Recent clinical data (1) suggest that c-erbB-2 overexpression/amplification might be associated with tamoxifen resistance in patients with estrogen receptor (ER)-positive tumors. This association is controversial, however, and the question of the efficacy of hormone therapy in these patients is still a matter of debate. In a recent issue of the Journal, Konecny et al. (2) provided some answers to this question. After considering c-erbB-2, ER, and progesterone receptors (PRs) as continuous variables, they reported that patients with higher levels of c-erbB-2 overexpression had statistically significantly lower ER and PR levels than patients with lower levels of c-erbB-2 overexpression. They suggested that this finding might explain the relative resistance of c-erbB-2–positive tumors to hormone therapy.

Given the small number of retrospective studies offering data relevant to this question, we strictly reproduced the methodology of Konecny et al. (2) in a retrospective series of 488 patients with primary breast cancer and a median follow-up of 10 years for whom c-erbB-2, ER, and PR expression had been measured by quantitative biochemical methods, allowing them to be analyzed as continuous variables. The patients’ characteristics have been published elsewhere (3). For this analysis, 101 (20.7%) of the 488 patients were considered to be c-erbB-2–positive (protein levels above 350 IU/mg protein), providing separation of patients with regard to disease-free survival ($P = .002$) and overall survival ($P < .001$). This c-erbB-2–positive frequency is in the range of published values (2, 4).

Our results were as follows. First, among patients with c-erbB-2–overexpressing tumors ($n = 101$), we found a negative correlation between c-erbB-2 and ER and PR levels (ER: $r = -0.41$, $P < .001$; PR: $r = -0.24$, $P = .01$). Second, patients with c-erbB-2–positive tumors had statistically significantly lower absolute ER and PR levels than patients whose tumors did not overexpress c-erbB-2 (Table 1). Third, when we divided the 101 patients with c-erbB-2–positive tumors into two subgroups of approximately equal size, the median ER level was statistically significantly lower in the 52 patients with higher c-erbB-2 overexpression than in the 49 patients with weaker c-erbB-2 overexpression. Fourth, when we restricted this analysis to patients with hormone receptor–positive tumors (Table 1), those with higher c-erbB-2 overexpression had a lower median ER level than those with lower c-erbB-2 overexpression. Differences in PR levels were not statistically significant.

Thus, by applying the methodology of Konecny et al. retrospectively to an independent population, we confirmed their results, i.e., the higher the level of c-erbB-2 overexpression, the lower the ER level, both in the overall population and in the subset of patients with hormone receptor–positive tumors. Because the response to endocrine therapy depends on ER and PR levels, not only on arbitrarily defined ER and PR status (positive versus negative), the lower ER and PR expression in c-erbB-2–positive/ER-positive tumors could explain the failure of this treatment in such patients. Indeed, there is compelling evidence that cross-talk between ER and growth factor receptor pathways, such as those involving the EGFR/c-erbB-2 family, can alter ER function and thereby contribute to tumor growth and tamoxifen resistance (5–7). Taken together, these results emphasize the importance of considering the quantitative levels of c-erbB-2 and ER rather than using dichotomous systems.

**REFERENCES**


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**Table 1.** Median estrogen receptor (ER) and progesterone receptor (PR) levels according to c-erbB-2 expression using data from (3)

<table>
<thead>
<tr>
<th>c-erbB-2 expression*</th>
<th>No. of patients</th>
<th>Median ER expression (fmol/mg)</th>
<th>$P$†</th>
<th>Median PR expression (fmol/mg)</th>
<th>$P$†</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-erbB-2-negative</td>
<td>387</td>
<td>99</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-erbB-2-positive</td>
<td>101</td>
<td>26</td>
<td>&lt;.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Lower overexpression</td>
<td>49</td>
<td>84</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher overexpression</td>
<td>52</td>
<td>4</td>
<td>&lt;.001</td>
<td>0</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* Mann–Whitney $U$ test.
† Cut-off for c-erbB-2 positivity for this analysis was 350 IU/mg protein. This cut-off, which is different from that used in (3) but is in a range in other studies, gave a frequency of c-erbB-2–positive cases more similar to what is presented by Konecny et al. (2).
‡ Cut-off for ER and PR positivity for this analysis was 15 fmol/mg protein; consequently, the number of ER- and PR-positive patients is slightly different from that in (3).

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**DOI:** 10.1093/jnci/djg068

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**DOI:** 10.1093/jnci/djg069