients who developed breast cancer during postmenopausal hormone replacement therapy. The mean age in this group was 55.6 years; the median age was 55.3 years (range 39.6–71.6). The mean duration of hormone replacement therapy was 61.3 months (range 6–153). An estrogen-progestogen combination was used in 84% of cases and estrogen alone in 12%. The estrogens used were 17β estradiol (E2) (66%), E2 valerate (12%), synthetic estrogens (10%), and conjugated estrogen and natural estrogen (2%). Progesterone and derivatives of 17-hydroxyprogesterone were used in 36% of patients, derivatives of 19-nortestosterone in 36%, and derivatives of 19-norprogesterone in 28%.

Group 2 comprised 272 patients who developed cancer with no previous hormone replacement therapy and in whom age and date of onset of cancer treatment were comparable to that observed in group 1. Matching based on age and date of onset of cancer treatment takes into account both age-related variations in prognostic factors and the recent use of routine mammography screening as well as progress in adjuvant therapy. Thus, the age distribution and date of onset of cancer treatment in group 2 was the same as in group 1. The mean age in this group was 56.0 years; the median age was 55.5 years (range 39.4–72.2).

Group 3 comprised 726 patients who developed cancer with no previous hormone replacement therapy. The mean age in this group was 63.6 years; the median age was 62.9 years (range 39.4–90.2). Group 2 was drawn from this group.

Treatment methods evolved over the years, but the basic principles were similar in all groups. Conservative surgery was performed in most cases (73.2%). Radical modified mastectomy was used for large tumors and in cases where the margins were pathologic. Lymph node dissection was performed in 91.5%. The breast or chest wall was irradiated in 91.7% (mean dose 49.7 Gy) and a boost was delivered on the tumor bed in 47.7% of patients (mean dose 10.6 Gy). Internal mammary lymph nodes were irradiated in patients with tumors involving the central and internal quadrants. The supraclavicular and internal mammary lymph nodes were irradiated in patients with axillary lymph node involvement (mean dose 45 Gy). Adjuvant therapy was administered when any of the following poor prognostic factors were present: large tumor, lymph node involvement, histoprognostic grade 3, or negative steroid receptor. Chemotherapy was used in patients with negative hormone receptors or involvement of more than four lymph nodes. The most common protocols were a combination of either cyclophosphamide, methotrexate, and 5-fluorouracil (5-FU), or adriblastine, cyclophosphamide, and 5-FU. Chemotherapy was performed in 19.7% of patients. Hormone therapy with tamoxifen was administered for 1–5 years to patients with positive hormone receptors. Hormone therapy was used in 23.9% of patients. There was no difference between the groups 1 and 2 with regard to adjuvant treatment.

The mean duration of surveillance in the three groups was 45.1, 47.8, and 50.8 months, respectively, and median follow-up was 32.3, 34.3, and 41.2 months, respectively. In most patients, surveillance consisted of a clinical examination three times a year and annual mammography, liver ultrasonography, and bone scintiscan. Tumor marker assays, computed tomography scan, and magnetic resonance imaging were performed only in symptomatic patients.

One or more metastases were observed in 127 patients, local recurrences in 51, and contralateral cancer in 22. Of the 90 deaths that occurred, the cause was breast cancer in 74 cases, concomitant cancer in four, therapeutic complications in one, and other causes in 11.

The following clinical data were noted: diagnostic modality (clinical examination or x-ray), delay between the first sign and histologic confirmation of cancer, clinical tumor size, disease stage, and surgical methods. The histological data were anatomic size, histologic type, degree of infiltration, histoprognostic grade (Scarff, Bloom, and Richardson), and lymph node involvement.

Estradiol receptor and progesterone receptor levels were determined either by radioligand binding assay or by enzyme immunoassay. All assays were carried out in the same laboratory.[9] Both techniques measure bound and unbound receptors; in the case of radioligand binding assay, this was achieved by an exchange technique. The cutoff point was 10 fmol/mg protein for radioligand binding assay and 15 fmol/mg protein for enzyme immunoassay. Radioligand binding assay was performed using the dextran-coated charcoal procedure with a single saturating dose assay. Enzyme immunoassay was performed using Abbott kits (Abbott Laboratories, Chicago, IL). Quality control was ensured by frequent testing within the framework of the European Organization for Research and Treatment of Cancer (EORTC) and by internal laboratory standards according to the recommendations of the Receptors and Biomarkers EORTC Group.[10–16]

Only data from groups 1 and 2 were compared. Findings from group 3 are given for reference. Group 2 was extracted from group 3 (patients without prior hormone replacement therapy) using a hazard table to identify patients whose age distribution and date of

Table 1. Diagnostic Modality for Cancer Detection and Delay Between the First Sign and Histologic Confirmation

	Group 1 (n = 68)	Group 2 (n = 272)	Group 3 (n = 726)
Method of detection			
Clinical	74.6%	67.4%	76.0%
X-ray	25.4%	32.6%	24.0%
Delay for diagnosis (mo)			
Median	1.6	2.2	2.2
Mean	5.7	7.8	7.2

Data did not reach level of significance.

Group 1) breast cancers detected in patients undergoing hormone replacement therapy for menopause; group 2) breast cancers detected in patients with no previous hormone replacement therapy and matched to group 1; group 3) breast cancers detected in patients with no previous hormone replacement therapy.

onset of cancer treatment matched those in group 1. The highest usable matching factor was 4. Variable frequency was compared using the χ^2 test and medians using the Wilcoxon test. Survival curves were calculated according to the Kaplan-Meier method[17] and compared with the log-rank test.[18] As recommended by Arriagada et al,[19] survival curves were calculated to exclude patients who presented a contralateral breast tumor or another primary malignancy. This was done to avoid overestimating the rate of local recurrence, metastasis, and death attributable to the primary breast cancer. The duration of recurrence-free survival, metastasis-free survival, and overall survival were calculated from the date of onset of cancer treatment. Recurrence was defined as local recurrence in the homolateral breast or chest wall. Only deaths related to breast cancer were taken into account in the calculation of overall survival.

Results

There was no significant difference between groups 1 and 2 with regard to the diagnostic modality, but it should be noted that x-ray detection was more common in group 2 (Table 1). Hormone replacement therapy did not change the radiologic features of cancer. Glandular opacities were observed in 66.6% of patients in group 1 and 58.7% in group 2, and microcalcifications in 20.4 and 21.6%, respectively. Opacity associated with microcalcifications were observed in 13 and 19.7%, respectively.

The delay between the first symptom and histologic confirmation of cancer was not significantly different in groups 1 and 2 (Table 1). Overall distribution of clinical stage (tumor, nodes, and metastases [TNM] classification) and clinical tumor size were not statistically different, but it should be noted that the number of stage

Table 2. Clinical Stage (TNM),* Clinical Size Distribution, and Mean Tumor Size

	Group 1 (n = 68)	Group 2 (n = 272)	Group 3 (n = 726)
Stage			
T0	17.9%	21.7%	16.6%
T1	20.9%	21.7%	118.7%
T2	52.2%	40.8%	49.1%
T3	6.0%	8.6%	8.0%
T4	3.0%	7.1%	7.6%
Clinical size distribution (mm)			
<10	16.4%	25.3%	19.9%
10–19	16.4%	17.7%	15.1%
20–39	55.7%	37.1%	43.5%
40–59	4.9%	11.8%	13.6%
>60	6.6%	8.1%	7.9%
Mean tumor size (mm)	24.2	23.9	26.5

There were significantly more tumors greater than 40 mm in group 2 (P = .01); otherwise, data did not reach level of significance.

* Tumor, nodes, and metastases classification.

T3 and T4 tumors as well as tumors larger than 40 mm was lower in group 1 (P = .01) (Table 2). Conservative surgery was more common in group 1 (P = .03) (Table 3).

There was no significant difference between groups 1 and 2 as to the macroscopic tumor size or the proportion of infiltrating and in situ cancer (Table 4). No significant difference was found as to histologic type or histoprognostic grade, although it should be noted that group 1 contained a higher proportion of infiltrating lobular cancer (21.5 versus 16.2%) and grade 1 cancer (30.9 versus 19.4%). There was no significant difference between groups 1 and 2 with regard to lymph node involvement. The number of patients with no lymph node involvement was the same in both groups, but the number of cases with extensive involvement (four or more nodes) was lower in group 1 (9.1 versus 18.0%) (Table 4).

Assessment of hormone receptivity revealed a positive and negative population. There was no significant difference in receptor status, regardless of whether E2 receptors and progesterone receptors were studied separately or together. However, the number of patients testing negative was higher in group 1 (Table 5).

There was no significant difference in the distribution of E2 and progesterone levels. However, it should be

Table 3. Surgical Methods

Treatment	Group 1 (n = 68)	Group 2 (n = 272)	Group 3 (n = 726)
Conservative surgery	83.8%	70.6%	65.6%
Mastectomy	16.2%	29.4%	34.6%

P = .03 for group 1 *vs* group 2.

Table 4. Histologic Type, Degree of Infiltration, Histoprognostic Grade (Scarff, Bloom, and Richardson) and Lymph Node Involvement

	Group 1 (n = 68)	Group 2 (n = 272)	Group 3 (n = 726)
Mean histological size (mm)	20.8	21.2	21.6
Degree of infiltration			
Infiltrating	93.8%	90.6%	90.4%
In situ and microinfiltrating	6.2%	9.4%	9.6%
Histological type			
Ductal	73.8%	79.3%	77.8%
Lobar	21.5%	16.2%	17.6%
Other	4.7%	4.5%	4.6%
Histoprognostic grade			
1	30.9%	19.4%	20.9%
2	43.6%	50.7%	51.0%
3	25.5%	29.9%	28.1%
Number of involved lymph nodes*			
0	60.6%	59.6%	56.9%
1–3	27.3%	22.4%	23.6%
4–7	4.5%	7.8%	7.7%
>7	4.6%	10.2%	11.8%

Data did not reach level of significance.
* The mean number of lymph nodes studied was 15.1 per patient.

noted that E2 levels were higher in group 2 (median levels 89.5 versus 31.5 fmol/mg). Median progesterone values were 20 fmol/mg in group 1 and 26 fmol/mg in group 2 (Table 6).

Metastasis-free survival curves showed that prognosis tended to be better (P = .05) in hormone-treated patients both overall and in stage T2 (Figures 1 and 2). There was no significant difference between groups 1 and 2 with regard to the probability of recurrence-free survival and overall survival. This lack of significance could be due to the small number of patients. Three-year local recurrence-free survival was 0.95 in groups 1 and 2. Three-year metastasis-free survival was 0.93 in group 1 and 0.86 in group 2. Three-year overall survival was 0.98 in group 1 and 0.93 in group 2.

Table 5. Estradiol Receptor and Progesterone Receptor Status

	Group 1 (n = 68)	Group 2 (n = 272)	Group 3 (n = 726)
ER−	33.3%	21.9%	22.3%
ER+	66.7%	78.1%	77.7%
PR−	42.9%	40.4%	37.8%
PR+	57.1%	59.6%	62.2%
ER−, PR−	28.6%	20.5%	18.8%
ER+, PR+	51.4%	58.4%	58.7%
ER−, PR+	5.7%	1.2%	3.0%
ER+, PR−	14.3%	19.9%	19.6%

ER = estradiol receptors; PR = progesterone receptors.
Data did not reach level of significance.
ER and PR cutoff values: radioligand binding assay, 10 fmol/mg protein; enzyme immunoassay, 15 fmol/mg protein.

Table 6. Distribution of Estrogen and Progesterone Receptor Levels

	Group 1 (n = 68)	Group 2 (n = 272)	Group 3 (n = 726)
Estradiol receptors			
25th percentile	7.0	16.0	19.7
Median	31.5	89.5	104.0
75th percentile	207.5	266.0	286.2
Mean	127.25	179.45	186.0
SD	29.8	20.7	9.2
Maximum value	649	2425	2425
ER > 100*	33.3%	46.4%	50.5%
Progesterone receptors			
25th percentile	6.25	2.75	3.0
Median	20.0	26.0	27.0
75th percentile	66.5	119.5	129.7
Mean	48.43	97.47	121.4
SD	13.7	13.6	8.8
Maximum value	444	1120	1429
PR > 100*	14.3%	27.9%	29.5%

ER = estradiol receptors; SD = standard deviation; PR = progesterone receptors.
Data did not reach level of significance.
* Receptor level values expressed in fmol/mg protein.

Discussion

Hormone replacement therapy is now widely used in postmenopausal women. Although this treatment does not increase the incidence of breast cancer, more and

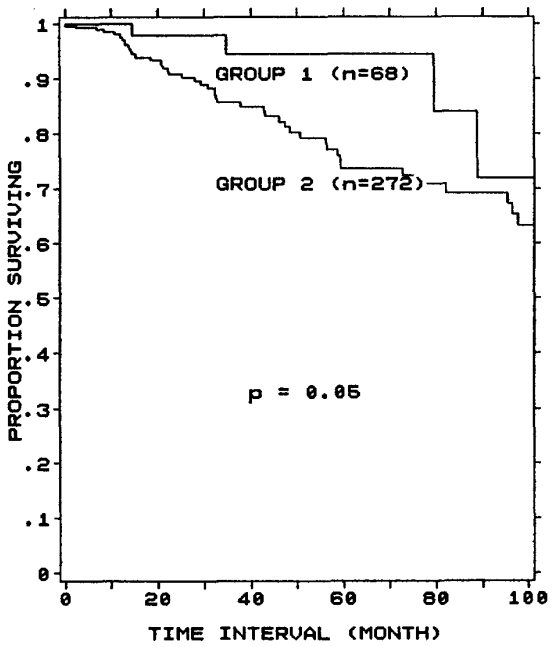

Figure 1. Kaplan-Meier estimates of the probability of metastasis-free survival in patients who developed breast cancer during hormone replacement therapy (group 1) and controls (group 2).

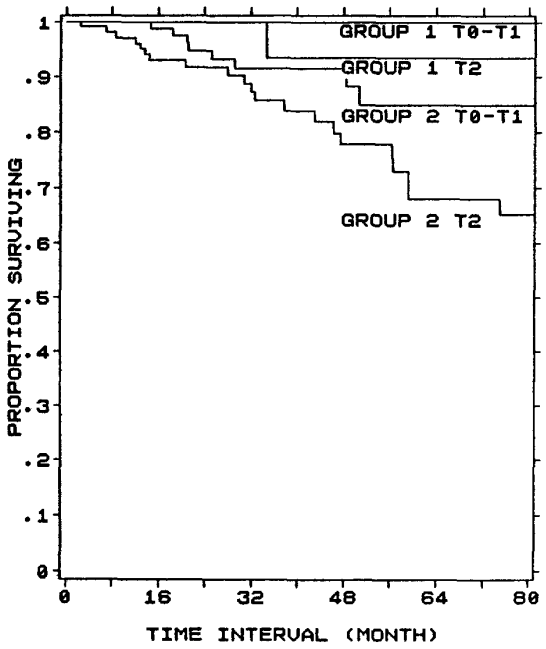

Figure 2. Kaplan-Meier estimates of the probability of metastasis-free survival according to stage in patients who developed breast cancer during hormone replacement therapy (group 1) and controls (group 2). Group 1, T0–T1: 28 cases; group 1, T2: 34 cases; group 2, T0–T1: 116 cases; group 2, T2: 109 cases. $P = .05$ between stage T2 patients in groups 1 and 2; no significant difference between stage T0–T1 patients in groups 1 and 2.

more cases are diagnosed concurrently. Some evidence suggests that hormone therapy may modify features and outcome of disease. Estrogens are known to enhance the growth rate of breast cancer.[20–24] Hormone therapy has been used as an adjuvant or palliative treatment.[25] The relation between steroid receptor status, the degree of differentiation, and the activity of carcinomas[26,27] as well as the correlation between receptor levels and outcome of disease[28–31] have been described previously.

In this study, we compared two groups of postmenopausal breast cancer patients. One group had undergone hormone replacement therapy for menopause, and the other group had not undergone such treatment. The two groups were matched for age and date of onset of cancer therapy. The purpose of this study was to detect any differences in clinical or biologic prognostic factors.

Few studies[32,33] have reported clinical, histologic, and biologic factors in patients who develop breast cancer during hormone replacement therapy. Minimal data come from cohort studies and case-control studies[1–5,34–38] designed to evaluate the risk of breast cancer associated with hormone replacement therapy. These studies do not give clinical and histologic prognostic factors concerning breast cancer occurring during hormone replacement therapy. In addition, they do not allow analysis in function of stage and age.

Current evidence seems to indicate a better prognosis in patients who develop breast cancer during hormone replacement therapy. Two possible explanations can be proposed. The first is that because these patients are kept under regular surveillance, diagnosis is achieved earlier.[3,32,33,37,39] In our study, x-ray detection was not more frequent in patients undergoing hormone replacement therapy. The delay between the first symptom and histologic confirmation of cancer was slightly but not significantly shorter in group 1. Analysis of the distribution of clinical tumor size and TNM stage showed that there were fewer large tumors (greater than 40 mm) and stage T3 and T4 tumors in group 1. Unexpectedly, the number of unpalpable and small tumors (T0 and T1) was higher in group 2. Although it was not significant, this difference could be related to a well-organized program of mass screening with mammography in our region.[40] Thus, regular clinical surveillance may reduce the number of large tumors as well as the incidence of extensive lymph node involvement (three or more nodes). Similar results regarding tumor distribution and lymph node involvement have been reported by Strickland et al.[33]

The second possible explanation for the better prognosis in hormone-treated patients is a higher incidence of differentiated cancers. Lobular cancers and histoprognostic grade 1 cancers were more frequent in patients undergoing hormone replacement therapy than in their counterparts who had not undergone hormone therapy (21.5 versus 16.2% and 30.9 versus 19.4%, respectively).

To evaluate the relation between hormone replacement therapy and differentiated tumors, we studied estrogen and progesterone receptor levels. Tumors with no receptors were more frequent in patients who underwent hormone therapy. This finding, which contrasts with the greater degree of differentiation, could be related to the fact that the estrogen and progesterone receptor levels in treated patients are closer to those observed in premenopausal women.[26,27] Differences in receptor distribution according to menopause status was confirmed in a recent EORTC study including 48,000 tumors (R. Leake, 1993, personal communication). The lower steroid receptor status could not have been due to a technical bias because both the measurement techniques used in our study (enzyme immunoassay and radioligand exchange assay) detect both free and bound receptors. The most likely explanation would be that natural processes triggered by receptor binding reduce intracellular receptor levels. In this

respect, hormone receptivity in premenopausal women is known to be correlated with circulating steroid hormone levels.[41] Consistent with this explanation, hormone receptor status in tumors detected in patients undergoing hormone replacement therapy documents responsiveness to exogenous hormones. This interaction, which is more frequent with lobular and grade 1 cancer, is directly proportional to the degree of tissue differentiation. A similar interaction has already been described with respect to the greater differentiation and better prognosis of endometrial cancer occurring during hormone therapy.[6–8] It remains unclear whether this is due to promotion or selection of hormone-sensitive tumor clones. It should be noted that Strickland et al[33] reported that, while there was no difference with respect to estrogen receptor levels, the number of patients with progesterone receptors was significantly higher after hormone replacement therapy.

In our study, the probability of metastasis-free survival tended to be better in hormone-treated patients. Strickland et al[33] reported a significantly higher survival rate in patients who developed breast cancer during hormone replacement therapy, but this difference disappeared for tumors of the same stage. It has been suggested that the differences observed are correlated with differences in clinical stage and tumor size. Bergkvist et al[32] a reported relatively longer survival in patients undergoing hormone replacement therapy, but his control group was not matched with the treated group and menopausal status was not taken into account for stratification. Without clinical and laboratory data, stage cannot be taken into account for stratification. Nevertheless, Bergkvist et al suggested that the female sex hormone has a favorable effect on the natural course of breast tumors by prolonging the premetastatic phase. Further study will be necessary to understand the interaction between malignant tissue and exogenous steroids.

The most clinically important finding of this study is that hormone replacement therapy is not an unfavorable factor for breast cancer. This finding supports the safety of widespread use of hormone replacement therapy.

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Address reprint requests to:
P. Bonnier, MD
Service de Gynécologie et Obstétrique A
Hôpital de la Conception
13385—Marseille CEDEX 5
France

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