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Steroid Receptors in Human Breast Cancer[1]

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Abstract

The measurement of cytoplasmic estrogen receptor in tumors from patients with breast cancer is now well established. Potential uses include prognosis of early recurrence following mastectomy, stratifying patients for adjuvant therapies, and selecting or rejecting endocrine therapy in advanced breast cancer.

The use of progesterone receptor measurements to improve our selection process has a good theoretical basis, and early reports now emerging indicate that the presence of both estrogen and progesterone receptor in a breast tumor predicts a high response rate to endocrine therapy. Further work in this area is required, however, since patients with estrogen receptor but not progesterone receptor still have an appreciable response rate.

Introduction

It is well accepted that, in normal estrogen target tissues such as uteri, the initial interaction of the steroid within the cell is with the cytoplasmic ER.[2] Subsequent steps leading to cell activation include translocation of the hormone-receptor complex to nuclei, binding to chromatin-associated acceptor sites, and finally stimulation of transcription and replication. Although the latter steps are not well understood at the present time, considerable data have accumulated regarding the initial binding of the hormone to the cytoplasmic ER. Some of the earliest work on this subject was performed in the laboratory of Jensen *et al.* (9) where the possible application of ER levels to the treatment of breast cancer patients was considered. It was reasoned that, since the stimulation of tissue growth by estrogens requires the presence of cytoplasmic ER, those breast tumors the growth of which was being stimulated by estrogens (and therefore might be reversed by ablative surgery designed to reduce circulating estrogens) should certainly contain cytoplasmic ER. Conversely, breast tumors growing independently of estrogens might not have cytoplasmic ER. These predictions have been substantiated by investigators all over the world (14, 15), and now in 1978 it is generally accepted that ER assays should be performed on every patient with breast cancer.

More detailed information on the significance of ER and also PGR is now emerging. It is the purpose of this communication to review data from my own laboratory on the use of steroid receptors in deciding treatment strategy for breast cancer. For a more comprehensive approach detailing the many important contributions from other laboratories, the reader is referred to a recent review (13).

Cytoplasmic ER in Primary Breast Cancer

Since we know that patients with tumor invasion of the axillary nodes are at very high risk of recurrence and that surgery and radiotherapy are effective only for local disease (3), there is now great impatience to determine whether systemic adjuvant therapies might delay or prevent these recurrences. At present there are only 2 published randomized studies of adjuvant chemotherapy, and curiously in both studies the benefit of adjuvant chemotherapy appears to be confined to premenopausal women (2, 4). The findings that 78% of women receiving combination chemotherapy (Cytoxan, 5-fluorouracil, methotrexate) developed amenorrhea (2) and independently that the same drug regimen decreased ovarian hormone production (17) have prompted the suggestion that the delay in tumor recurrence in premenopausal women is the result of a "medical ovariectomy" induced by the cytotoxic drugs. This idea has considerable merit but largely ignores the direct cytotoxic effects of the drugs on the tumor itself. If we consider both the ER distribution and ER level in tumors from pre- and postmenopausal patients (Table 1), we find that premenopausal patients are more likely to be ER−; if they are ER+, the ER values are likely to be lower compared to those of postmenopausal patients. Lower values result in lower response rates to endocrine therapy. This point is discussed further later. It has been reported recently that ER− tumors have a higher growth fraction (16), and cytotoxic agents are known to be more effective in rapidly proliferating tissues. Therefore the beneficial effects of cytotoxic therapy in premenopausal women may in part be explained by the fact that there are more ER−, aggressive tumors in this group compared to the postmenopausal group. Direct studies of response to chemotherapy and correlation with tumor ER status are now emerging, but the early results are conflicting (1, 5) and more time will be required to settle the issue.

The concept that ER− tumors are more aggressive is supported by a pilot study in San Antonio, where a group of approximately 150 women with operable breast cancer had ER measurements in their primary tumors and were then followed (10). As shown in Table 2, regardless of age, nodal status, or size of the primary tumor, the patients with ER− tumors had a higher recurrence rate at 18 months compared to ER+ patients.

It seems plausible, then, that adjuvant cytotoxic therapy is particularly effective in premenopausal patients for at least 2 reasons. First, there is a higher likelihood of aggressive ER− tumor cells with high growth fractions and therefore with higher probability of responding to chemotherapy. Second, the ovary seems to be particularly sensitive to cytotoxic therapy, and certain of the ER+ tumor cells may

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[2] The abbreviations used are: ER, estrogen receptor; PGR, progesterone receptor.

Table 1
ER distribution in human breast cancer

	Total	ER+ (%)	Mean ER (fmol/mg protein)
Premenopausal	540	61	30.3
Postmenopausal	1397	75	108.1

Table 2
Interaction of ER's and other factors in recurrence rate of breast cancer

	% of recurrence at 18 mos.[a]	
Category	ER−	ER+
Age		
<50	34	14
>50	35	8
Nodes		
0	12	6.5
1-3	38	12.5
≥4	62	27.0
Size		
<2 cm	33	0
>2 cm	31	14

[a] Adapted from Ref. 10.

be regressing due to a decrease in ovarian hormone production. Of course the interesting corollary is that postmenopausal patients with their higher proportion of ER+ tumor cells might be expected to respond to an adjuvant endocrine therapy.

Cytoplasmic ER and the Treatment of Advanced Breast Cancer

Although endocrine therapy for advanced breast cancer has been used for many years, the fact that only 20 to 40% of unselected patients demonstrate objective tumor regression with this approach, coupled with the recent success of combination chemotherapy in achieving remission in approximately 60% of unselected patients, has left endocrine therapy in a secondary role. However, a renewal of interest in endocrine therapy has resulted from the numerous studies that show that ER assays can be used to select or reject endocrine therapies with considerably more confidence than in the past (14). Our own data are probably representative of most data in the literature and are illustrated in Table 3. Regardless of the type of endocrine therapy, whether ablative surgical or additive hormonal, ER− tumors rarely respond whereas ER+ tumors have a respectable response rate of 57%. Most reports in the literature simply record ER data as positive or negative, rich and poor, etc. Since the actual quantitative values for ER range from a few to thousands of fmol/mg of cytosol protein, we inquired whether there might be a correlation between the objective response rate and the actual ER value. The data in Table 4 indicate that low values are associated with a low response rate and high values are associated with a high response rate. A reasonable approach might therefore be to reserve ablative endocrine therapy for those patients with the highest ER values and to use less aggressive additive hormonal therapy or antiestrogens in those patients with intermediate ER values. The patients in the latter category who respond could then be considered for subsequent ablative therapy.

PGR and Therapy of Advanced Breast Cancer

Although cytoplasmic ER is now proving to be very helpful in designing treatment strategies for patients with advanced breast cancer, there are many ER+ patients who fail to respond to endocrine therapy. This has prompted many investigators to search for additional markers that might discriminate between ER+ responders and nonresponders. Some time ago we suggested that PGR might be such a marker (8), and we have subsequently demonstrated that PGR is estrogen dependent both in animal mammary tumor systems (6) and in human breast cancer cells in long-term tissue culture (7). The distribution of ER and PGR in our patients is seen in Table 5. In contrast to ER, which is more frequent in postmenopausal patients, PGR is found equally in pre- and postmenopausal patients.

The real question of course is whether the measurement of PGR improves our selection for endocrine therapy. Table 6 is a listing of all of the available PGR data, including personal communications as well as published studies. It is not at all correct simply to total up the responses in each category since there is no reason to assume that the patient groups, criteria for objective response, or assays for PGR are comparable. Nevertheless, certain overall points can be made. Patients with tumors containing both PGR and ER do have the most favorable response rates. However, contrary to our prediction, patients with tumors containing ER but not PGR have a low but appreciable response rate to endocrine therapy. There are several possible explanations for this. One is that assays as currently reported are misinterpreted. In our own case, for example, we have considered only those tumors containing an 8S [^{3}H]R5020 binding peak in a sucrose gradient as positive for PGR. More recent

Table 3
ER in metastatic biopsies and objective response to endocrine therapy

	ER−	ER+
Ablative	1/19	25/43
Additive	0/9	10/20
Antiestrogens and medical adrenalectomy	1/5	9/14
Total	2/33 = 6%	44/77 = 57%

Table 4
ER values and objective response to endocrine therapy

ER (fmol/mg cytosol protein)	Response
<3	2/33 = 6%
3-100	24/52 = 46%
101-1000	21/26 = 80%

Table 5
ER and PGR distribution in 1366 biopsies

	Distribution (%)	
	Premenopausal	Postmenopausal
ER−, PGR−	30	19
ER−, PGR+	9	3
ER+, PGR−	12	23
ER+, PGR+	49	55

Table 6
Objective response to endocrine therapy (231 cases) by receptor content

	ER−, PGR−	ER−, PGR+	ER+, PGR−	ER+, PGR+
McGuire *et al.*	0/11		7/17	13/16
Degenshein *et al.*[a]	0/7	1/1	1/9	16/18
King *et al.*[b]	1/5	1/2	1/7	8/9
Skinner *et al.*[c]	5/17		0/3	4/7
LeClercq *et al.* (11)		0/1	1/3	1/3
Matsumoto *et al.* (12)	2/20	0/1	9/25	12/20
Young *et al.* (18)	1/3	1/1	1/7	13/18
Totals	9/63 = 14%	3/6	20/71 = 28%	67/91 = 74%

[a] Personal communication.
[b] R. J. B. King, S. Redgrave, R. D. Rubens, R. Millis, and J. A. Hayward, manuscript in preparation.
[c] L. G. Skinner, D. M. Barnes, and G. G. Ribeiro, manuscript in preparation.

work in our laboratory, as yet unpublished, indicates that during the standard overnight gradient centrifugation, there is some dissociation of the ligand from the 8S peak resulting in an underestimation of PGR levels. Furthermore, we have not included the 4S peak in our receptor calculations. This may be incorrect. Although much of the 4S peak may be due to R5020 binding to factors other than PGR, some of the 4S binding is probably due to PGR. Further work is needed to clarify this situation.

Another consideration is that some tumors are assayed when PGR is in a basal unstimulated state. We know that in human breast cancer cells PGR synthesis is estrogen dependent (7). It is therefore possible that some PGR-negative tumors are false negatives; if the patients had been given 2 to 3 days of estrogen priming prior to biopsy, perhaps some of the PGR-negative tumors would have been PGR positive. Finally, we must consider the possibility that our original hypothesis was incorrect. PGR, although a real product of estrogen stimulation, may be removed from the actual pathways involved in DNA replication and tumor growth and regression. In any case, with all of the current work going on with PGR and other receptors, the role of additional receptor assays in the management of breast cancer should soon be clarified.

Future Considerations

There is little doubt that ER assays are valuable in the setting of advanced breast cancer and they should be performed routinely. Their use in primary breast cancer to predict the likelihood of early recurrence appears promising, and additional independent confirmation is required. A well-designed adjuvant trial of chemotherapy for ER− tumors and of endocrine therapy (possibly antiestrogens) for ER+ tumors in node-positive patients would be invaluable. The question of whether ER− tumors respond better to chemotherapy because of their high growth fraction and more aggressive behavior is uncertain at present and needs to be unequivocally resolved. Finally, do we gain anything by measuring other receptors such as PGR? The answers may soon be in hand.

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