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17ß-Hydroxysteroid dehydrogenase type 1 as predictor of tamoxifen response in premenopausal breast cancer

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ABSTRACT

17ß-Hydroxysteroid dehydrogenases (17HSDs) are involved in the local regulation of sex steroids. 17HSD1 converts oestrone (E1) to the more potent oestradiol (E2) and 17HSD2 catalyses the reverse reaction. The aim of this study was to investigate the expression of these enzymes in premenopausal breast cancers and to analyse if they have any prognostic or tamoxifen predictive value. Premenopausal patients with invasive breast cancer, stage II (UICC), were randomised to either 2 years of adjuvant tamoxifen ($n = 276$) or no tamoxifen ($n = 288$). The median follow-up was 13.9 years (range 10.5–17.5). The expression of 17HSD1 and 17HSD2 was analysed with immunohistochemistry using tissue microarrays. The enzyme expression level (–/+/++/+++) was successfully determined in 396 and 373 tumours, respectively. Women with hormone-receptor positive tumours, with low levels (–/+/++) of 17HSD1, had a 43% reduced risk of recurrence, when treated with tamoxifen (Hazard Ratio (HR) = 0.57; 95% confidence interval (CI), 0.37–0.86; $p = 0.0086$). On the other hand high expression (+++) of 17HSD1 was associated with no significant difference between the two treatment arms (HR = 0.91; 95% CI, 0.43–1.95; $p = 0.82$). The interaction between 17HSD1 and tamoxifen was significant during the first 5 years of follow-up ($p = 0.023$). In the cohort of systemically untreated patients no prognostic importance was observed for 17HSD1. We found no predictive or prognostic value for 17HSD2. This is the first report of 17HSD1 in a cohort of premenopausal women with breast cancer randomised to tamoxifen. Our data suggest that 17HSD1 might be a predictive factor in this group of patients.

1. Introduction

Oestrogens and especially estradiol play an important role in the development of breast cancer and 60–80% of the tumours express oestrogen receptor alpha (ERα),[1] which mediates the proliferative effect of oestradiol. In premenopausal women, oestrogens are produced mainly in the ovary and in the circulation mainly present in an inactive form, oestrone sulphate.[2] Synthesis of the more potent oestradiol occurs in the peripheral tissues. Both normal breast tissue and breast tumours contain all the enzymes responsible for the local biosynthesis.[3,4] The main enzymes involved in the synthesis of

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oestradiol in premenopausal women are oestrone sulphatase and 17ß-hydroxysteroid dehydrogenases (17HSDs), the latter enzymes responsible for the final step in the formation of oestradiol. There are multiple members of 17HSDs expressed in breast tissue and in breast cancer, of which 17HSD1 and 17HSD2 are the two most studied.[5–9] 17HSD1 converts oestrone (E1) to estradiol (E2) using NADP(H) as a cofactor and 17HSD2 carries out the reverse reaction (E2–E1) using NAD(H) as a cofactor.[10] Both 17HSD1 and 17HSD2 are expressed in the normal breast and in breast cancer cells. 17HSD1 is frequently expressed in hormonal dependent tumours and 17HSD2 dominates in normal breast tissue.[11–13]

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 oestrogen receptor (ER) positive breast cancer;[5,7,8,14] however, it is unclear if the value of 17HSD1 and 17HSD2 is prognostic or treatment predictive. This could not be distinguished in earlier studies, but one recent study based on a randomised clinical trial suggests that the ratio of 17HSD1 and 17HSD2 predicts the benefit from tamoxifen in postmenopausal breast cancer.[9] Furthermore, previous studies have mainly focused on postmenopausal women with breast cancer.

Adjuvant tamoxifen significantly improves recurrence-free survival and reduces the mortality in premenopausal breast cancer patients.[15,16] However, a number of patients do not benefit although the tumour is ER positive, thus better predictive and prognostic markers are needed.

The aim of this study was to investigate if 17HSD1 or 17HSD2, using tumour material from a randomised controlled trial, have any predictive or prognostic value in premenopausal women with hormone-receptor positive breast cancer treated with adjuvant tamoxifen. This is the first study of 17HSDs including only premenopausal women who participated in a randomised controlled study.

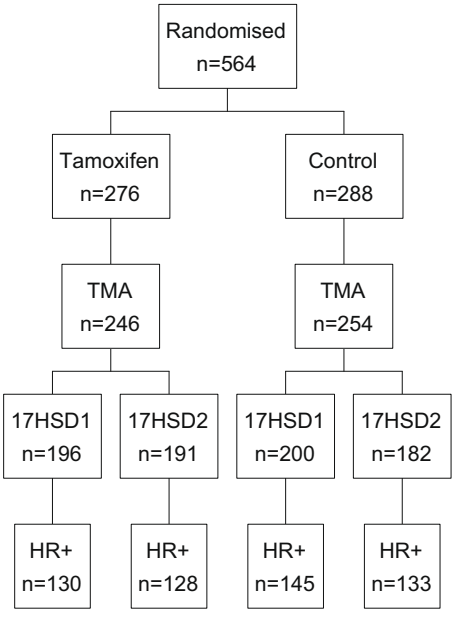

Fig. 1 – Flowchart showing the number of patients in the original study, number of tumour samples available, and number of samples successfully analysed in this study. HR+: hormone-receptor positive (oestrogen receptor (ER) and/or progesterone receptor (PR) positive) tumours.

2. Patients and methods

2.1. Patients

A prospective randomised controlled trial with adjuvant tamoxifen or no systemic treatment, including 564 women was conducted in Sweden between 1986 and 1991. The patients were premenopausal or under 50 years (they were considered premenopausal until 1 year after their last menstruation) at the time of inclusion, with stage II (pT2N0M0, pT1N1M0 and pT2N1M0) invasive breast cancer. They were included independently of the hormone-receptor status of the tumour.

Patients were randomised to receive postoperative adjuvant tamoxifen for 2 years ($n = 276$) or no treatment

Table 1 – Tumour and clinical characteristics for all patients and for those with tumours scored for 17HSD1 and 17HSD2.

Variable	All ($n = 564$) n (%)	17HSD1 ($n = 396$) n (%)	17HSD2 ($n = 373$) n (%)
Age (years)			
<40	113 (20.0)	78 (19.7)	74 (19.8)
40–50	362 (64.2)	255 (64.4)	241(64.6)
>50	89 (15.8)	63 (15.9)	58 (15.6)
Lymph node status			
N0	160 (28.5)	107 (27.2)	98 (26.4)
N+	402 (71.5)	287 (72.8)	273 (73.6)
Missing	2	2	2
Tumour size (mm)			
0–20	207 (36.8)	147 (37.2)	138 (37.0)
>20	356 (63.2)	248 (62.8)	235 (63.0)
Missing	1	1	0
Receptor status			
ER– and PR–	158 (29.1)	118 (30.0)	110 (29.6)
ER+ and/or PR+	385 (70.9)	275 (70.0)	261 (70.4)
Missing	21	3	2
PR < 75%	284 (61.6)	233 (62.6)	223 (64.1)
PR > 75%	117 (38.4)	139 (37.4)	125 (35.9)
Missing	103	24	25
Nottingham grade			
1	58 (11.3)	41 (10.8)	37 (10.3)
2	222 (43.2)	161 (42.4)	154 (42.9)
3	234 (45.5)	178 (46.8)	168 (46.8)
Missing	2	2	2
HER2			
Negative (–/+/++)	363 (84.8)	298 (84.7)	279 (84.5)
Positive (+++)	65 (15.2)	54 (15.3)	51 (15.5)
Missing	136	41	43
Randomised			
Control	288 (51.1)	200 (50.5)	182 (48.8)
Tamoxifen	276 (48.9)	196 (49.5)	191 (51.2)

17HSD: 17ß-hydroxysteroid dehydrogenase; ER: oestrogen receptor; PR: progesterone receptor; and HER2: human epidermal growth factor receptor 2.

($n = 288$). Two centres in Sweden were enrolled in the trial. Study centre 1 included 137 patients and used a daily dosage of 40 mg tamoxifen and study centre 2 included 427 patients and used 20 mg tamoxifen. In postmenopausal patients the results of tamoxifen 20 mg or 40 mg daily have been reported to be similar.[17] All patients had radical surgery (mastectomy or breast-conserving surgery with axillary dissection, level one and two). After breast-conserving surgery, all patients received radiotherapy (50 Gy) to the breast. Patients with axillary lymph-node metastases had locoregional radiotherapy. Adjuvant chemotherapy with cyclophosphamide, methotrexate and fluoro-uracil (CMF) or hormonal treatment with goserelin was given to 9 patients (less than 2%) of the study population. The median follow-up for patients without a breast cancer event was 13.9 years (range 10.5–17.5). Tumour samples from 500 patients were available for the present investigation.

Clinical and tumour characteristics and the main result of the original study have earlier been presented.[16] We found that adjuvant tamoxifen significantly increased recurrence-free survival (RFS) in patients with hormone-receptor positive tumours.

The Ethical Committees at Lund University and Linköping University approved retrospective analysis of archived tumour tissue.

2.2. *Tissue microarray (TMA)*

Prior to the construction of tissue microarrays (TMA), all tumours were histopathologically re-evaluated.[16] Areas representative of invasive cancer were marked on haematoxylin & eosin-stained slides and two tissue cores (0.6 mm) were taken from each paraffin block and mounted in recipient blocks with a total number of 200 cores/block. TMA blocks were then cut in 4 μm sections and mounted on frost-coated slides.

2.3. *Immunostaining for 17HSD1 and 17HSD2 expression*

Tumour samples from the patients were analysed for 17HSD1 and 17HSD2 expression using immunohistochemistry. The TMA slides were deparaffinised in xylene, rehydrated in a series of ethanol and thereafter rinsed in distilled water. Antigen retrieval was performed by incubating the slides in 78 °C for 20 h in citrate buffer (pH 6.0). Endogenous peroxidase activity was blocked with 3% (v/v) H_2O_2/methanol for 5 min and then protein block (DAKO, Glostrup, Denmark) was applied for 10 min. The sections were then incubated with a polyclonal 17HSD1 antibody, H-158 (Santa Cruz Biotechnology, Santa Cruz, CA, USA) or 17HSD2 antibody (a kind gift from Professor Fernand Labrie and Professor Van Luu-The, Laval University, Quebec, Canada), diluted 1:200 and 1:2000, respectively, at 4 °C for 20 h, followed by incubation with the secondary antibody Envision, anti-rabbit (DAKO, Glostrup, Denmark) for 30 min at room temperature. Then the specimens where incubated in 3,3-diaminobenzidine tetrahydrochloride (DAB/H_2O_2) for 8 min to visualise the immunoreactivity. Finally the slides were counterstained with haematoxylin, dehydrated and mounted. The specificity of the antibodies has previously been evaluated by Western blot (17HSD1) or after siRNA treatment (17HSD2) in our laboratory.[9] Both antibodies were found to be specific.

For evaluation of 17HSD1 and 17HSD2 expression the samples were categorised into four different groups, respectively, based on the intensity of the staining; negative (–), weak (+), moderate (++) or strong (+++) expression. When expressed, the proteins were in general visualised in all tumour cells and therefore the frequency of positive cells was not scored. All staining was evaluated independently by two investiga-

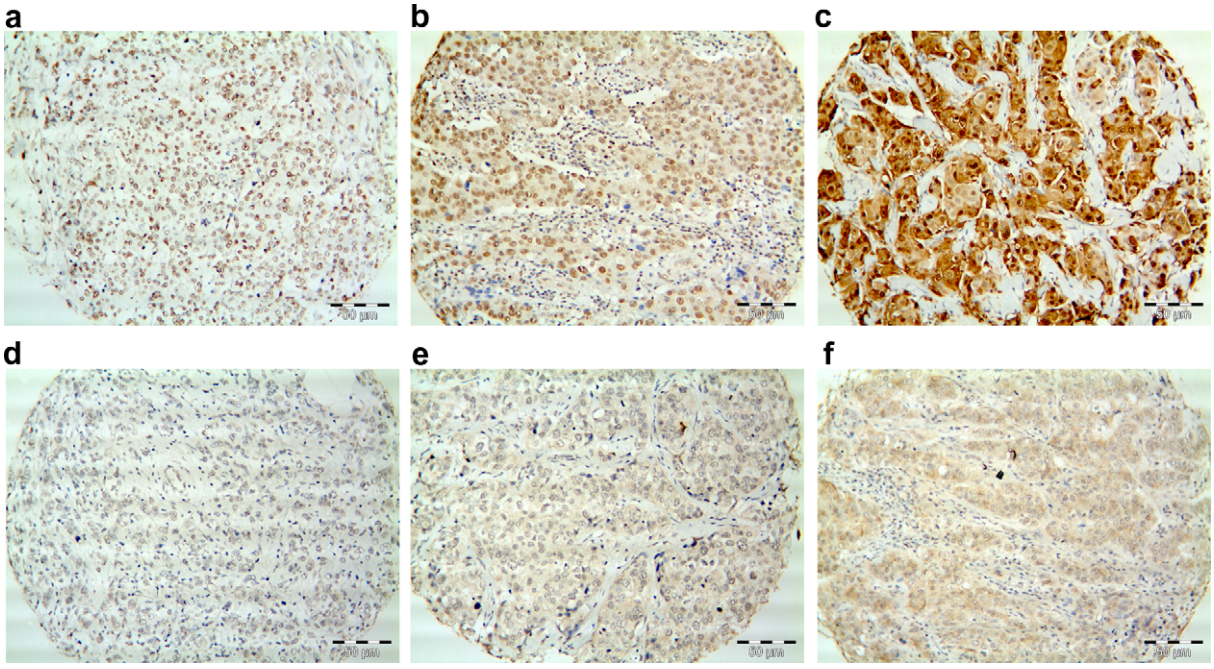

Fig. 2 – Immunohistochemical detection of 17HSD1 (a–c) and 17HSD2 (d–f) using tissue microarray. Staining intensity for 17HSD1: weak (a), moderate (b), strong (c) and for 17HSD2: negative (d), weak (e), and moderate (f).

tors, blinded to pathological and clinical data, and in case of discrepancy, a new joint examination was performed to reach consensus.

2.4. Oestrogen and progesterone receptor status

Oestrogen and progesterone receptors (PRs) were known for 453 tumours from the time of surgery by standard methods. For another 88 tumours the receptor status was determined by immunohistochemistry using TMA, and tumours with more than 10% positive cells were considered positive.[16] Tumours positive for ER and/or PR were defined as receptor positive.

2.5. Nottingham histological grade

Paraffin blocks from the primary tumour were available in 500 patients and Nottingham histological grade (NHG) was re-examined in 491 tumours.[16]

2.6. HER2 immunohistochemistry

Protein expression of HER2 was determined by immunohistochemistry on TMA slides and results were available for 428 tumours. Details of the procedure have been published elsewhere.[18]

Table 2 – 17HSD1 and 17HSD2 expression in relation to tumour and clinical characteristics.

Variable	17HSD1 (n = 396)			p-Value	17HSD2 (n = 373)			p-Value
	Weak –/+ n (%)	Moderate ++ n (%)	Strong +++ n (%)		Negative – n (%)	Weak + n (%)	Moderate/strong ++/ +++ n (%)	
All patients	99 (25)	219 (55)	78 (20)		98 (26)	192 (52)	83 (22)	
Age (years)								
<40	31 (40)	40 (51)	7 (9)		14 (19)	42 (57)	18 (24)	
40–50	57 (22)	142 (56)	56 (22)		75 (31)	118 (49)	48 (20)	
50+	11 (17)	37 (59)	15 (24)	0.00046	9 (16)	32 (55)	17 (30)	0.72
Lymph node status								
0	26 (24)	60 (56)	21 (20)		32 (33)	53 (54)	13 (13)	
1–3	52 (26)	107 (54)	40 (20)		42 (22)	95 (51)	51 (27)	
4+	20 (23)	51 (58)	17 (19)	0.91	22 (26)	44 (52)	19 (22)	0.09
Tumour size (mm)								
0–20	37 (25)	77 (52)	33 (22)		32 (23)	66 (48)	40 (29)	
21+	62 (25)	141 (57)	45 (18)	0.57	66 (28)	126 (54)	43 (18)	0.039
Receptor status								
ER– and PR–	33 (28)	69 (58)	16 (14)		32 (29)	61 (55)	17 (15)	
ER+ and/or PR+	66 (24)	148 (54)	61 (22)	0.09	66 (25)	131 (50)	64 (25)	0.11
PR 0–10%	34 (27)	72 (58)	19 (15)		37 (32)	65 (55)	15 (13)	
PR 11–50%	19 (33)	29 (51)	9 (16)		17 (29)	30 (51)	12 (20)	
PR 51–75%	15 (29)	29 (57)	7 (14)		12 (26)	19 (40)	16 (34)	
PR > 75%	25 (18)	75 (54)	39 (28)	0.0059	28 (22)	67 (54)	30 (24)	0.016
PR < 75%	68 (29)	130 (56)	35 (15)		66 (30)	114 (51)	43 (19)	
PR > 75%	25 (18)	75 (54)	39 (28)	0.00072	28 (22)	67 (54)	30 (24)	0.12
Nottingham grade								
1	10 (24)	20 (49)	11 (27)		9 (24)	21 (57)	7 (19)	
2	41 (25)	92 (57)	28 (17)		41 (27)	67 (44)	46 (30)	
3	43 (24)	98 (55)	37 (21)	0.93	47 (28)	98 (58)	23 (14)	0.07
HER2								
Neg (–/+/++)	72 (24)	170 (57)	56 (19)		75 (27)	145 (52)	59 (21)	
Pos (+++)	16 (30)	25 (46)	13 (24)	0.95	13 (25)	27 (53)	11 (22)	0.82
Randomised								
Control	51 (26)	109 (54)	40 (20)		45 (25)	98 (54)	39 (21)	
Tamoxifen	48 (25)	110 (56)	38 (19)	0.95	53 (28)	94 (49)	44 (23)	0.83

Missing	17HSD1		17HSD2	
	Node status	2	Node status	2
	Tumour size	1	Tumour size	0
	Receptor status	3	Receptor status	2
	PR	24	PR	25
	NHG	16	NHG	14
	HER2	41	HER2	43

17HSD: 17ß-hydroxysteroid dehydrogenase; ER: oestrogen receptor; PR: progesterone receptor; and HER2: human epidermal growth factor receptor 2.

2.7. Statistics

The relationships between grouped variables were analysed with χ^2 test and Spearman's rank order correlation. Recurrence-free survival (RFS) and breast cancer survival (BCS) curves were calculated according to the Kaplan–Meier method. Differences in RFS and BCS between groups were analysed using the log-rank test. Univariate and multivariate analysis of recurrence rate and mortality rate was performed with Cox proportional hazard regression. RFS included local, regional, distant recurrences and breast cancer specific death, but not contralateral breast cancer, as primary event. $p < 0.05$ was considered as significant.

The statistical calculations were made using Statistica 7.0 (Stat Soft Scandinavia AB, Uppsala, Sweden).

3. Results

3.1. Protein expression of 17HSD1 and 17HSD2

The protein expression of 17HSD1 and 17HSD2 could be scored in 396 and 373 tumours, respectively. A flowchart showing the original number of tumours and the number that could be scored is shown in Fig. 1. The dropout was due to the loss of tumour material or the absence of malignant cells in the core samples. Patient's and tumour characteristics showed no significant differences between the analysed subset and the patients in the original study (Table 1). The staining for 17HSD1 expression was negative in 1.0% (4/396), weak in 24.0% (95/396), moderate in 55.3% (219/396) and strong in 19.7% (78/396). Concerning 17HSD2, 26.3% (98/373) showed negative, 51.5% (192/373) weak, 20.4% (76/273) moderate and 1.8% (7/373) strong expression (Fig. 2). As there were only 4 tumours that scored negative for 17HSD1 and 7 with strong expression of 17HSD2, they were analysed as weak and moderate respectively. The percentage of tumours in the different staining groups for 17HSD1 and 17HSD2 were similar in tumours from patients treated with tamoxifen and from the control group (Table 2). There was a significant positive correlation between 17HSD1 and age ($p = 0.00046$) and between 17HSD1 and PR ($p = 0.00072$). When looking at only receptor positive tumours the correlation to high content of PR was still significant ($p = 0.0045$). There was a significant negative correlation between 17HSD2 and tumour size ($p = 0.039$) (Table 2).

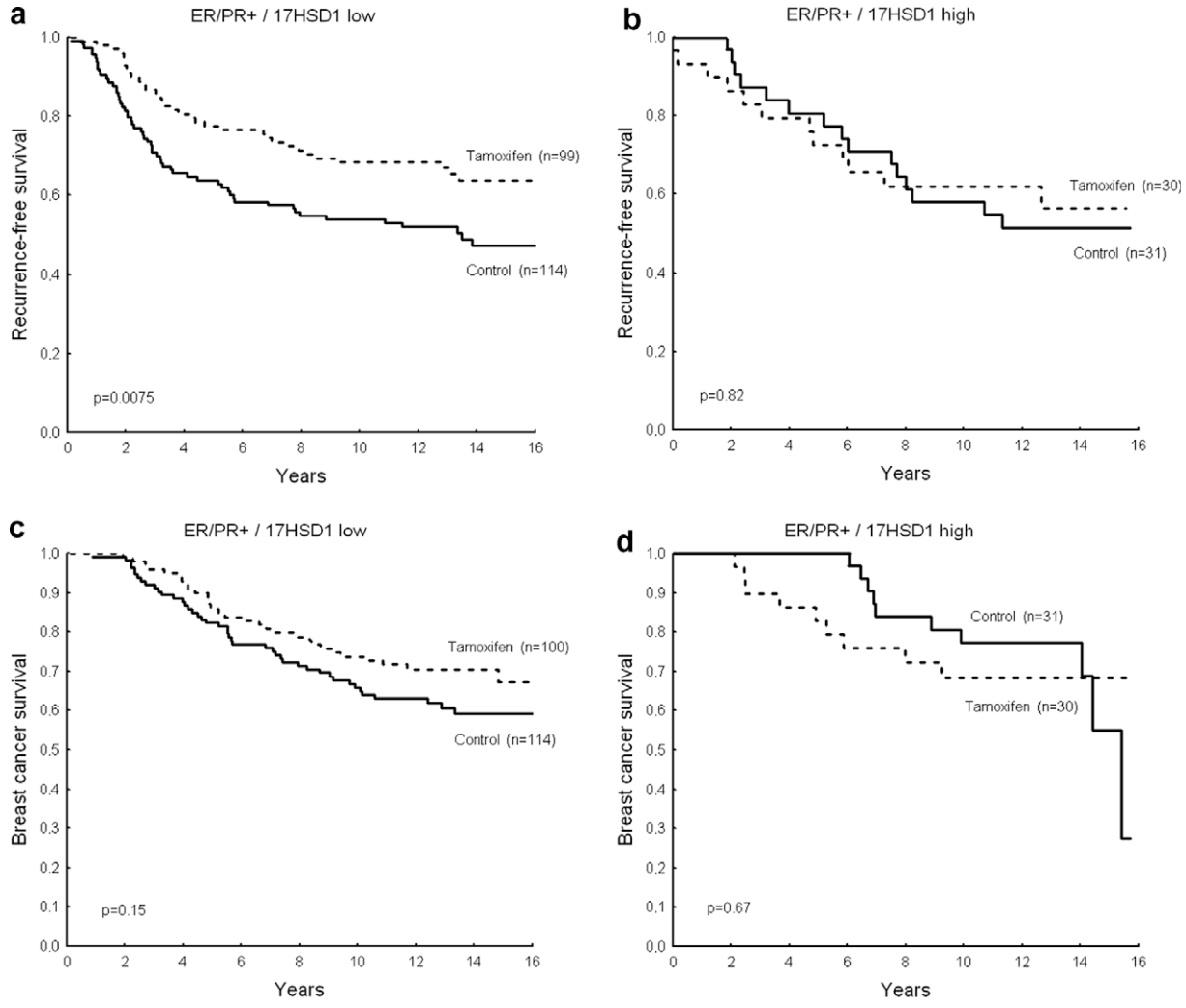

Fig. 3 – Kaplan–Meier plots of recurrence-free survival (RFS) (a, b) and breast cancer specific survival (BCS) (c, d) for patients with receptor positive tumours according to the treatment arm and in relation to 17HSD1 expression, low (a, c) or high (b, d). The log-rank test was used to calculate the *p*-values.

3.2. Predictive value of 17HSD1 and 17HSD2 expression for the benefit from adjuvant tamoxifen

In the analysis of recurrence-free survival with and without tamoxifen, patients were categorised according to the expression of 17HSD1 and 17HSD2 (negative/weak, moderate and strong for 17HSD1 and negative, weak, moderate/strong for 17HSD2). We found similar hazard ratios (HR) for the groups with negative/weak and moderate expression of 17HSD1 and between groups with negative and weak expression of 17HSD2. 17HSD1 was therefore classified as low (negative, weak and moderate) or high (strong) and 17HSD2 as low (negative and weak) or moderate (moderate and strong).

Patients with receptor positive tumours with low expression of 17HSD1 had a significant benefit from tamoxifen treatment according to RFS (HR = 0.57 (95% CI 0.37–0.86), $p = 0.0086$) whereas patients with high 17HSD1 expression did not benefit from tamoxifen (HR = 0.91 (95% CI 0.43–1.95), $p = 0.82$) (Fig. 3 and Table 3). The interaction between 17HSD1 and tamoxifen benefit was significant during the first 5 years of follow-up ($p = 0.021$) (Table 3).

High expression of PR (>75%) has earlier shown to be a strong predictor of tamoxifen response in this study population.[19] We therefore wanted to analyse this subset of patients separately. We found that patients with tumours with high content of PR and low expression of 17HSD1 did benefit even better from adjuvant tamoxifen and had a 71% reduced risk of recurrence (HR = 0.29 (95% CI 0.15–0.58), $p = 0.00047$) and when compared with high expression of 17HSD1 (HR = 0.65 (95% CI 0.24–1.76), $p = 0.39$), a significant difference between the HR values was shown in a multivariate analysis ($p = 0.023$) (Table 3).

Low expression of 17HSD1 along with high content of PR was associated with a better breast cancer specific survival (BCS) after adjuvant tamoxifen than without ($p = 0.0058$), and compared with high 17HSD1 the difference in hazard ratio was nearly significant ($p = 0.056$) (Fig 4 and Table 3). No predictive importance of 17HSD2 could be observed for the benefit from tamoxifen (Table 3).

3.3. Prognostic value of 17HSD1 and 17HSD2 expression in systemically untreated patients

In the control group with no tamoxifen treatment there was no difference in recurrence rate in relation to high versus low expression of 17HSD1 (HR = 0.73 (95% CI 0.44–1.21),

Table 3 – Recurrence and breast cancer death rate with and without tamoxifen for patients with hormone-receptor positive tumours in subgroups divided by 17HSD1/2 and PR content.

ER+ and/or PR+		Recurrence rate			Breast cancer death rate		
		HR (95% CI)		Test for interaction[a] p-value	HR (95% CI)		Test for interaction p-value
17HSD1 (n = 274)	Low (–/+/++) (n = 213)	0.57 (0.37–0.86)	$p = 0.0086$	0.021	0.71 (0.45–1.13)	$p = 0.15$	0.054
	High (+++) (n = 61)	0.91 (0.43–1.95)	$p = 0.82$		1.22 (0.49–3.01)	$p = 0.67$	
17HSD2 (n = 260)	Low (–/+) (n = 196)	0.57 (0.37–0.89)	$p = 0.014$	0.26	0.65 (0.32–1.88)	$p = 0.073$	0.69
	Moderate (++/+++) (n = 64)	0.60 (0.43–1.25)	$p = 0.17$		0.78 (0.32–1.88)	$p = 0.58$	
PR > 75%							
17HSD1 (n = 134)	Low (–/+/++) (n = 96)	0.29 (0.15–0.58)	$p = 0.00047$	0.023	0.34 (0.16–0.73)	$p = 0.0058$	0.056
	High (+++) (n = 38)	0.65 (0.24–1.76)	$p = 0.39$		1.03 (0.33–3.0)	$p = 0.96$	
17HSD2 (n = 125)	Low (–/+) (n = 95)	0.38 (0.19–0.74)	$p = 0.0045$	0.86	0.44 (0.21–0.92)	$p = 0.030$	0.31
	Moderate (++/+++) (n = 30)	0.38 (0.13–1.10)	$p = 0.074$		0.40 (0.11–1.42)	$p = 0.16$	

17HSD: 17ß-hydroxysteroid dehydrogenase; ER: oestrogen receptor; PR: progesterone receptor; and HER2: human epidermal growth factor receptor 2.

[a] The interaction tests were performed with Cox proportional hazard models including the variables tamoxifen, 17HSD1 or 17HSD2, an interaction term, and other characteristics included in Table 1. The follow-up period in the models was 5 years for recurrence and 10 years for breast cancer death.

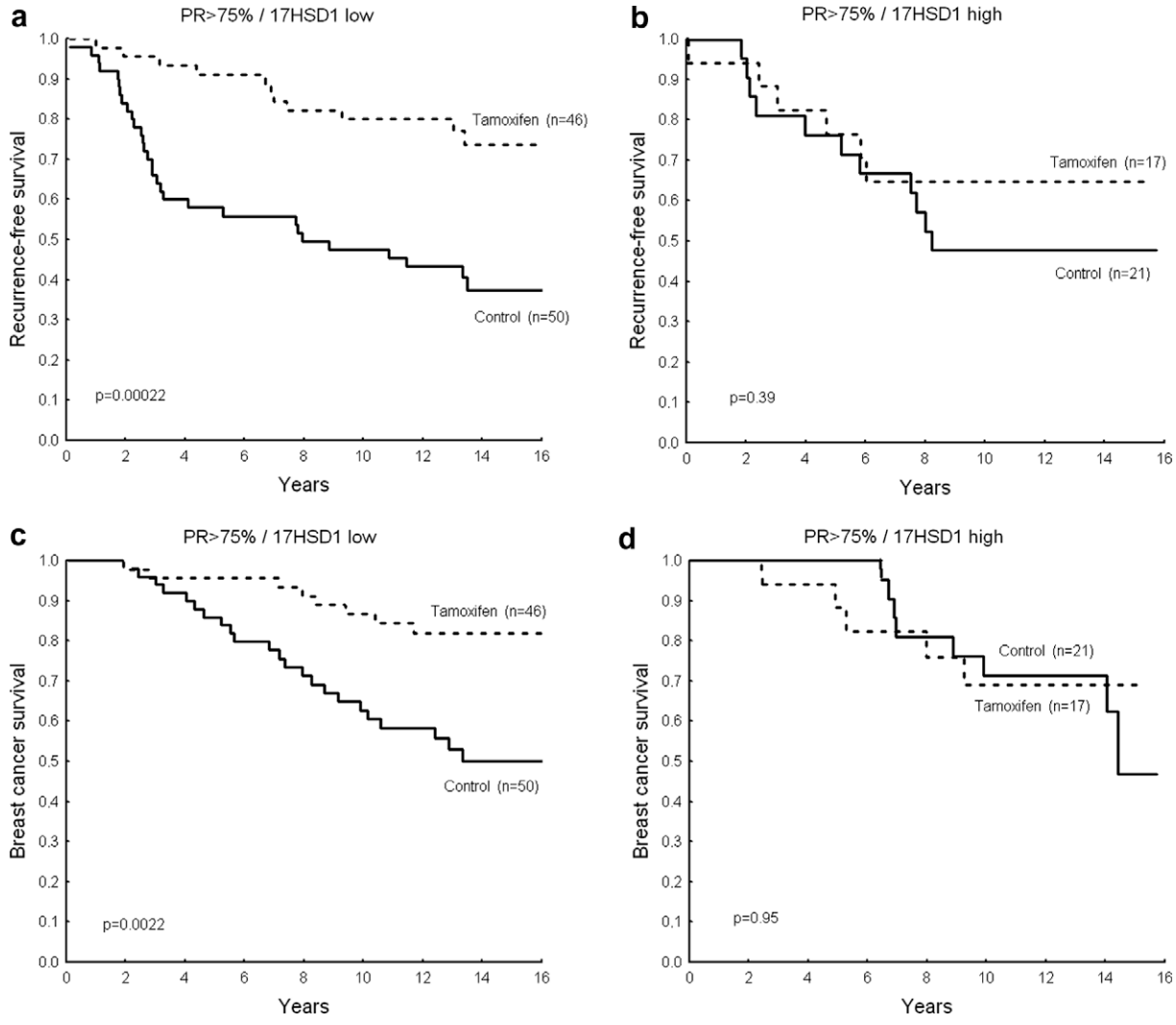

Fig. 4 – Kaplan–Meier plots of recurrence-free survival (RFS) (a, b) and breast cancer specific survival (BCS) (c, d) for patients with tumour progesterone receptor (PR) over 75% according to the treatment arm and in relation to 17HSD1 expression, low (a, c) or high (b, d). The log-rank test was used to calculate the *p*-values.

$p = 0.23$). No prognostic importance of 17HSD2 was observed (HR = 1.07 (95% CI 0.66–1.72), $p = 0.78$).

4. Discussion

In this unique material including only premenopausal women with breast cancer allocated to 2 years of tamoxifen or no endocrine treatment, we found that women with receptor positive breast cancer with low expression of 17HSD1 did benefit from adjuvant tamoxifen, while patients with high expression of 17HSD1 appeared to have no benefit. Oestrogens are important stimulators of growth in breast cancer and local production of oestradiol is significant for the progression of the disease. Local synthesis of hormones occurs in hormone-dependent breast tumours of both pre- and postmenopausal women.[20] Previous studies have shown the importance of 17HSD1 and 17HSD2 in breast cancer. 17HSD1 activity dominates in ER+ tumours and 17HSD2 in ER– tumours according to some report.[21] The ratio 17HSD1 to 17HSD2 seems to be increased in tumours of women with hormone-dependent tumours[6] and high levels of 17HSD1 as well as low levels of 17HSD2 have been associated with decreased recurrence-free survival in oestrogen-receptor positive breast cancer.[5,7,8] However, the majority of the patients included in these studies received adjuvant tamoxifen, so the prognostic and treatment predictive value were not possible to distinguish. Jansson and colleagues[9] found that the 17HSD1 to 17HSD2 ratio predicted the outcome of tamoxifen treatment in postmenopausal women, whereas no prognostic significance was found.

Earlier studies have shown a wide range of expression of both mRNA and protein for 17HSD1 and 17HSD2. The proportion of tumours showing protein expression of 17HSD1 varies in studies from 20% to 92% and 17HSD2 from 0% to 93%.[7,9,22,23] We found that 99% of the tumours expressed 17HSD1 and 74% expressed 17HSD2. Oduwole and colleagues[7] found expression of 17HSD1 in 20%, which corresponds to the number with high expression of 17HSD1 in the present study. The

causes of variation in expression of 17HSD1 and 17HSD2 are not known, but may be explained by different methodologies. In some studies the tumour samples have been frozen material and in others taken from formalin-fixed tumours, if this affects the results is not clear. In the immunohistochemistry studies different antibodies have been used. The antibodies employed in the present study have previously been shown to be specific.[9] Some studies comprised only postmenopausal women while in other studies both pre- and postmenopausal women were included.

Association between 17HSD1 and ER has been reported,[7,9] while others found a correlation between 17HSD1 and ER and PR content.[23] We found a trend between 17HSD1 and ER, but a strong correlation between high expression of 17HSD1 and PR, especially if there was a high content of PR (>75%). PR expression indicates that ER is activated although the lack of expression does not necessarily show that ER is inactive.[24] Progestins may influence 17HSD1 and 17HSD2 expression in breast cancer cells and in endometrial cells.[25,26] In epithelial cells of normal breast some progestins may increase the expression of 17HSD2 and inhibit epithelial growth.[22,25] The expression of 17HSD2, like that of progestins, varies during the menstrual cycle and is highest at the end of the cycle so it may by difficult to draw any conclusions on tumour expression of 17HSD2 in premenopausal women.[27,28] Progestins can also induce 17HSD1 expression in breast cancer cell lines which has been reported in several studies.[10,22,26]

We found that patients with low expression of 17HSD1 had a significantly better RFS with adjuvant tamoxifen if compared with high expression of 17HSD1, especially if the tumour had high content of PR. High content of PR (>75%) has earlier been reported as a better predictive factor than ER content in this study population.[19] The hypothesis has been that the amount of PR in the tumour reflects a functioning ER pathway activated by oestrogens, thereby predicting the effect of endocrine treatment. Recent studies show that ER+/PR– tumours are less sensitive to endocrine therapy.[29] We observed no benefit of tamoxifen with high expression of 17HSD1. Tamoxifen is a competitive inhibitor and at higher levels of oestradiol higher, dosage of tamoxifen might be required for full inhibition. We found no association between 17HSD2 expression and prognosis or response to tamoxifen. As 17HSD2 in normal breast cells varies during the menstrual cycle and we do not know on which day in the cycle the patients was operated on, it is difficult to draw any conclusions about the prognostic significance of the enzyme.[28] In postmenopausal women the level of progesterone is low and does not vary over time so the influence on 17HSD2 expression is different from that in premenopausal women.

The 17HSD1 enzyme could be a target for inhibition because of its selectivity and tissue-specific expression both in pre- and postmenopausal women. There are substances, like inhibitors of sulphatase as well as of 17HSD1, under development but not yet in clinical use[30].

In conclusion, this is the first report on 17HSDs in premenopausal women with receptor positive breast cancer allocated to 2 years of adjuvant tamoxifen or no adjuvant medical treatment in a randomised controlled trial, with a long follow-up. We found a predictive value of 17HSD1 for the benefit from tamoxifen and this value was still significant if the tumour had a high content of PR. Our data suggest that 17HSD1 might be used as a predictive factor for tamoxifen response in hormone-receptor positive breast cancer in premenopausal women. In the future 17HSD1 may be a target for new hormonal treatments.

Conflict of interest statement

None declared.

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