Relationship of Estrogen and Progesterone Receptors to Prognosis in Breast Cancer

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To ascertain the role of estrogen (ER) and progesterone (PR) receptors as prognostic indicators of resectable breast cancer, the records of 204 patients were analyzed whose receptor studies were done at the Maimonides Medical Center from 1975 to 1983. All patients had radical or modified radical mastectomies and did not show any evidence of distant metastases at the time of operation. Median follow-up was 37 months. An additional 117 patients received some form of adjuvant therapy, mainly chemotherapy, and were analyzed separately. Life table analysis using the log rank test for measuring significance, and a Cox multivariate analysis was performed. At 48 months, 22% of the ER positive (ER+) group *versus* 33% of the ER negative (ER−) group had recurred as compared to 16% and 35% for the PR+ *versus* PR− groups, respectively. Life table analysis of the disease free interval (DFI) showed that the difference between the ER+ and ER− groups was not significant ($p > 0.1$), while the difference in DFI between the PR+ and PR− groups was significant ($p < 0.05$). Multivariate analysis revealed that the most important factors in predicting the DFI were nodal status ($p < 0.001$), tumor size ($p < 0.025$), and progesterone receptor status ($p < 0.05$). Estrogen receptor status was not found to be significant. In conclusion, PR− patients have a shorter DFI than PR+ patients and that PR status is a more valuable predictor of DFI than ER status.

THE IMPORTANCE of hormonal receptors in predicting the likelihood of response to hormonal manipulation in patients with metastatic breast cancer is well established.[1] Patients who are hormone receptor-positive are likely to respond to a variety of hormonal treatments whereas receptor-negative patients virtually never respond. This probably accounts for the longer survival of receptor-positive patients.

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Less clear, however, is the possible influence of hormonal receptors on the likelihood of remaining disease free. Most early studies on this subject focused on the estrogen receptor content. Progesterone receptor measurement did not enter routine clinical practice until the late 1970s, and the relationship between the PR and prognosis is less well studied. Since Horowitz and McGuire first proposed the value of the progesterone receptor as a clinical tool, attention has been focused at defining its utility as a predictor of prognosis.[2]

There is a controversy in the literature regarding the value of estrogen receptors in predicting the disease free interval (DFI).[3–9] This variance in the literature may be due to several factors including differences in laboratory methodology and standardization, variations in study entry criteria regarding stage and primary treatment modalities, and statistically insignificant study samples or follow-up periods.

Another significant methodologic difference is the inclusion in many published series of patients who have received hormonal and/or cytotoxic adjuvant therapy. Adjuvant therapies have been shown to prolong the DFI in various subsets of patients.[10–13] Thus, the inclusion of a significant fraction of patients who received adjuvant therapy in all probability bias any evaluation of the predictive value of hormonal receptors on the natural history of surgically treated breast cancer.

The present report analyzes a series of 204 patients who were not treated with any adjuvant therapy, eliminating this confounding variable. We analyzed the effects of estrogen and progesterone receptors on the DFI and sought to identify other factors that might have an impact on the prognosis of breast cancer.

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Supported in part by Maimonides Research Foundation.

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Submitted for publication: July 14, 1987.

TABLE 1. *Patient Characteristics*

Total no. of patients	204
Age (yr)	
Average	63
Median	65
Menopausal status (%)	
Premenopausal or perimenopausal	18
Postmenopausal	82
Median follow-up (mo)	
All patients	37
Disease free patients	43
Stage	
Stage I	69 (34%)
Stage II	100 (49%)
Stage III	35 (17%)

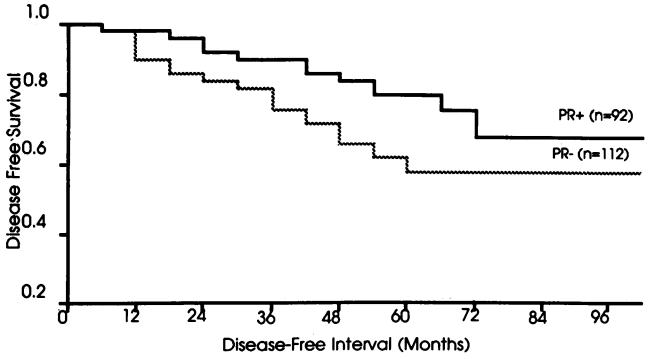

FIG. 2. Life table analysis of PR+ *versus* PR− ($p < 0.05$). Only patients not receiving adjuvant therapy are included.

Methods

Estrogen receptor determinations have been performed in our laboratory since 1974 and progesterone receptors since 1975. Between 1975 and 1977 the sucrose density gradient method was used, and later replaced by dextran-coated charcoal. The assay was considered negative if <3 fmol of receptor protein/mg of cytosol protein was present; borderline was determined at 3–10 fmol and positive for >10 fmol. For the purpose of this study all borderline values were considered positive. The technique of receptor analysis is described elsewhere.[14]

All patients in this study had localized breast cancer and underwent either a radical or modified radical mastectomy. Receptor studies were done on the primary tumor. Any patient who had evidence of metastatic disease at the time of surgery or previous breast malignancy was excluded. A total of 321 patients satisfied the above criteria and were available for analysis. Of these, 117 received some form of adjuvant therapy and were analyzed separately. A total of 204 patients remained, and they constitute the basis of this report.

For the purposes of this study adjuvant therapy is defined as any postoperative treatment: hormonal, cytotoxic, and/or radiation therapy. No attempt was made to differentiate among these groups since the subgroups were too small for any meaningful analysis.

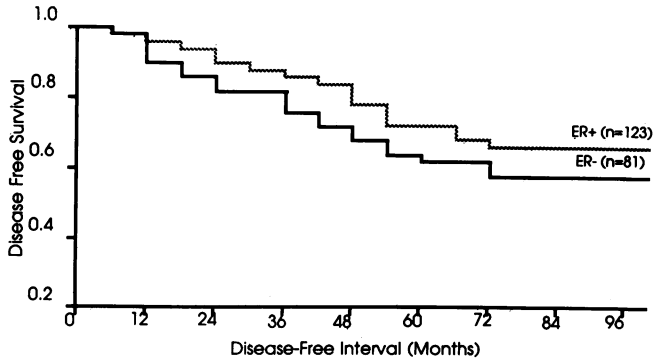

FIG. 1. Life table analysis of ER+ *versus* ER− ($p > 0.1$). Only patients not receiving adjuvant therapy are included.

The date of recurrence was the date of clinical detection of recurring tumor. Follow-up data was obtained from hospital and clinic records and from attending physicians.

Life table analyses were performed using standard actuarial methods. Differences between curves were analyzed using the log rank test for censored survival data. Cox's partially nonparametric regression model was used to evaluate the contribution of various factors in the prediction of the DFI.[15] Computations were performed with SAS computer programs release 82.3.

Results

Table 1 presents patient characteristics. It should be noted that a high percentage of our patients are postmenopausal, a patient group more likely to have a positive hormonal assay.

After 48 months, 8% of stage I patients had recurred *versus* 22% and 60% for stages II and III, respectively. This increased to 21%, 33%, and 70%, respectively, for those patients with 72 month follow-up. In all instances, these differences were significant ($p < 0.01$). The recurrence rate at 48 months for the ER+ *versus* ER− group was 22% *versus* 33%, respectively, while for the PR+ *versus* PR− group it was 16% *versus* 35%, respectively.

Figure 1 compares the ER+ *versus* ER− groups. The ER+ group showed a longer DFI, but this trend was not statistically significant ($p > 0.1$). Figure 2 shows the life table comparison of PR+ *versus* PR− patients. This difference was significant ($p < 0.05$).

Table 2 reports the results of hormonal receptor determinations.

The group of 117 patients who received some form of adjuvant therapy were included in the study group and

TABLE 2. *Receptor Values*

ER+	123 (60%)
ER−	81 (40%)
PR+	92 (45%)
PR−	112 (55%)
ER+/PR+	82 (40%)
ER+/PR−	41 (20%)
ER−/PR+	10 (5%)
ER−/PR−	71 (35%)

the life table analysis was repeated. Again, the difference between the ER+ and ER− groups was not found to be significant ($p > 0.1$), while the difference between the PR+ and PR− groups was significant ($p < 0.025$). The life tables for estrogen and progesterone are shown in Figures 3 and 4, respectively.

A Cox multivariate analysis was performed to measure the significance of each of the following factors: nodes (0 vs. 1–3. vs. >3) $p < 0.001$, tumor size (T_1 vs. T_2 vs. T_3), $p < 0.025$, progesterone receptor (+ vs. −) $p < 0.05$, estrogen receptor (+ vs. −) $p > 0.25$, age, $p > 0.5$, and adjuvant therapy (yes vs. no) $p > 0.25$. These factors are listed in Table 3. These results show that PR positivity, independent of all other factors, is a significant determinant of the DFI. This is not so for the estrogen receptor.

Discussion

The finding of an insignificant difference between the estrogen positive and negative groups is not unexpected and has been reported previously. Kinne et al.[4] found only borderline ($p = 0.06$) significance after 14 months of follow-up despite a very large series containing 1034 patients. Hilf et al.[5] and Skinner et al.[7] also did not find a significant difference. The majority of studies, however, do show a difference.[6,8,9] Wide variation in patient population size, length of follow-up, and the inclusion of patients who received adjuvant therapies are among factors likely to be responsible for the divergent results.

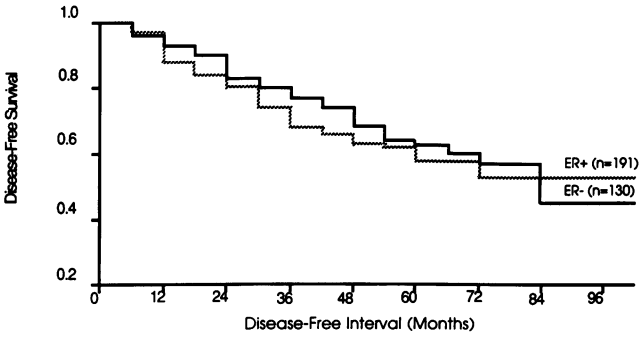

FIG. 3. Life table analysis of ER+ *versus* ER− ($p > 0.1$). Patients receiving adjuvant therapy are included.

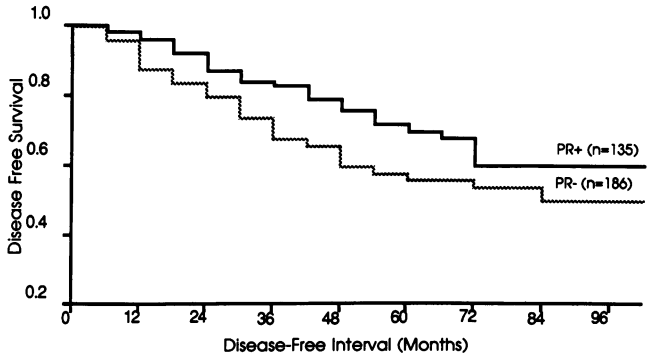

FIG. 4. Life table analysis of PR+ *versus* PR− ($p < 0.025$). Patients receiving adjuvant therapy are included.

The potential value of the progesterone receptor content has not been studied as extensively as the estrogen receptor. Published data suggest that it is at least equal to if not better than the estrogen receptor for predicting the DFI.[8,16] In this study the progesterone assay was a more sensitive indicator of recurrence potential of the tumor. In addition, the results of the Cox regression analysis indicated that unlike progesterone, estrogen was not a significant independent predictor of the DFI when all the other factors are controlled.

In a recent study, Clark et al.[8] analyzed 189 patients with stage II disease using similar statistical methods. Their patient group differed from those in the present study in that all patients had received adjuvant chemotherapy and two out of three had received tamoxifen. Median follow-up was 32 months. Significant differences in the DFI were found using life table analysis of the data subdivided according to either estrogen or progesterone receptor content. Despite these life table findings, analysis using the Cox multiregression model showed that estrogen receptor was not a significant independent variable. Thus, the study by Clark et al.[8] and ours both show that once the other factors in the regression analysis are known, namely, nodal status, tumor size, and progesterone receptor content, the knowledge of the estrogen receptor content is of little additional help in predicting the DFI. Our data also extend these observations to a group of patients treated solely by primary surgery without adjuvant therapies.

TABLE 3. *Factors Considered in the Multivariate Model*

Factor	p Value
Nodes (0 *vs.* 1–3 *vs.* >3)	<0.001
Tumor size (T_1 *vs.* T_2 *vs.* T_3)	<0.025
Progesterone receptor (+ *vs.* −)	<0.05
Estrogen receptor (+ *vs.* −)	>0.25
Age	>0.5
Adjuvant therapy (yes *vs.* no)	>0.25

Treatment with tamoxifen, with or without cytotoxic chemotherapy, has been shown to prolong the DFI of postmenopausal patients who are ER+.[10,13] Cytotoxic chemotherapy has been convincingly demonstrated to prolong the DFI of premenopausal patients without apparent regard to hormonal status.[11,12] Whether chemotherapy exerts a significant effect in postmenopausal patients is still debated.[17] Thus, the effect of adjuvant therapy on the DFI can be difficult to predict and will likely exert dissimilar effects on various subsets. For example, Lippman et al.[18] reported that ER+ tumors respond less well to adjuvant therapy than ER− tumors. Kiang et al.[19] and others,[20,21] however, have come to the opposite conclusion. Others have not found any relationship or have found a relationship only in premenopausal women.[5,22,23] Regardless of the effect on specific subsets, adjuvant therapy is likely to confound the evaluation of the relationship of receptor status on the natural prognosis of breast cancer.

With the widespread implementation of adjuvant treatments, especially chemotherapy, commencing in the late 1970s, adequate study of the natural history of breast cancer relative to hormonal receptors became increasingly difficult. In contrast to other reported series, the current group of patients consists entirely of patients who never received postmastectomy treatment. Our laboratory began to analyze hormonal receptors in 1974, thus affording us an opportunity to evaluate the potential prognostic significance of estrogen and progesterone receptors in a cohort of patients treated with mastectomy alone. The homogeneity of the group with regard to treatment removes adjuvant therapy as an additional confounding variable, a problem that hampers evaluation of a number of published series.

Knowledge of the relationship of hormonal receptor status and the natural history of the disease is of some importance in patient management after primary surgery. Conventionally, adjuvant chemotherapy is withheld from stage I patients. It has been suggested that there is a subgroup of patients at high risk for early recurrence who may well be candidates for treatment. Among the proposed high risk criteria is receptor negativity.[24,25] Our study supports this view, especially with regard to the progesterone receptor.

In the present study the inclusion of our adjuvant therapy group in the life table analysis did not alter the results (Figs. 3 and 4). The difference in the DFIs remained significant in the PR+ *versus* the PR− groups. However, patients treated with adjuvant therapy did worse than those not so treated. Presumably, this is a patient selection artifact since patients with more advanced disease were more likely to be treated with adjuvant therapy. Fifty per cent of stage III patients had adjuvant therapy whereas only 12% of those with stage I were so treated. In addition, those patients entering the study at a later date were more likely to have adjuvant therapy. This is also supported by the lack of significance of adjuvant therapy in the regression model. In essence, the decreased DFI observed in the adjuvant group can be attributed to changes in the other significant factors of the model, namely, nodal status, tumor size, and progesterone. It must be cautioned that this study was not designed to analyze adjuvant therapy, and no conclusions can be drawn from these data about its efficacy.

Thus, this study confirms that the progesterone receptor is a valuable indicator of the recurrence potential in breast cancer, independent of estrogen receptor positivity and treatment with adjuvant therapies.

Acknowledgment

The authors thank Susan Fallon and Anne Zabinsky for their help in data collection.

References

1. Elwood JM, Godolphin W. Oestrogen receptors in breast tumours: associations with age, menopausal status and epidemiological and clinical features in 735 patients. Br J Cancer 1980; 42:635–644.
2. Horowitz KB, McGuire WL, Pearson OH, Segaloff A. Predicting response to endocrine therapy in human breast cancer: a hypothesis. Science 1975; 189:726–727.
3. Bloom ND, Degenshein GA. Estrogen receptors and disease-free interval: a dissenting opinion. Breast Dis 1980; 6:25–27.
4. Kinne DW, Ashikari R, Butler A, et al. Estrogen receptor protein in breast cancer as a predictor of recurrence. Cancer 1981; 47:2364–2367.
5. Hilf R, Feldstein ML, Gibson SL, Savlov ED. The relative importance of estrogen receptor analysis as a prognostic factor for recurrence or response to chemotherapy in women with breast cancer. Cancer 1980; 45:1993–2000.
6. Furmanski P, Saunders DE, Brooks SC, Rich MA. The prognostic value of estrogen receptor determinations in patients with primary breast cancer: an update. Cancer 1980; 46(Suppl 12):2794–2796.
7. Skinner JR, Wanebo HJ, Betsill WL, et al. Evaluation of the pathologic and prognostic correlates of estrogen receptors in primary breast cancer. Ann Surg 1982; 196:636–641.
8. Clark GM, McGuire WL, Hubay CA, et al. Progesterone receptors as a prognostic factor in stage II breast cancer. N Engl J Med 1983; 309:1343–1347.
9. Osborne CK, Yochmowitz MG, Knight WA, McGuire WL. The value of estrogen and progesterone receptors in the treatment of breast cancer. Cancer 1980; 46(Suppl 12):2884–2888.
10. Fisher B, Redmond C, Brown A, et al. Treatment of primary breast cancer with chemotherapy and tamoxifen. N Engl J Med 1981; 305:1–6.
11. Fisher B, Fisher ER, Redmond C. Ten-year results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trial evaluating the use of L-phenylalanine mustard (L-PAM) in the management of primary breast cancer. J Clin Oncol 1986; 4:929–941.
12. Bonadonna G, Valagussa P. Adjuvant systemic therapy for resectable breast cancer. J Clin Oncol 1985; 3:259–275.

13. Cummings FJ, Gray R, Davis TE, et al. Adjuvant tamoxifen treatment of elderly women with stage II breast cancer. A double-blind comparison with placebo. Ann Intern Med 1985; 103:324–329.
14. Degenshein GA, Ceccarelli F, Bloom ND, Tobin EH. Hormone relationships in breast cancer: the role of receptor-binding proteins. Curr Probl Surg 1979; 16:1–59.
15. Cox DR. Regression models and life-tables. J R Stat Soc 1972; 34:187–200.
16. Pichon MF, Pallud C, Brunet M, Milgrom E. Relationship of presence of progesterone receptors to prognosis in early breast cancer. Cancer Res 1980; 40:3357–3360.
17. Adjuvant chemotherapy for breast cancer. NIH Consensus Development Conference Statement, vol. 5. 1985.
18. Lippman ME, Allegra JC, Thompson EB, et al. The relation between estrogen receptors and response rate to cytotoxic chemotherapy in metastatic breast cancer. N Engl J Med 1978; 298:1223–1228.
19. Kiang DT, Frenning DH, Gay J, et al. Estrogen receptor status and response to chemotherapy in advanced breast cancer. Cancer 1980; 46(Suppl 12):2814–2817.
20. Chang JC, Wergowske G. Correlation of estrogen receptors and response to chemotherapy of cyclophosphamide, methotrexate, & 5-fluorouracil (CMF) in advanced breast cancer. Cancer 1981; 48:2503–2506.
21. Paone JF, Abeloff MD, Ettinger DS, et al. The correlation of estrogen and progesterone receptor levels with response to chemotherapy for advanced carcinoma of the breast. Surg Gynecol Obstet 1981; 152:70–74.
22. Hilf R, Feldstein ML, Savlov ED, et al. The lack of relationship between estrogen receptor status and response to chemotherapy. Cancer 1980; 46(Suppl 12):2797–2800.
23. Stephens RB, Abeloff MD, Mellits ED, Baker RR. The role of estrogen receptor status in predicting the response of carcinoma of the breast to adjuvant chemotherapy. Surg Gynecol Obstet 1982; 154:200–204.
24. Valagussa P, DiFronzo G, Bignami P, et al. Prognostic importance of estrogen receptors to select node negative patients for adjuvant chemotherapy. *In* Salmon SE, Jones SE, eds. Adjuvant Therapy of Cancer, vol. 3. Philadelphia: Grune & Stratton, 1981; 329–333.
25. Freidman MA, Dorr FA, Perloff M. Adjuvant therapy for breast cancer patients with negative lymph nodes. *In* Proceedings of the NIH Consensus Development Conference on Adjuvant and Endocrine Therapy for Breast Cancer, NCI Monographs. 1986; 139–143.