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POSTER

Syndecan-1 (CD138) expression in human breast carcinoma is associated with an aggressive phenotype and appears related to a poor prognosis and low response to adjuvant chemotherapy

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Background: Syndecan-1 is a cell-surface transmembrane heparan-sulfate proteoglycan (HSPG) which appears to play an important role in cell to cell adhesion, cell motility, invasiveness, proliferation and matrix interactions.

Material and methods: Syndecan-1 expression was investigated, by immunohistochemistry (IHC) using the B-B4 antibody, in a retrospective study on 254 consecutive infiltrating breast carcinomas (BC) (110 NO, 144 N1, 207 infiltrating ductal carcinomas, 47 special types; 46 G1, 64 G2, 133 G3, Gx 11). Among these patients, 78 were <50 years, 63 were aged 51-59 and the remaining were 60 or more years old. 80 pts were treated with adjuvant chemotherapy and 92 with hormonal therapy. Median follow-up was 86 months for disease free survival (DFS) and 95m for overall survival (OS).

Results: High Syndecan-1 immunoreactivity (>10% + cells) was seen in 42% of BC, and was associated with larger tumor size, higher grade and mitotic count, and negative ER status. High Syndecan-1 expression was related to poor DFS and OS in the whole series. Multivariate analysis in the whole series of cases unadjusted for grade showed that syndecan-1 expression was significantly and independently associated with a 1.7 fold mortality. In different age subgroups, the multivariate analysis was adjusted for grade, estrogen receptor status and lymphnodes involvement, showing that CD138 has a strong prognostic value for women aged 50-59 ($p=0.0049$, Risk Ratio 5.207), moderate for women <50 ($p=0.1569$, RR 1.850) and null for women aged 60 or more. Among patients who received adjuvant chemotherapy, a restricted model (without ER which was not significant) showed that Syndecan-1 was significantly associated with poorer OS ($p=0.0345$, risk ratio 2.153) along with nodal status ($p=0.0569$, risk ratio 6.941) and grade ($p=0.0395$, risk ratio 2.040).

Conclusions: Syndecan-1 is frequently overexpressed in breast carcinomas and is associated with tumor aggressiveness. It appears from our clinical data that Syndecan-1 may play an important role in human breast cancer, leading to a poor prognosis and lower response to adjuvant chemotherapy at least in some subgroups of patients.

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Risk factors for breast cancer in women residing in an urban area in the Northeast of Italy. Multivariate analysis using a logistic regression model

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Introduction: Breast cancer (BC) is the most common malignancy among women in Western society, and its prevalence varies widely in different countries. Several risk factors (RF) have been reported, but none was able to give reliable epidemiological information on clinical outcome for each patient population. The aim of this study was to provide information about the relationship between BC and different RF to be considered at the time of diagnosis in women residing in the Northeast of Italy.

Patients and Methods: The study included 404 BC cases (median age 60 years, range 26-89) and 1,480 population-based age-matched controls. All patients lived in the same urban area and spontaneously underwent clinical breast examination; those with other or previous cancer were excluded. The following parameters were considered: age, family history of BC, menstrual and reproductive factors age at menarche, menstrual pattern, number of births and abortions, age at first birth) lactation, use of oral contraceptives and hormonal replacement therapy, smoking, alcohol consumption, occupational and sedentary activity, body mass index.

Results: Univariate analysis showed significant differences ($p<0.01$, Student's t-test and chi-squared test) between cases and controls in: (1) age at menarche (12.3 ± 1.6 vs 12.7 ± 1.5 years) and menopause (49.5 ± 4.1 vs 47.3 ± 5.3 years), (2) number of births (1.4 ± 1.1 vs 1.8 ± 1.3) and age of first birth (25.3 ± 4.4 vs 24.4 ± 3.6 years), (4) estrogen replacement therapy (43.9 ± 30.3 vs 33.7 ± 28.1 months), (5) smoking (5.94% vs 12.53%), and

(6) alcohol abuse (5.69% vs 2.32%). Multivariate analysis using a logistic regression model showed that only four independent parameters correlated with BC: age at menarche (years), number of births, lactation, and estrogen replacement therapy. The Odds ratio (OR) for BC calculated from the observed vs predicted values obtained using the logistic regression function was 5.05 (95% CI 3.6-7.1), while the OR of single variables was < 3 (95% CI 1.51-4.32).

Conclusions: The results confirm that some recognized RF, such as age of menarche and the prolonged (>3 years) use of estrogen replacement therapy, are strong determinants of BC. However, in this study, many classical parameters did not result useful as RF, suggesting that to correctly select the high risk population both different primary RF and other environmental and external factors should be considered for each population.

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A comparison of young and old women with early stage breast cancer

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Purpose: There is controversy regarding the effect of age on breast cancer. Stages I and II breast cancer are associated with a better outcome. The aim of this study was to assess the influence of young age on outcome in women with early stage breast cancer

Methods: One hundred eight patients with breast cancer less than 2 cm submitted to surgery between March 1985 and November 1992 were divided into two age groups: a) patients with 35 years or less b) patients with more than 35 years old integrated in a breast cancer surgical protocol. The total was 108 patients being 46 young women and 62 with more than 35 years; the median age was 32 for the first group and 54 for the second. The comparability of the groups was assessed in terms of clinical factors, histological factors and treatment related factors. Outcome was evaluated for overall and disease free survival.

Results: All the 108 patients were stage I or IIa. The median follow-up was 90 months with a range of 8 to 171 months. Younger women were significantly more likely to have estrogen receptor negative tumors (37,5% versus 7,5%, $p=0,003$) and more nodal involvement (50% versus 27,4%, $p=0,01$).

95,7% of the young women had breast lumps as presentation. Patients less than 35 years were treated more often with mastectomy (65,2% versus 48,4%, $p=0,08$) and adjuvant chemotherapy (37% versus 11,3%, $p=0,02$)

For axillary node-negative women, young age was associated with a statistically significant increased recurrences (34,8% versus 11,1%, $p=0,01$).

There were no statistically significant differences among the two groups for overall survival; therefore there was a significant difference for disease free survival (DFS). DFS at 5 and 10 years for young women was 61% and 53% and for old women was 79% and 78% ($p=0,008$).

Conclusion: The present analysis demonstrates that young women with early stage breast cancer do significantly worse when compared to older women in terms of recurrences and disease free survival. Despite aggressive treatment, most commonly with mastectomy and chemotherapy, local and distant failure rates are higher in women with 35 years or less.

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Evaluation of Microtubule Associated Parameters (MTAPs) as predictive markers for Advanced Breast Cancer (ABC) patients treated with docetaxel

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Introduction: We analyzed the possible predictive value of MTAPs regarding response to docetaxel.

Methods: A retrospective study was performed in 54 ABC women treated with docetaxel. Among the 41 eligible pts (evaluable response and available pre-treatment paraffin-embedded tumor tissue) mean age was 52 yrs (31-75), site of metastasis: visceral 76%, soft tissue 70%, bone 32%. The majority of pts received at least 1 prior line of treatment for ABC. Samples of primary and/or metastatic tumor were evaluated by immunohistochemistry for the following MTAPs: α - and β -tubulin, class II, III and IV β -tubulin isotypes, and tau protein. The clinical response was correlated with the MTAPs' status.

Results: PR 54%, NC 29% and PD 17%. α - and β -tubulin and class IV β -tubulin isotype were strongly expressed in the majority of samples and therefore no correlation with docetaxel activity was possible. Only 4 pts had tau negative tumors and 2/4 had no objective response. An inverse correlation was found between class II expression and docetaxel activity. Outcome was similar in the two groups of Class III expression.

MTAP	N	PR	NCIPD
Tau			
-	4	2	2
+	32	19	13
NE	5	1	4
Class II			
<50%*	15	11	4
>50%*	18	7	11
NE	8	4	4
Class III			
<50%*	11	7	4
>50%*	20	11	9
NE	10	4	6

Legend: % positive cells, NE: non evaluable

Conclusion: The limited number of analyzed pts softens the strength of our conclusions, however, according to these preliminary data, the evaluation of tau protein and class II β -tubulin deserves further investigation as potential predictive markers for docetaxel activity.

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Prognostic factors of breast cancer patients with 1 to 3 lymph node metastases after adjuvant chemotherapy

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Purpose: To analyze prognostic factors of patients with breast cancer who had 1 to 3 axillary lymph nodes metastases after adjuvant chemotherapy.

Methods: From 1990 to 1998, a total of 572 breast cancer patients with 1 to 3 axillary lymph nodes metastases were studied. Among them, 443 received adjuvant chemotherapy with CMF (cyclophosphamide, methotrexate, fluorouracil), 23 patients received CAF (A: adriamycin), 53 patients received CEF (E: epirubicin), and 53 patients refused any adjuvant therapy. The median follow-up period was 37.5 months. Prognostic factors including tumor size, status of steroid receptors, administration of tamoxifen, tumor ploidy, S-phase fraction, SBR grading, age (less than 40 vs older), and angiolymphatic permeation were analyzed by Cox regression methods for overall survival (OS) and disease free survival (DFS).

Results: The median age was 47 years. The estimated 5-year OS and DFS was 85.6% and 77.4%, respectively. The local recurrent rate was 6.3%, and distant metastases rate was 16.5% to date. Patients did not received adjuvant chemotherapy survived significantly worse than those who received adjuvant chemotherapy. Univariate analysis revealed tumor size (<3 vs >3 cm), estrogen receptor, progesterone receptor, and age (less than 40 vs older) were significant prognostic factors for OS. While multivariate analysis revealed tumor size, age and estrogen receptor were three independent prognostic factors of OS. Tumor size, age, estrogen receptor and more than one positive node are the independent factors of DFS. The 5-year survivals for age less than 40 years and older years were 82 and 89.7%, respectively. (p value: 0.0025) While 5-year survivals for positive estrogen and negative estrogen were 91.7 and 85.4% respectively. (p value: 0.0042) The 5-year survival for tumor <3 and >3 were 89.6 and 80.4%, respectively. (p value: 0.048)

Conclusion: The study showed that the predictive factor of worse OS in patients with 1 to 3 positive axillary nodes were age less than 40 years, tumor size larger than 3 cm and negative estrogen receptor.

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Ductal carcinoma in situ, pure infiltrating and combined DCIS-infiltrating breast cancers: comparison in a series of 2071 patients

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Purpose: There is much debate as to whether an infiltrating breast tumor (BC) is always the last step in the evolution of a tumor that starts 'in situ' and then acquires greater malignancy until it becomes infiltrating. We

therefore compared the characteristics of pure ductal carcinoma in situ (IS), pure infiltrating ductal (IN) and combined (DCIS and infiltrating- CO) breast tumors in a series of 2071 patients (PTS) with BC (176 IS, 1241 IN and 654 CO) who underwent surgery in Verona hospitals.

Methods: We recorded the age of every PTS at diagnosis, menopausal status, modality of diagnosis (symptomatic or clinically silent BC), familial history (no, first, or second degree), diameter (mm), axillary nodal status (0, 1-3, >3 positive nodes), G (1, 2, 3), ER and PgR (<10%, 11-100% of positive/total cells), Ki-67 (<10%, 11-25%, >25% of positive/total cells), and c-erb B2 expression (- or +). The association between the variables was studied using the chi-square-test.

Results: The frequency of IS decreased and that of IN and CO tumors increased with increasing age (p<0.01); as expected, we had 60% of the IS, 27% of the IN and 38% of the CO patients who were asymptomatic (p<0.01). We also found 45%, 32% and 22% of IS, 16.5%, 45.5% and 38% of IN, and 24%, 45% and 30% of CO tumors with diameters of respectively <10 mm, 10-20 mm and >20 mm (p<0.01); but no differences were found in the distribution of ER (p=0.418) and PgR (p=0.264); 6.5% of the IS, 20.1% of the IN and 18.2% of the CO tumours had high Ki-67 values (p<0.01); G3 was found in 54% of the IS, 30% of the IN, and 31% of the CO tumors (p<0.01).

We also repeated all of the correlations after a diameter-adjusted analysis: statistically significant results were obtained considering Ki-67, G and ER in IN and CO but not in IS.

c-erb B2 was interestingly distributed, being positive in 69% of IS, 40% of IN and 50% of CO (p<0.01); the associations were: IS vs IN vs CO, p=0.000079; IS vs IN, p=0.000117; IS vs CO, p=0.013579; IN vs CO, p=0.010498

Conclusion: In our study DCIS is more often diagnosed in younger and asymptomatic PTS, is smaller, and has lower Ki-67 values: it may therefore appear as a tumor in an initial phase that can evolve to IN with greater malignancy. We also found that many DCIS have a higher G and higher percentage of c-erb B2 positivity than CO and IN, which suggests that not all infiltrating cancers (i.e. low-grade and/or c-erb B2 negative tumors) derive from an in situ counterpart.

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Prognosis after breast conservative treatment in a T1 tumour group patients

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Purpose: To evaluate risk factors related to local recurrence after breast conservative treatment and the association with subsequent distant metastases.

Patients and Methods: Between 1983 and 1999, 452 patients (pts) with T1, N0-1 breast cancer, underwent conservative surgery and adjuvant radiotherapy. Pts were irradiated to the ipsilateral breast to a dose of 46 Gy and a boost was delivered to a total dose of 14-20Gy. Pts with positive nodes were submitted to adjuvant systemic therapy, and postmenopausal pts received hormone therapy. There were 17 patients with \leq 5mm tumors (Group 1); 112 pts with >5- \approx 10 mm tumors (Group 2); 323 pts with >10- \approx 20mm tumors (Group 3). Local recurrence (LR) risk factors were studied: age, histological multifocality, surgical margins, histologic grade, nodal status, tumor size. The end points considered were LR and distant metastases (DM).

Results: With a median follow-up time of 53 months (range:12-214), 15 patients developed a LR, as first event, and the median interval to-LR was 38 months (range: 8-133). Five of these pts developed a subsequent DM with a median interval between both events of 14 months (range: 4-30). Twenty five patients developed DM, as first event, and the median interval to DM was 32 months (range 7-124). Median time to-LR was shorter in pts who developed DM, 15 months (range 11-43). The 10 years probability of survival for the whole group of pts was 80.2% (95%CI: 72.3-86.1%). The 10 years probability of LR and DM for Group 1 was 0% and 10% (1.5-52.7%) respectively; for Group 2 was 3.2% (1.0-9.6%) and 6.6% (3.0-4.4%), and for Group 3 was 6.5% (3.3-12.3%) and 10% (6.6-15.0%). The 5 and 10 years probability of survival after isolated LR was 72.0% (41.1-88.6%) and 54% (17-80%), and the relative risk of DM after LR was 4.7 (95% CI: 1.8-12.1), p=0.002.

Conclusion: LR after breast conservative treatment (BCT) is associated with DM and poor prognosis. Pts with early LR after BCT, are at high risk.