RESEARCH ARTICLE

A shift from membranous and stromal syndecan-1 (CD138) expression to cytoplasmic CD138 expression is associated with poor prognosis in breast cancer

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Abstract
Syndecan-1 (CD138) is a transmembrane proteoglycan expressed in normal and malignant tissues. It is of interest because of a possible prognostic effect in tumors and as a target for Indatuximab, a monoclonal antibody coupled to a cytotoxic agent. To assess the prognostic role of CD138 expression in breast cancer (BCa), a tissue microarray containing 1535 BCa specimens was analyzed by immunohistochemistry. Cytoplasmic, membranous, and stromal CD138 staining was separately analyzed. In normal breast tissue, CD138 staining was limited to epithelial cell membranes. In cancers, membranous staining tended to become weaker or even disappeared (38.3% of cancers with absence of membranous staining) but cytoplasmic and stromal staining newly appeared in 29.7% and 58.1% of cancers. Loss of membranous epithelial CD138 staining as well as presence of cytoplasmic and stromal CD138 positivity were—to a variable degree—associated with high pT, high grade, nodal metastasis, estrogen receptor-negative, progesterone receptor-negative, human epidermal growth factor receptor 2+, and poor overall patient survival. A combined analysis of epithelial and stromal CD138 expression revealed a link to overall patient survival (P < .0001) with best prognosis for patients with stromal positivity and absence of cytoplasmic staining, the worst prognosis for cancers with cytoplasmic staining and stromal negativity and intermediate prognosis for patients having either cytoplasmic staining or stromal negativity. In multivariate analyses, CD138 was not independent of established prognostic features. In summary, these data reveal a compartment depending prognostic...
INTRODUCTION

Breast cancer (BCa) is the most frequent malignant tumor in women. Standard of care consists of surgical removal of the tumor followed by adjuvant systemic therapy in high-risk cases. Currently used prognostic features for assessing a cancers aggressiveness mainly include tumor size, histological grade, lymph node metastasis, as well as immunohistochemical assessment of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and tumor cell proliferation (Ki67 labeling index). As these parameters are statistically powerful but not sufficient to safely predict cancer properties in every patient, additional molecular parameters are analyzed in an increasing number of cases. Molecular classifiers that are commercially available are based on the analysis of RNAs of 21 to 70 genes. It is a major disadvantage of these tests that isolated RNAs from cancer tissues always include a variable quantity of noncancer cells.

Syndecan-1 (CD138) is the first member of the four-member syndecan family encoded by the SDC1 gene. It is built out of three structural domains from which one is an extracellular domain capable to bind heparin sulfates and chondroitin sulfates. As a cell surface protein, it plays a central role in cell-cell and cell-matrix interactions, functions as a coreceptor for chemokines and growth factors and is involved in cell proliferation, migration, and the organization of the cytoskeleton. In normal tissues, CD138 is expressed on epithelial cells of various tissues and on plasma cells. Altered CD138 expression has previously been described in various malignant tumors. Overexpression of CD138 has been found in breast, gallbladder, urinary bladder, pancreatic, ovarian, endometrial, and prostate cancer. Reduced CD138 expression as compared to normal tissues has been reported for lung, head/neck, gastric, renal, and colorectal cancer. In several of these tumor types either reduced or increased CD138 expression was linked to unfavorable tumor phenotype and poor patient prognosis.

Thirteen different studies have analyzed the impact of CD138 expression on BCa prognosis analyzing 37 to 254 cancers by immunohistochemistry and described complex staining patterns including membranous, cytoplasmic, and stromal staining. The conclusions from these studies were highly controversial, however, the authors described both increased and decreased CD138 expression in BCa as compared to normal breast epithelium and reported associations of high CD138 expression with possibly favorable and unfavorable prognosis.

To learn more on the prognostic role of CD138 expression in BCa and the potential impact of different staining patterns, a tissue microarray (TMA) was analyzed containing more than 1500 tumors with clinical follow-up data.

MATERIALS AND METHODS

Patients

A TMA containing 1545 human BCa samples from paraffin-embedded tissue specimens fixed in 4% neutral buffered formalin was used. Consecutive BCa samples had been collected from patients that were operated between 2007 and 2012 at the Niels Stensen Clinic of Osnabrück and whose tumor samples had been analyzed at the Institute of Pathology at the Clinical Center Osnabrück. The median patient’s age was 62 (range: 24-98) years. Raw survival data were available from 877 patients (177 patients with and 700 without event). The mean follow-up time was 47 months (range: 0-88 months). The patient cohort is described in detail in Table 1. The TMA manufacturing process was described earlier in detail. In short, from each patient one 0.6 mm core was taken from a representative cancer tissue block. All tissues were distributed among four TMA blocks, each containing between 414 and 522 samples. Four-micrometer sections of the TMA blocks were transferred to an adhesive coated slide system (Instrumedics Inc, Hackensack, NJ) for immunohistochemistry analysis. Molecular data used in this study were available for HER2, ER, and PR immunohistochemistry. The use of archived diagnostic leftover tissues for manufacturing of TMAs and their analysis for research purposes as well as patient data analysis has been approved by the local ethics.

### TABLE 1 Patient cohort used in our study (n = 1545)

<table>
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<th>Subtype (no.)</th>
<th>Ductal carcinoma of NST (1265), lobular (171), mucinous (36), medullar (11), basal cell (8), tubular (9), papillary (4).</th>
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</tr>
<tr>
<td>Grading (no.)</td>
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<td>Age (y)</td>
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<tr>
<td>Event (no.)</td>
<td>Event/no event/no data:177/700/668</td>
</tr>
<tr>
<td>Follow-up time (mo)</td>
<td>Range: 0-88; median: 47</td>
</tr>
</tbody>
</table>

Abbreviation: NST, nonspecial type.
committee (Ethics commission Hamburg, WF-049/09). All work has been carried out in compliance with the Helsinki Declaration.

2.2 | Immunohistochemistry

Freshly cut TMA sections were stained in one experiment at 1 day. Slides were deparaffinized and exposed to heat-induced antigen retrieval for 5 minutes in an autoclave at 121°C in pH 9 Dako Target Retrieval Solution Buffer. A primary antibody specific for total syndecan-1 (1:200; mouse monoclonal antibody, clone JASY1; Dianova, Hamburg, Germany) was applied at 37°C for 60 minutes. Bound antibody was then visualized using the EnVision Kit (Dako, Glostrup, Denmark) according to the manufacturer’s directions. High-resolution images were taken from each tumor spot and presented to a pathologist (SK) together with an image of corresponding hematoxylin and eosin (H&E) stained spot obtained from a consecutive TMA section. This was to facilitate the distinction of cancer cells from noncancerous tissue on the CD138 stained spots. The need for differential scoring based on the location of Syndecan expression in immunohistochemistry was described by Choi et al.21 For tumor tissues, the percentage of positive cells and the staining intensity were separately evaluated for membranous and cytoplasmic staining. The staining intensity was quantitated as 0 (negative), 1+ (weak), 2+ (moderate), and 3+ (strong). For both cytoplasmic and membranous staining, these results were then further categorized into four groups for statistical analyses (Table S1). Tumors without any staining were considered as negative. Tumors with 1+ staining intensity in ≤70% of cells and 2+ intensity in ≤30% of cells were considered weakly positive. Tumors with 1+ staining intensity in >70% of cells, 2+ intensity in 31% to 70%, or 3+ intensity in ≤30% were considered moderately positive. Tumors with 2+ intensity in >70% or 3+ intensity in >30% of cells were considered strongly positive. The analysis of the stroma staining included a pattern analysis (diffuse/peritumoral) and an estimate of the percentage of stromal staining by relating the positive stroma area to the whole tissue area. For classification of diffuse/peritumoral staining into negative, weak, moderate and strong, the same procedure was used as described for epithelial staining.

2.3 | Statistics

JMP 12.0 software (SAS Institute Inc, NC) was used. Contingency tables were calculated to study associations between different parameters of CD138 expression and clinicopathological variables, and the $\chi^2$ (likelihood) test was used to find significant relationships. Kaplan-Meier curves were used for survival analyses. The log-rank test was applied to test for significant differences between stratified survival functions. To test the statistical independence and significance between pathological and molecular variables, Cox proportional hazards regression analysis was performed.
3 | RESULTS

3.1 | Technical issues

A total of 1310 of 1545 tumor samples (84.8%) were interpretable in our TMA analysis. Missing tissue samples and the absence of unequivocal cancer tissue in TMA spots were the causes for noninformative cases (15.2%).

3.2 | CD138 in epithelial cells

Representative images of normal breast staining and cancers with purely cytoplasmic and membranous staining are shown in Figure 1. In normal breast tissue, a moderate to strong strictly membranous immunostaining was seen for CD138 in excretory duct cells and in myoepithelial cells, stroma was completely negative. In cancers, membranous staining was recorded in 61.7% of interpretable cases, including 23.9% with a weak, 11.3% with a moderate, and 26.5% with a strong staining (Table S2). A cytoplasmic staining of cancer cells was seen in 29.7% of cases, including 21.4% with a weak, 5.7% with a moderate, and 2.6% with a strong staining (Table S2). For the tumor cell membrane, reduced CD138 staining tended to be associated with unfavorable tumor features, but this was statistically not always significant (Figure 2A). Presence of cytoplasmic staining was, however, significantly linked to all evaluated unfavorable tumor features (Table S2, \( P \leq .0032 \)) and also to reduced overall survival (Figure 2B, \( P = .0038 \)). A combinatorial approach defining four groups according to the presence or absence of membranous and cytoplasmic staining showed that only tumors with purely cytoplasmic (without concomitant membranous) staining—behaved particularly poor (Figure 2C, \( P = .0037 \)). Accordingly, the best prognostic distinction was seen if tumors were divided into tumors with pure "cytoplasmic staining" (membrane negative and cytoplasma positive) vs all "others" (membrane positive/cytoplasma positive; Figure 2D, \( P = .0021 \)).

3.3 | CD138 in tumor stroma

Normal breast tissue completely lacked stromal CD138 staining. Stromal staining was present in 58.1% of cancers (Table S3). Its intensity was unrelated to clinicopathological or outcome data (data...}

FIGURE 2 Patient survival in relation to membranous (A), and cytoplasmic (B) CD138 staining of their breast cancer (BCa), the combination of both parameters (C), and the latter regrouped in cytoplasmic only (cytoplasmic positive and membranous negative) BCa and membranous or negative BCa (D) [Color figure can be viewed at wileyonlinelibrary.com]
not shown) and was thus disregarded. Two distinct staining patterns were seen (Figure 3). In the peritumoral pattern, a distinct frame of high-intensity stromal staining of acellular material was surrounding cancer cells (Figure 3A). In the diffuse staining pattern, CD138 staining was not topically related to cancer cells and potentially involved stromal cells such as fibroblasts or myofibroblasts in desmoplastic tumor stroma (Figure 3B). Combinations of peritumoral and diffuse patterns did also occur (Figure 3C). Both peritumoral and diffuse stromal staining were significantly linked to all analyzed favorable tumor features except HER2 status (Table S3) and were also associated with favorable patient outcome (Figure 4A and 4B, \( P \leq .0011 \) each). A combined analysis of the parameters “diffuse” and “peritumoral” stromal staining showed that tumors with complete absence of stromal CD138 staining had a particularly poor prognosis, while the remaining three groups did not markedly differ in their clinical outcome (Figure 4C, \( P = .0004 \)). Accordingly, we classified the stromal staining of our cancers as “environment negative” (peritumoral neg. & stroma neg.) and “environment positive” (peritumoral positive/stroma positive), which resulted in the best statistical distinction of prognostic groups (Figure 4D, \( P < .0001 \)).

### 3.4 Combined epithelial and stromal CD138 analysis

On the basis of the results of the epithelial and stromal analysis we categorized cancers in four patterns A-D defined by presence or absence of cytoplasmic and stromal CD138 staining. Definitions of these patterns are detailed in Figure 5A. The patterns were significantly linked to all analyzed molecular and clinicopathological tumor features (\( P < .001 \) each, Table 2) and patient outcome (Figure 5B). Patient prognosis was worst in cancers with purely cytoplasmic CD138 positivity in the absence of stromal staining (pattern D) and best in patients with stromal staining but absence of cytoplasmic cancer cell positivity (pattern A, \( P < .0001 \)).

### 3.5 CD138 and histological tumor subtypes

The relationship between CD138 and histologic tumor subtypes is given in Table 2. Cancers of no special type (NST) and lobular carcinomas—the two largest histopathologically defined subgroups—differed significantly in their stroma staining, which was particularly
common in NST tumor. NST tumors constitute the biggest part of breast tumors and were previously defined in the WHO nomenclature as “invasive ductal carcinoma not otherwise specified (NOS).” If there is no sufficient evidence that this subtype arises from ductal tissue, the WHO renounces the term “ductal” in their classification. A separate analysis of NST tumors showed a significant prognostic impact of cytoplasmic (Figure S1, \( P = .0413 \)), environment (Figure S1, \( P = 0.0006 \)), and combined cytoplasmic/environment immunostaining (Figure S1, \( P = .0027 \)). This was also retained if nodal positive cancers were separately analyzed (Figure S1, \( P = .0376 \)). Significant associations between CD138 expression and tumor phenotype were also seen in the subgroup of NST cancers (Table S4).

### 3.6 Multivariate analysis

Separate multivariate analyses were performed to test the independent prognostic impact of cytoplasmic CD138 staining (model 1), stromal CD138 staining (model 2), and the CD138 pattern (model 3). For this purpose, CD138 data were compared with the classical histopathological prognosticators pT, pN, grade as well as the ER and PR status. In all three models, the pathological stage was the only histopathological parameter that predicted patient prognosis independently from the other parameters (\( P < .0001 \) each). Neither cytoplasmic CD138 (\( P = .3010 \)), nor CD138 in the tumor environment (\( P = .3081 \)) or the CD138 pattern (\( P = .5417 \)) provided prognostic information independently from the tumor stage. All data are summarized in Table 3.

### 4 DISCUSSION

The results of this study demonstrate a pattern dependent prognostic role of CD138 immunostaining in BCa.

In our BCa samples, CD138 immunostaining often showed complex features rendering interpretation difficult. A particularly thorough approach was thus selected to analyze our TMA staining including a parallel analysis of H&E stained and CD138 immunostained images from all TMA spots. This was instrumental to reliably distinguish CD138 stained invasive cancer cells from stromal cells. The analysis of 1310 CD138 immunostained TMA spots enabled us
to define four distinct recurrently occurring CD138 staining patterns including cytoplasmic, membranous, peritumoral and diffuse stromal staining. The comparison with tumor phenotype and patient prognosis revealed that the localization of staining (patterns A-D)—and not the staining intensity—was decisive for the prognostic impact of CD138 staining. The reciprocal prognostic effect of membranous staining (associated with good prognosis) and cytoplasmic staining (associated with poor prognosis) consistent with the perceived membrane-bound function of CD138. Both the loss of physiological membranous CD138 and the cytoplasmic accumulation of CD138 reflect aberrant conditions that can develop during cellular dedifferentiation. Loss of membranous syndecan-1 expression had been shown to induce reduced cell adhesion, increased invasive potential, and dysregulated growth of mammary epithelial cells in vitro.28 The observed peritumoral and stromal CD138 staining could be a consequence of enzymatic cleavage of membrane-bound CD138, which is then shed as soluble SDC1 (sSDC1) into the tumor environment.12

Our data identified a striking patient protective effect of stromal CD138 staining in BCas. Stroma staining exhibited two distinct patterns. The peritumoral pattern displayed a dense acellular rim-like CD138 positive zone demarcating the cancer cells from the stroma. The diffuse pattern was defined by staining of spindle-shaped cellular elements, morphologically reminiscent of fibroblasts or myofibroblasts. We cannot exclude, however, that another more specific cell type was detected by CD138 in these cases. Sharpe et al29 recently described a new CD138 positive cell type in the stroma of high-grade prostate cancers. These cells were excluded to represent typical stromal, epithelial or immune cell types by multicolor immunofluorescence.29 The same peritumoral and diffuse patterns of CD138 stroma staining as described in this study had earlier been reported by Stanley et al.28 Either alone or in combination, these stroma patterns occurred in 58.1% of our cancers. This frequency is comparable to the findings of most of the earlier studies, which had described stromal staining in smaller cohorts in the range of 9% to 63%17,19,20,22,23,30-32 (Table S4). Seven of these eight studies had
failed to show a prognostic role of stromal CD138 and one study on 80 patients found a significantly worse prognosis in patients with stromal CD138 staining than in those tumors without. We assume that the discrepancy between our data and previous studies are preferentially caused by the relatively small number of cases included in most of these studies. The reason for the protective effect of stromal CD138 is not clear. Possible explanations include growth inhibitory or yet unrecognized immune-stimulatory effects of CD138. For example, an inhibitory effect of sSDC1 on cell proliferation had been reported from wound healing experiments in mice and from human MCF-7 BCa cells. CD138 plays a role in plasma cell differentiation and represents a central component of the plasma cell membrane. CD138 is also frequently upregulated in HIV associated B-cell neoplasms, where CD138 increases B-lymphoid cell extravasation in response to HIV-1 Tat, the main HIV-transactivating factor. The absence of stromal CD138 expression in normal breast tissues is compatible with earlier reports on stroma-to-carcinoma signaling pathways involving proteoglycans such as CD138 that are specifically activated only during cancer development.

A total of 13 studies had earlier analyzed the prognostic role of CD138 in BCa in cohorts of 30 to 254 tumors (Table S5). None of these studies had comprehensively analyzed membranous, cytoplasmic, and stromal CD138 staining. We do, however, not assume that different analysis criteria represent the pivotal cause for the considerable discrepancies between these studies and as compared to our data. Multiple authors have analyzed comparable parameters as in our study. Seven studies had failed to find a prognostic impact of CD138 stroma staining, and. Two studies had specifically analyzed cytoplasmic CD138 staining and found either no association with patient outcome or an association between high expression and poor outcome, the same of what we found. Most likely explanations for discrepant results include the relatively low numbers of tumors included in several studies as well as differences in the antibody properties and applied protocols for immunohistochemical staining. Five different antibodies have been employed in 13 earlier studies on CD138 in BCa. The current discussion on the use of different antibodies for PD-L1 testing underscores the potential variability of antibodies.
TABLE 3  Cox proportional hazard ratios for raw survival of established prognostic markers and cytoplasmic CD138 (model 1), environmental CD138 (model 2) and the CD138 staining pattern (model 3)

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Abbreviations: CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor.

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Conflict of Interests

The authors declare that there are no conflict of interests.

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References


**SUPPORTING INFORMATION**
Additional supporting information may be found online in the Supporting Information section.

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