Cancer Therapy: Clinical

Ratio of 17HSD1 to 17HSD2 Protein Expression Predicts the Outcome of Tamoxifen Treatment in Postmenopausal Breast Cancer Patients

Agneta Jansson,1 Lovisa Delander,1 Cecilia Gunnarsson,2 Tommy Fornander,3 Lambert Skoog,4 Bo Nordenskjöld,1 and Olle Stål1

Abstract Purpose: Estrogens have great significance in the development of breast cancer. After menopause, most estrogen biosynthesis is done in peripheral tissue, and the main enzymes involved in balancing the amount of estrone against estradiol are 17β-hydroxysteroid dehydrogenases (17HSD). The aim of this study was to investigate the prognostic and tamoxifen predictive values of 17HSD1 and 17HSD2 expression.

Experimental Design: Tumors from low-risk breast cancer patients randomized to adjuvant tamoxifen therapy or no adjuvant treatment were analyzed with immunohistochemistry to investigate protein expression of 17HSD1 and 17HSD2 in 912 cases. All patients had lymph node-negative breast cancer and were postmenopausal at the time of diagnosis.

Results: Low 17HSD1 expression was associated with significant benefit from tamoxifen treatment among patients with estrogen receptor (ER)-positive tumors (P < 0.001). For patients with a 17HSD1 score not exceeding that of 17HSD2, tamoxifen increased the rate of distant recurrence-free survival (hazard ratio, 0.37; 95% confidence interval, 0.23-0.60) and breast cancer-specific survival (hazard ratio, 0.30; 95% confidence interval, 0.16-0.54), whereas no apparent effect was observed when the 17HSD1 score was higher than that of 17HSD2. The interaction was significant for both distant recurrence-free survival (P = 0.036) and breast cancer-specific survival (P = 0.014). In the cohort of systemically untreated patients, no prognostic importance was observed.

Conclusions: This is the first report that clearly distinguishes between the prognostic and predictive importance of 17HSD1 and 17HSD2 in ER-positive breast cancer treated with or without tamoxifen. Our data suggest that the 17HSD1/17HSD2 ratio might be useful as a predictive factor for tamoxifen treatment in ER-positive breast cancer patients.

Estrogens are of great importance in the development of breast cancer. After menopause, estrogen biosynthesis in peripheral tissue has an almost exclusive role and several different enzymes are of significance for the availability of active estrogens.

The main enzymes involved in the formation are aromatase, estrone sulfatases and 17β-hydroxysteroid dehydrogenases (17HSD), the latter controlling the last step in the formation of estrogens. There are multiple 17HSD family members expressed in breast tissue, although 17HSD1 and 17HSD2 have been mostly investigated in breast cancer this far (1–8). 17HSD1 catalyzes the reduction of estrone to estradiol with NADP(H) as a cofactor and is mostly expressed in breast tumor tissue. 17HSD2 catalyzes the oxidation of estradiol to estrone with NAD(H) as a cofactor and is expressed in normal epithelium of the breast but is frequently lost in malignant cells (9, 10). High expression of 17HSD1 and amplification of HSD17B1, the gene coding for 17HSD1, as well as low expression of 17HSD2 have been associated with decreased survival in estrogen receptor (ER)-positive breast cancer (1, 2, 5, 11, 12).

Adjuvant tamoxifen therapy significantly improves the survival of ER-positive breast cancer patients. Clinical trials have shown further decreased recurrence rates with the use of aromatase inhibitors (13, 14). A large proportion of the patients do not benefit from the treatment, and better indicators for predicting the outcome of the therapy would be beneficial. We...
have previously reported that ER-positive patients with a low 17HSD2/17HSD1 ratio have a shorter survival (1). However, it still remains unclear if 17HSD enzyme levels are prognostic markers and/or if they can be used for the prediction of the outcome of tamoxifen treatment. We hypothesize that the expression levels of 17HSD1 and 17HSD2 may alter the estrogen balance in the tumor and influence the response to tamoxifen treatment in breast cancer.

The purpose of this study was to investigate the prognostic and predictive significance of expression levels of 17HSD1 and 17HSD2 as investigated by immunohistochemistry for patients randomized to no systemic treatment or adjuvant tamoxifen treatment of breast cancer.

**Patients and Methods**

**Patients**

A randomized tamoxifen trial comprising 1,780 low-risk breast cancer patients were conducted in the Stockholm region from 1976 to 1990 (15). The patients were all postmenopausal at the time of diagnosis and were included in a clinical trial comparing tamoxifen for 5 years versus no treatment and thereafter into a follow-up study. All patients had estrogen receptor-positive tumors. In cases where the scoring results did not agree, a consensus interpretation was limited to the invasive tumor.

**Methods**

**Hormone receptor status.** ER and progesterone receptor (PR) status of the tumors was evaluated retrospectively with immunohistochemistry using the Ventana automated slide stainer (Ventana Medical Systems) with the monoclonal Ventana Medical Systems CONFIRM mouse anti-ER primary antibody and the Ventana Medical Systems CONFIRM mouse anti-PR primary antibody. Cutoff level was set to 25% stained tumor cell nuclei. Data from the immunohistochemistry were the primary source to determine ER and PR status, but if data were missing, results obtained in clinical routine practice were used (15). The cutoff level was set to 0.05 fmol/μg DNA. In this way, ER and PR status could be defined for 97% and 87%, respectively, of the 912 tumors.

**Immunohistochemical analysis of HER-2.** Immunohistochemical staining for HER-2 was done on formalin-fixed, paraffin-embedded tissue sections. Sections were stained using the DAKO A0485 polyclonal rabbit antibody (DAKO Cytomation) following the manufacturer’s guidelines. The immunohistochemical staining was scored as follows: 0, no staining at all or membrane staining in <10% of cells; 1, weak or barely perceptible staining in >10% of cells; 2, weak to moderate staining in the whole membrane in >10% of cells; and 3, strong staining in the whole membrane in >10% of cells. In all cases, interpretation was limited to the invasive tumor.

**Breast cancer tissue microarrays.** Representative tissue blocks were selected as donor blocks for tissue microarray. Sections were cut from each donor block and stained with H&E. From these slides, three morphologically representative regions were chosen in each of the 912 tumor samples. Three cylindrical core tissue specimens with a diameter of 0.8 mm were taken from these areas in each case and mounted in recipient blocks, with at most 243 cores/block. The tissue microarrays were constructed using a manual arrayer (Beecher Instruments).

**Immunostaining for 17HSD1 and 17HSD2 expression.** Tissue microarray blocks were cut in 4 μm sections and mounted on frosted-coated slides. The specimens were deparaffinized in xylene, rehydrated in ethanol, and thereafter rinsed in distilled water. Antigen retrieval was done by incubating the slides in 78°C for 20 h in citrate buffer (pH 6.0). Endogenous peroxidase activity was blocked with 3% H₂O₂/methanol for 5 min and then protein block (DAKO) was applied for 10 min. The sections were incubated with a polyclonal 17HSD1 antibody H-158 (Santa Cruz Biotechnology) or 17HSD2 antibody (a kind gift from Profs. F. Labrie and V. Luiu-Thec) at 1:200 and 1:2,000, respectively, at 4°C for 18 h followed by incubation with the secondary antibody Envision, anti-rabbit (DAKO), for 30 min at room temperature. Thereafter, 3,3′-diaminobenzidine/H₂O₂ was used for 8 min to visualize the immunoreaction. Finally, the slides were counterstained with hematoxylin, dehydrated, and mounted.

The samples were categorized in four different groups based on the intensity of staining: negative (−), weak (+), moderate (++) and strong (+++) expression. Two individuals independently performed the evaluation (L.D. and C.G.) without knowledge of clinicopathologic information. In cases where the scoring results did not agree, a consensus score was reached after reevaluation.

**Western blotting.** To determine the specificity of the 17HSD1 antibody, lysates from MCF-7, T47D, and ZR75-1 cells were investigated.
Thelysates were diluted, and the same amounts of protein/lane were loaded on a 4% to 15% gradient precast gel (Criterion; Bio-Rad). The proteins were transferred to polyvinylidene fluoride membranes that were further incubated overnight with 17HSD1 antibody (1:2,000). To control for equal loading, the membrane was incubated with β-actin antibody (1:2,000). Binding of the antibodies to the membranes was detected with a commercial Enhanced Chemiluminescence Plus kit (GE Healthcare UK).

Small interfering RNA. To examine the specificity of the 17HSD2 antibody, small interfering RNA (siRNA) against 17HSD2 and a scrambled siRNA control were used in human mammary epithelial cells with endogenous 17HSD2 expression as described previously (16). The cells were attached to glass slides with cytopsin preparation 48 h after siRNA treatment, then after the 17HSD2 expression was examined in the cells using the 17HSD2 antibody.

Statistical analysis. The relationships between grouped variables were analyzed with χ² test for trend and Spearman’s rank-order correlation. The survival curves were produced according to the lifetable method described by Kaplan and Meier. Differences in distant recurrence-free survival (DRFS) were estimated with the log-rank test. Multivariate analysis of recurrence and mortality rates was done with Cox proportional hazards regression. The statistical package Statistica 7.0 (StatSoft Scandinavia) was used for all calculations. All P values are two-sided, and P values < 0.05 were considered as significant.

Results

Protein expression of 17HSD1 and 17HSD2. The protein expression of 17HSD1 and 17HSD2 was analyzed in tumors from 912 patients. The flow of patients through the study is described in Fig. 1. It was possible to score 17HSD1 and 17HSD2 expression in 95.5% and 94% of the patients, respectively. There were 8.4% 17HSD1 negative cases, 51.3% showed weak expression, 36.7% showed moderate expression, and 3.6% showed strong protein expression (Fig. 2). Concerning 17HSD2, 7.6% were negative, 56.9% showed weak expression, 32% showed moderate expression, and 3.5% showed strong protein expression (Fig. 2). In the survival analysis, patients were categorized according to 17HSD1 and 17HSD2 expression, one with negative and weak expression (low) and one with moderate and strong expression (high).

Table 1. Expression of 17HSD1 and 17HSD2 in relation to tumor characteristics and tamoxifen treatment analyzed with Spearman's rank-order correlation

<table>
<thead>
<tr>
<th>Tumor size (mm)</th>
<th>17HSD1 (%)</th>
<th>17HSD2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n - + ++ +++</td>
<td>n - + ++ +++</td>
</tr>
<tr>
<td>≤20</td>
<td>664 8.6 50.9 36.9 3.6</td>
<td>656 6.9 57.3 32.3 3.5</td>
</tr>
<tr>
<td>&gt;20</td>
<td>182 5.5 56.0 34.6 3.9</td>
<td>179 9.5 54.8 31.8 3.9</td>
</tr>
<tr>
<td>ER status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>651 7.4 50.4 37.8 4.5*</td>
<td>639 7.4 56.5 32.6 3.6</td>
</tr>
<tr>
<td>ER-</td>
<td>193 10.4 54.4 34.2 1.0</td>
<td>193 9.3 58.6 29.0 3.1</td>
</tr>
<tr>
<td>PR status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR+</td>
<td>366 6.6 51.4 37.2 4.9</td>
<td>368 7.3 56.5 32.6 3.5</td>
</tr>
<tr>
<td>PR-</td>
<td>406 9.1 50.5 37.7 2.7</td>
<td>398 8.8 56.8 31.2 3.3</td>
</tr>
<tr>
<td>HER-2 status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>488 11.9 51.2 33.8 3.1†</td>
<td>488 11.1 54.3 31.8 2.9</td>
</tr>
<tr>
<td>1+</td>
<td>149 3.4 50.3 42.9 3.4</td>
<td>145 0.7 61.4 34.5 3.4</td>
</tr>
<tr>
<td>2+</td>
<td>78 2.6 46.1 48.7 2.6</td>
<td>78 1.3 61.5 33.3 3.9</td>
</tr>
<tr>
<td>3+</td>
<td>91 3.3 49.4 41.8 5.5</td>
<td>92 3.3 63.0 28.3 5.4</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No tamoxifen</td>
<td>424 5.7 52.9 37.5 4.0</td>
<td>414 8.0 56.0 32.4 3.6</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>447 11.0 49.9 36.0 3.1</td>
<td>444 7.2 57.7 31.8 3.4</td>
</tr>
</tbody>
</table>

*P = 0.029.
†P = 0.00007.
There was a significant positive correlation between 17HSD1 and 17HSD2 expression ($P < 0.0001$; correlation coefficient = 0.19). We also found a weak positive correlation between 17HSD1 and ER status ($P = 0.029$; correlation coefficient = 0.08) and a significant positive correlation between 17HSD1 and HER-2 expression ($P = 0.00007$; correlation coefficient = 0.14). No other significant associations between 17HSD1 or 17HSD2 and clinicopathologic characteristics were found (Table 1). The percentage of tumors in the different staining intensity groups for 17HSD1 and 17HSD2 was similar in tumors from patients treated with tamoxifen and the control group.

The specificity of the antibodies were examined with Western blot (17HSD1) and siRNA (17HSD2). There were specific bands at 34.5 and 69 kDa representing the protein as monomer and homodimer when investigating 17HSD1 in the cells (Fig. 3). The expression was stronger for the T47D than the MCF-7 and ZR75-1 cells regarding 17HSD1. The expression of 17HSD2 was clearly reduced in human mammary epithelial cells treated with siRNA against 17HSD2 mRNA compared with the negative control (Fig. 3).

**Predictive value of 17HSD1 and 17HSD2 expression in tamoxifen-treated patients.** Patients with ER-positive tumors with low 17HSD1 expression had a significant benefit from tamoxifen treatment concerning DRFS [hazard ratio (HR), 0.42; 95% confidence interval (95% CI), 0.26-0.69; $P = 0.00045$], whereas patients with high 17HSD1 expression did not benefit (HR, 0.66; 95% CI, 0.37-1.17; $P = 0.15$). No significant difference between the HR values was shown ($P = 0.24$; Table 2).

Patients with ER-positive tumors with either low or high expression of 17HSD2 had a significant benefit from tamoxifen treatment concerning DRFS (HR, 0.50; 95% CI, 0.32-0.80; $P = 0.0032$ and HR, 0.52; 95% CI, 0.28-0.99; $P = 0.042$).

For patients with ER-positive tumors, a 17HSD1 score not exceeding that of 17HSD2, tamoxifen decreased the rate of distant recurrence (HR, 0.37; 95% CI, 0.23-0.60; $P = 0.00002$) and breast cancer-specific mortality (HR, 0.30; 95% CI, 0.16-0.54; $P = 0.00002$) with 63% and 70% respectively (Table 2), whereas no effect was observed when the score of 17HSD1 was higher than that of 17HSD2 (Fig. 4). The interactions were significant for both DRFS ($P = 0.04$) and breast cancer-specific survival (BCS; $P = 0.01$). When the tamoxifen predictive value was examined in the group of patients with ER-positive/HER-2 negative (0-2+) tumors, we found an even stronger benefit from tamoxifen treatment in the patients with tumors with a 17HSD1 score not exceeding that of 17HSD2 regarding both DRFS (HR, 0.35; 95% CI, 0.21-0.58; $P = 0.00004$) and BCS (HR, 0.26; 95% CI, 0.14-0.50; $P = 0.00006$), whereas no effect was observed when the score of 17HSD1 was higher than that of 17HSD2. The interactions were significant for both DRFS ($P = 0.03$) and BCS ($P = 0.008$).

**Prognostic value of 17HSD1 and 17HSD2 expression in systemically untreated patients.** In the cohort of systemically untreated patients

### Table 2. Cox regression analysis of recurrence rate and breast cancer related deaths for patients with ER-positive tumors in relation to 17HSD1 and 17HSD2

<table>
<thead>
<tr>
<th></th>
<th>DRFS</th>
<th>BCS</th>
</tr>
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<tbody>
<tr>
<td>Tamoxifen vs no tamoxifen</td>
<td>HR (95% CI)</td>
<td>$P$</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen vs no tamoxifen</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>17HSD1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-/+</td>
<td>0.42 (0.26-0.69)</td>
<td>0.00045</td>
</tr>
<tr>
<td>+++/+++</td>
<td>0.66 (0.37-1.17)</td>
<td>0.15</td>
</tr>
<tr>
<td>17HSD2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-/+</td>
<td>0.50 (0.32-0.80)</td>
<td>0.0032</td>
</tr>
<tr>
<td>+++/+++</td>
<td>0.52 (0.28-0.99)</td>
<td>0.042</td>
</tr>
<tr>
<td>17HSD1 and 17HSD2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17HSD1 ≤ 17HSD2</td>
<td>0.37 (0.23-0.60)</td>
<td>0.00002</td>
</tr>
<tr>
<td>17HSD1 &gt; 17HSD2</td>
<td>0.88 (0.46-1.67)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Fig. 3. Western blot analysis of 17HSD1 in TH7D, MCF7, and 2R75-1. A, 17HSD1 monomer at 34.5 kDa and the homodimer at 69 kDa. B, 17HSD2 expression in siRNA-treated human mammary epithelial cells. C, 17HSD2 expression in human mammary epithelial cells treated with scrambled siRNA.
patients, no prognostic importance of 17HSD1 (HR, 0.90; 95% CI, 0.61-1.64; \(P = 0.60\)), 17HSD2 (HR, 0.99; 95% CI, 0.66-1.48; \(P = 0.97\)), or 17HSD1>17HSD2 (HR, 0.80; 95% CI, 0.52-1.23; \(P = 0.31\)) expression levels was observed.

**Discussion**

Estrogens are important as mitogenic stimulators in breast cancer and local production of estrogens is significant for the progression of the disease. Previous studies have shown the importance of 17HSD1 and 17HSD2 in breast cancer. High levels of 17HSD1 as well as low levels of 17HSD2 have been associated with decreased survival in ER-positive breast cancer (1, 2, 5). Data from previous studies regarding 17HSD1 and 17HSD2 in breast cancer show a wide range of expression on both mRNA and protein levels. In the present study, 91.6% of the specimens showed 17HSD1 expression and 92.8% showed 17HSD2 expression. Oduwole et al. (5) detected 17HSD1 in 16% to 20% of their specimens examining both mRNA and protein levels. On the contrary, Gunnarsson et al. (1, 2) showed 17HSD1 mRNA expression in all tumors. A similar variation in results concerning 17HSD2 has been reported. The rate of mRNA-positive cases ranges from 14% to 25% (1, 2, 5) and protein expression from 0 to 61% (5, 6, 17, 18). Reasons for the differences are not known. Different methodologies have been used in the analyses and Oduwole et al. (5) showed that protein levels and mRNA expression did not correlate. The tumors in the studies have either been stored in frozen condition or formalin-fixed, whether this affects the results is not clear. Furthermore, different antibodies have been used in the immunohistochemistry studies. However, in this study, we have investigated the specificity of the antibodies with Western blot and siRNA. We found that the 17HSD1 antibody gives rise to bands of expected size and that cell lines with low (MCF-7) or high (T47D) mRNA expression showed the same difference on protein level (16). In MCF-7 cells, the number of HSD17B1 gene copies are normal, but in T47D cells, the HSD17B1 gene is amplified (12). Human mammary epithelial cells with high 17HSD2 expression were treated with siRNA; the levels of 17HSD2 immunostaining clearly decreased as a consequence. These results support that the antibodies employed in this study are truly specific.
We found that the expression of 17HSD1 and 17HSD2 was significantly correlated, which indicates that the enzymes are coregulated. It is known that progesterone and progesterone influence 17HSD1 and 17HSD2 expression in breast cancer cells and endometrial cells (19, 20). However, in this study, such influences are less likely because the patients were postmenopausal. Furthermore, it has been suggested that some cytokines may act as cofactors to regulate 17HSD expression (21, 22). We also found a correlation between 17HSD1 and ER status but no correlation between 17HSD2 and ER. In earlier studies, ER status has been both positively and inversely correlated to 17HSD1 (5, 17), but no association to 17HSD2 has been found (1, 5). We did not find any association to PR, which might have been expected. PR expression indicates that ER is activated, but the opposite does not necessary show that ER is inactive. Akt activation inhibits the PR expression via the phosphatidylinositol 3-kinase/Akt pathway in breast cancer cells and this is not mediated via a reduction of ER levels or activity (23).

HSD17B1 is located on chromosome 17q12 close to the HER-2 gene. We have shown that gene amplification of HSD17B1 is correlated to HER-2 amplification (11), and our results in this study support this by elucidating a significant correlation between 17HSD1 expression and HER-2 status.

In this unique large material consisting of tumors from 912 breast cancer patients treated with tamoxifen or no endocrine treatment, we have been able to decide whether 17HSD1 and 17HSD2 are prognostic and/or predictive markers. In another group of patients, we have shown earlier that ER-positive patients with high 17HSD1 expression or low 17HSD2 have a higher risk for relapse (1, 2) and Oduwole et al. (5) found that 17HSD1 was associated with a shorter overall and disease-free survival. We could not confirm that high 17HSD1 expression is associated to shorter DRFS or that 17HSD2 expression is a prognostic factor in the group of systemically untreated patients. This may reflect that, in the previous studies, most of the patients had received endocrine treatment. The patients investigated in our previous studies (1, 2) received tamoxifen for at least 2 years. Oduwole et al. (5) did not describe if the patients received endocrine treatment, but this seems very likely.

The ER-positive patients with low 17HSD1 expression and patients with either low or high 17HSD2 expression had a significantly longer DRFS with tamoxifen than without this treatment. This suggests that 17HSD1 has greater effect on clinical outcome of tamoxifen treatment than 17HSD2. Gunnarsson et al. (1) showed better DRFS and BCS for ER-positive breast cancer patients with a high 17HSD2/17HSD1 ratio. Interestingly, in the present series of breast cancer patients randomized to tamoxifen, we found that if the expression of 17HSD1 exceeded that of 17HSD2, we observed no benefit from tamoxifen treatment regarding DRFS and BCS. The significance of the enzymes as predictors of tamoxifen efficiency was supported by interaction analysis. This indicates that the relative balance between 17HSD1 and 17HSD2 levels might be a better predictor than each one of them alone. The results regarding the significance of the enzymes as predictors of tamoxifen efficiency did not change if the analysis was restricted to patients that did not overexpress HER-2. Similar results were presented in a study investigating premenopausal women and 17HSD1 and 17HSD2 (24). Patients with ER-positive tumors with low 17HSD1 expression showed a significantly reduced risk of DRFS when treated with tamoxifen. No associations were found with 17HSD2 and survival. In premenopausal women, 17HSD2 is regulated by progesterone during the menstrual cycle, and because it was not known on which day of the cycle the patients were operated on, it is difficult to draw conclusions based on 17HSD2 in this group (20, 25).

The data concerning expression of 17HSD1 and 17HSD2 separately or presented in relation to each other suggest that tamoxifen has a better clinical effect in patients with low 17HSD1 expression. This indicates low local production of estradiol in these tumors. We have previously shown that 17HSD1 has greater influence on the proliferation rate in ER-positive breast cancer cell lines than 17HSD2 (16). Our data indicate that, with 17HSD1 exceeding the level of 17HSD2, the resulting high estradiol levels successfully compete with tamoxifen. An important issue is whether patients with ER-positive tumors with expression of 17HSD1 that exceeds the levels of 17HSD2 would benefit from treatment with aromatase inhibitors instead of tamoxifen and whether 17HSD enzymes may be predictors of response to aromatase inhibitors.

In conclusion, this is the first report that clearly distinguishes between the prognostic and predictive importance of 17HSD1 and 17HSD2 in ER-positive breast cancer patients treated with or without tamoxifen. Our data suggest that the ratio of 17HSD1 to 17HSD2 might be used as a predictive factor for tamoxifen response in ER-positive postmenopausal breast cancer patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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