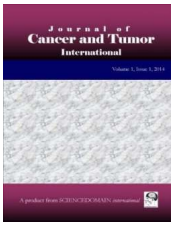

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Impact of ADAM17 Expression as a Potential Prognostic Biomarker and Target for Therapy in Node-negative Breast Carcinoma

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Authors' contributions

This work was carried out in collaboration between all authors. Authors RS, CL and OM designed the study and wrote the protocol. Authors RS, CC and SVN performed and managed the statistical analysis of the study. Authors RS and SVN wrote the first draft of the manuscript. Author RS managed the literature searches and performed the laboratory work. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To evaluate the expression and the possible prognostic impact of the tissue-based protein ADAM17 in node-negative breast cancer and investigate its association with clinical and pathological features to aid in differentiating indolent node-negative breast cancer from aggressive node-negative breast cancer.
Study Design: Cross sectional.
Place and Duration of Study: Department of Pathology and Molecular Immunology, Institute of

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Biomedical Sciences Abel Salazar (ICBAS), University of Porto, from December 2012 to June 2013.

Methodology: 50 cases of breast cancer patients (40 node-negative and 10 node-positive) with ages ranging from 24 - 89 and with tumor size ranging from 0.6 cm to 4.7 cm were used. The ADAM17 protein expression was confirmed by immunohistochemistry analysis, which was performed on formalin-fixed, paraffin-embedded, 3 micro meters thick tissue sections using the avidin-biotin-peroxidase complex method. In addition, the presence of HER2, Ki67, Progesterone and Estrogen receptors were also determined.

Results: Both node-negative and node-positive breast cancer showed ADAM17 expression with more expression in node-negative cases. The anti-ADAM17 antibodies showed immunostaining with 19 strong expression (38% - 19/50) and 31 weak expression (62% - 31/50) .In addition to ADAM17, other markers such as ER, PR, HER2 and Ki67 were also expressed. In analyzing the relationship between ADAM17 expression and clinicopathological parameters, the expression level did not present any statistical relationship with all the conventional prognostic factors with P value >0.05 except histological type with P value of .009 and .01.

Conclusion: Our study shows ADAM17 protein expression may be involved in human breast cancer initiation, progression and distant metastasis and its prognostic impact could be independent of conventional prognostic factors. In grouping high expression against low, we had 19 high risks and 31 low risks. Upon further confirmation, ADAM17 could be used to determine individuals who may need adjuvant chemotherapy and those who could be spared from the toxic effect of chemotherapy.

Keywords: ADAM17; node-negative; node-positive; carcinoma; adjuvant chemotherapy.

1. INTRODUCTION

Breast cancer is the most frequently diagnosed and the second most common cause of cancer related mortality in women worldwide. The disease accounts for 23% (1.38 million) of the total new cancer cases and 14% (458,400) of the total cancer deaths in 2008, with approximately 40,000 deaths occuring annually [1,2].

In the United States for instance, more than 230,000 new cases were diagnosed and about 40,000 deaths were recorded in 2014 [3]. The most common form of breast cancer is node-negative and in places where there is widespread of screening and awareness among women, its rate is more likely to fall within 65%–70%. Patients therefore have a good prognosis since the disease is at its earliest stage [4].

Currently, giving adjuvant chemotherapy to patients in addition to loco-regional therapy requires proper patient selection. Unlike node-positive which is associated with an overall mortality of 20%, clinicians/oncologist hesitates before indicating chemotherapy in node-negative patients due to the uncertainty in determining whether patients with node-negative disease will actually benefit from chemotherapy [5]. Prognostic and predictive factors that influence adjuvant chemotherapy in patients with early stage breast cancer include: histological type, nodal status, tumor size, tumor stage and tumor grade. Other factors include hormone receptor status, Ki-67 status, HER2 amplification and patient age [6]. However, by using these traditional histomorphologic and clinical factors alone, about 60-90% of node-negative patients may be candidate for adjuvant chemotherapy leading to overtreatment of patients [5-9]. Although patients can be cured by surgery alone, about 30% of them will relapse and thus need adjuvant chemotherapy [10,11]. It is therefore likely that detection of early additional markers is paramount to predict individual risk that may or may not benefit from adjuvant chemotherapy. This will avoid unnecessary exposure of women to the potential toxicity and side-effects of such treatment, and also to reduce the overall cost of breast cancer treatment and management. Nevertheless, several reports have indicated a benefit for adjuvant chemotherapy in patients with high-risk, node-negative breast cancer [12,13], with further confirmation by meta-analyses studies [14-16].

Tumor invasion and metastasis involving the interaction between tumor cells and extracellular matrix are carried out by certain proteinases including ADAMs. The ADAMs (A Disintegrin and Metalloproteases) family, are modular type I transmembrane proteins which belongs to the zinc protease superfamily. Although forty gene members have been identified so far, it is believed that about 21 is functional in humans [17]. They have been reported to support both

proteolytic activity and cell adhesion, making them candidates to mediate both the remodeling of the extracellular matrix (ECM) and the changes in cell adhesion that characterize certain pathological processes such as tumor development and tumor metastasis [18]. Furthermore, a number of selective ADAM inhibitors, especially against ADAM10 and ADAM17, have been shown to have anti-cancer effects which led to the proposal of these metalloproteases as putative targets of anti-tumor therapy [19-22] and they are the best characterized members of ADAMs family [23].

One of the first ADAMs shown to have diagnostic potential was ADAM12 in breast cancer. ADAM-12, an apoptosis-modulating gene accelerated the development of tumor by delaying tumor cell apoptosis [24,25]. There has been an enhanced level in the urine of breast cancer patients indicating a potentially important non-invasive biomarker in breast cancer [26].

ADAM17 is also named as tumor necrosis factor-alpha-converting enzyme, (TACE) and was first identified to cleave the prodomain of TNF-α [27, 28,29]. In addition to the signal peptide, it contains four functionally distinct extracellular domains followed by a transmembrane region and a cytoplasmic tail [30,31]. It is the most extensively studied ADAMs to have a role in malignancy due to its persistent cleavage abilities with respect to the large variety of substrates it is able to cut and has recently been identified in senescent cells [32,33]. Certain growth factors and receptors can be activated and inactivated respectively by ADAM17 by shedding their extracellular domain from the cell membrane. Besides, it can detach cells by cleaving cell adhesion molecules. As a primary sheddase for multiple EGFR pro-ligands, it can transform growth factor-alpha (TGF-a), heparin-binding epidermal growth factor (HB-EGF), and amphiregulin and all these ligands have been implicated in cancer development and progression [29,33,34,35,36]. Through EGFR/PI3K/ AKT pathway, ADAM17 has been reported to be overexpressed in tumors such as the breast cancer, ovarian cancer, colon cancer etc. [37]. In a study conducted by McGowan et al, the overexpression of ADAM- 17 in breast cancer cells increased invasion and proliferation [38]. In another study, it was shown that the human breast cancer cell lines, MCF-7 and MDA-MB453, strongly express ADAM17 [39].

There have been several reports on the expression and prognostic impact of ADAM17 in various cancers [40-43]. However, its expression and association specifically in node-negative breast cancer is limited. Hence, the aims of this study were to evaluate the expression and the possible prognostic impact of the tissue-based protein ADAM17 in node-negative breast cancer, and investigate its association with clinical and pathological features. This will help to differentiate those patients who may benefit from adjuvant chemotherapy and those who may be spared from the toxic effect due to their low risk of the disease recurrence.

2. MATERIALS AND METHODS

2.1 Patients and Tissue Sample

All samples were obtained with institutional board approval from St. Anthony Hospital, Porto, Portugal. In 2012, 50 Cases of cancer patients who have undergone modified radical/partial mastectomy with no prior treatment, with ages ranging from 24 - 89 were obtained from Saint Anthony General Hospital. Patients involved were pathologically confirmed of the following node-negative and node-positive breast cancer: invasive ductal carcinoma, in situ ductal carcinoma and invasive lobular carcinoma with histological grades 1 to 3. There were 40 node-negative cases and 10 node-positive cases with tumor size ranging from 0.6 cm to 4.7 cm. In addition to ADAM17, HER2, Ki67, Progesterone and Estrogen receptors expression were also determined. The ADAM17 protein expression in breast cancer tissue samples were confirmed by immunohistochemistry analysis, which was performed on formalin-fixed, paraffin-embedded, 3 micro meters thick tissue sections using the avidin-biotin-peroxidase complex method.

2.2 Immunohistochemistry Analysis

The procedure for immunohistochemical analysis was the Avidin-Biotin-Peroxidase Complex method. All specimens were fixed in 10% neutral formalin, paraffin-embedded and sliced (thickness, 3 μm). Tissue sections were deparaffinized with two changes of xylene for 5 min, followed by two washes in absolute ethanol, 95 and 70% ethanol for 3 min each. The sections were then incubated with corresponding antibodies at room temperature for 1 hour. Immunohistochemical staining (Hematoxylin and eosin staining) were then carried out. However, in our work we used water bath to increase the antigenicity by using 50 ml of 10% Dako target

retrieval solution. Also we used a dilution factor of 1:150 for ER, PR and HER2, 1:100 for Ki67 and 1:300 for ADAM17.

2.3 Evaluation of Immunostaining Scores

Following a Hematoxylin counterstaining, HER-2/neu was considered negative when scores of 0 and +1, and positive when scores of +2 and +3 were recorded. To be considered as +2, +3, the cellular membrane should be completely stained in more than 10% of the tumor cells. In the cases where a score 2 was found by IHC, it was further studied by FISH and classified as positive or negative according FISH results. Cells without staining, or with weak staining in part of the cell membrane and in less than 10% of the tumor cells were considered negative. In the case of ER and PR they were graded by considering 10% of tumor cells stained in the nucleus as negative and more than 10% of stained tumor cells as positive. With Ki67, scores were obtained by counting at least 100 cells (excluding mitotic cells) and taken the percentage of stained cells in the nucleus. The cells were counted at places where there was high proliferation of cells.

ADAM17 levels of expression were determined by using staining intensity. The staining intensity was evaluated using three-tier grading system (0- negative; 1-weak; and 2-strong). To delineate between low and high levels of ADAM17 expression, the tumors with strong ADAM17 expression were grouped against those with none to weak expression.

2.4 Statistical Analysis of Results

Statistical significance was calculated using contingency table with Fisher's exact test to assess the relationships between ADAM17 protein expression and different clinical parameters through IBM SPSS Statists 20.0 software. This is due to the smaller sample size and the fact that some of the cells had values less than five. Significance was accepted at $p<0.05$.

3. RESULTS

3.1 ADAM17 Expression in Node-negative and Positive Breast Cancer

The expression was predominantly expressed in the cytoplasm and less common at the cell membrane. Both node-negative and node-positive breast cancer showed ADAM17 expression with more expression in node-negative cases.(Table 1). The anti-ADAM17 antibodies showed immunostaining with 19 strong expression, 38% (19 out of 50), (Fig. 3) and 31 weak expression 62% (31 out of 50), (Fig. 4). There was also expression in cancerous cases compared to their adjacent non-cancerous tissues (Fig. 2), with very few of the cases giving no expression (Fig. 1).

In addition to ADAM17, other markers expressed were ER, PR, HER2 and Ki67. From the results obtained, we realised that some cases with high Ki67 expression and positive ER, PR and HER2 expression corresponded to weak ADAM17 expression and vice versa (Table 1). There was also 6 triple negative cases from our studies but two of these corresponded to high ADAM17 expression and four corresponded to low ADAM17 expression. We were also able to differentiate among grade 2 patients into low and high risk based on the level of ADAM17 expressed (Table 1).

3.2 Association of ADAM17 Protein Expression with Standard Prognostic Factors

The association between ADAM17 expression and standard prognostic factors of breast cancer was further analyzed. The results obtained showed there were no relationship between ADAM17 expression and age, tumor size, nodal status, grade, ER, HER, Ki67 expression with *P* value >0.05 except histological type with *P* value of 0.009 and 0.011 (Table 1).

4. DISCUSSION

In this study, our main focus was on the expression of ADAM17 in node-negative breast cancer and its ability to identify individuals who may be classified as high or low risk. We investigated its impact on other clinicopathological features of breast cancer and in that essence we engaged other prognostic markers such as ER, PR, HER2 and Ki67 expression.

ADM17 is the most extensively studied ADAMs known to have role in malignancy and it carries out its role by shedding a variety of important cell surface molecules, which includes cytokines, growth factors, and adhesion molecules [34]. For example, it has been shown that ADAM17-mediated EGFR ligand cleavage enhances the proliferation and survival of squamous cell carcinoma cells as well as lung cancer cells [44].

ADAM-17 was also overexpressed in pancreatic ductal adenocarcinoma (PDAC) and pancreatic cancer cell lines [45]. Brain tumor cell lines cultured under hypoxic conditions demonstrated an upregulation of ADAM-17 expression levels, and its activity correlated with increased tumor cell invasion [46].

A number of selective ADAM17 inhibitors have been reported, suggesting their role in targeted therapy in cancer [19-22,47,48]. Examples are D1 (A12), INCB3619, INCB7839, WAY-022 and GW280264X. In a study by Witters et al. [49], combining INCB7839 with lapatinib completely prevented growth of human breast cancer xenografts in mice. WAY-022, which is a selective inhibitor of ADAM-17, was found to decrease DNA replication and cell growth in colorectal cancer cells [50]. In preclinical models, INCB3619 synergized with paclitaxel inhibited the growth of breast cancer in a xenograft model [51]. In a recent study, D1 (A12) was found to significantly inhibit the release of TGFα, and to decrease downstream EGFR-dependent cell signalling. These lead to reduced proliferation in two-dimensional clonogenic assays, as well as growth in three-dimensional culture. It was also reported to reduce invasion of HCC1937 cells and decreased migration and enhancing cell death in HCC1143 cells [19].

Table 1. ADAM17 protein expression and standard prognostic factors

Age (years)	No. of cases	ADAM17 expression (n, %)		p-value
		Low expression	High expression	
≤ 50	22	14(63.63)	8 (36.37)	
> 50	28	17(60.71)	11 (39.29)	1.000
Tumor size (cm)				
≤ 2	30	19 (63.33)	11 (36.67)	
> 2	20	12 (60.00)	8 (40.00)	1.000
Nodal status				
Negative	40	24 (60.00)	16 (40.00)	
Positive	10	7 (70.00)	3 (30.00)	0.722
Histological Grade				
Grade 1	9	6(66.67)	3 (33.33)	
Grade 2	23	17 (73.91)	6 (26.09)	0.685
Grade 3	18	8 (44.44)	10 (55.56)	0.419
ER expression				
Negative	6	3 (50.00)	3 (50.00)	
Positive	44	28 (63.64)	16 (36.36)	0.661
PR expression				
Negative	9	6 (66.67)	3 (33.33)	
Positive	41	25 (60.98)	16 (39.02)	1.000
HER2 expression				
Negative (0)	45	28 (62.22)	17 (37.78)	
Negative (+1)	3	2 (66.67)	1 (33.33)	1.000
Positive (+2)	2	1 (50.00)	1 (50.00)	1.000
Histological type				
IDC	32	14 (43.75)	18 (56.25)	
DCIS	7	7(100.00)	0 (0.00)	**0.009***
ILC	11	10 (90.91)	1 (09.09)	**0.011***
Ki67 expression (%)				
≤ 10	13	6 (53.85)	6 (46.15)	
> 10	37	24 (64.87)	13 (35.13)	0.497

*IDC*DCIS P = 0.009; IDC*ILC P = 0.011*

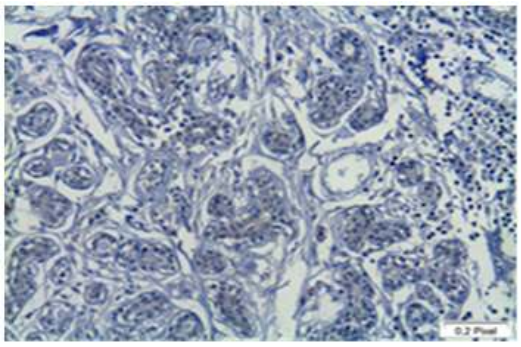

Fig. 1. Immunohistochemical staining of negative ADAM17 expression in node-negative breast tissue. (IHC-Mayer's Hematoxylin, 100x), where IHC stands for immunohistochemistry and Mayer's Hematoxylin is the counterstain.

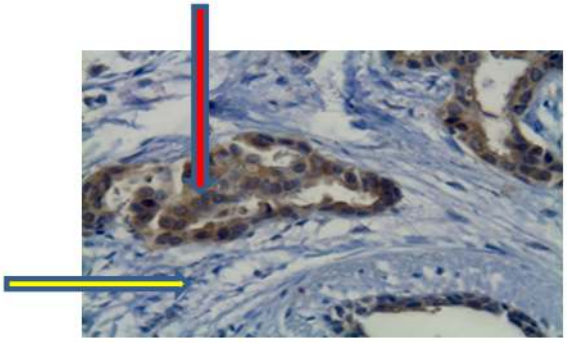

Fig. 2. Positive Immunohistochemical staining of ADAM17 expression of node negative breast cancer (red arrow) and its corresponding negative expression (yellow arrow) in non-cancerous breast tissue in node-negative invasive ductal carcinoma. (IHC-Mayer's Hematoxylin, 100x), where IHC stands for immunohistochemistry and Mayers's Hematoxylin is the counter stain

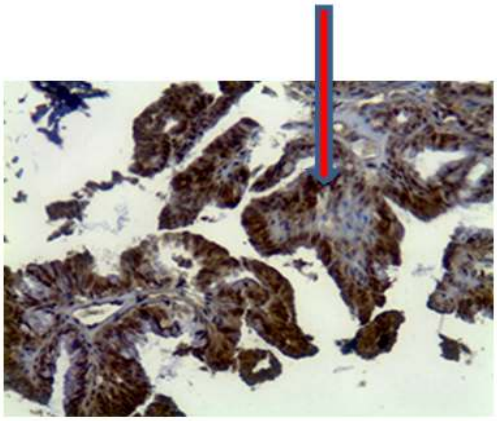

Fig. 3. Immunohistochemical staining of strong ADAM17 expression (red arrow) in node negative invasive ductal carcinoma. (IHC-Mayer's Hematoxylin, 100x), where IHC stands for immunohistochemistry and Mayer's Hematoxylin is the counterstain

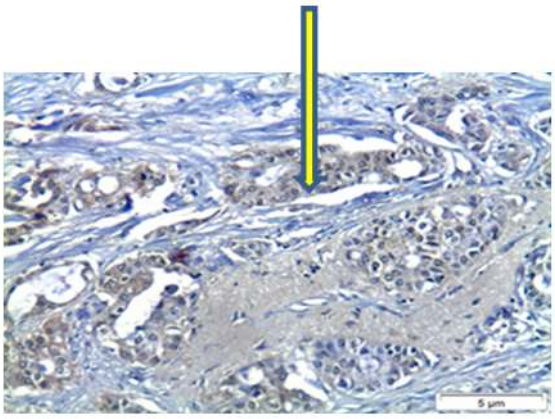

Fig. 4. Immunohistochemical staining of weak ADAM17 expression (yellow arrow) in node positive invasive ductal carcinoma. (IHC-Mayer's Hematoxylin,100x), where IHC stands for immunohistochemistry and Mayer's Hematoxylin is the counterstain

In our study, there was expression of ADAM17 protein in both node-negative and positive breast cancer, (Figs. 2-4) which was verified by immunohistochemistry analysis. There was high and low expression of ADAM17 in both cases. However in general, we obtained higher number of low expression as compared to high ADAM17 expression. This could be due to the fact that our study involves higher number of node-negative as compared to node-positive cases. Most works that showed higher frequency of ADAM17 expression was carried out in advance or node-positive cases in contrary to our study with a focus on node-negative breast cancer. We found significantly higher concentration of ADAM17 expression in grade 3 which confirms its expression in advanced cases. The high expression we observed are also in accordance with other published reports, [39,52].

In addition, some cancerous cases showed the presence of ADAM17 protein expression but was

absent in their adjacent non-cancerous tissues (Fig. 2). This supports previous works on ADAM17. For instance in a study performed by Lendeckel U et al. [39] on 24 breast cancer specimen and corresponding non-cancerous tissue, mRNA expression of ADAMs 9,12 and 17 were increased in cancerous tissue compared to normal adjacent tissues. Again, it was reported that, in a study on ADAM expression in breast cancer tissue, there was an elevated expression ADAM 17 [53] in breast carcinomas compared with non-neoplastic or adjacent healthy tissue. The evidences of low expression in some of the node-negative cases through to high expression in some of the node-positive cases, and its absence in non-cancerous cases are interesting. These may indicate that ADAM17 expression may be involved in processes leading to the initiation of tumor, its progression and distribution of tumor cells to lymph nodes and lead to distant metastasis in breast cancer.

We again observed weak ADM17 expression in some high Ki67 expression, positive ER, PR and HER2 expression and vise versa. Following current guidelines, patients in this category may be recommended for adjuvant chemotherapy. However, our current studies using ADAM17, indicate they may be spared from adjuvant chemotherapy if confirmed by further studies.

Ductal and lobular are the two common breast cancer types, with ductal being the most common. From our results, there was more expression in ductal than lobular, confirming a work done by McGwan PM et al. [52] which suggest a different role played by ADAM17 in ductal and lobular carcinoma formation.

In analyzing the relationship between ADAM17 expression and clinicopathological parameters of breast cancer, our results obtained in agreement with a study published by McGowan et al [52] showed that ADAM17 expression level did not present a statistical significance relationship with all the conventional prognostic factors, except histological type. Present results may suggest ADAM17 as an independent prognostic factor upon further studies.

In determining the high and low risk category, we grouped strong ADAM17 expression against none to weak expression, since we were not able to carry out a quantitative analysis that will enable us set up a cut off point by which we can confidently group cases into high and low risk patients. By doing so, we obtained 19 high risks and 31 low risks. Another limitation of our study was the small sample size. Due to that we were not able to carry out a multivariate analysis. Nevertheless, this is one of the few works already established to assess the expression level of ADAM17 in node-negative breast cancer specifically, and its possible prognostic impact. Our results further confirm the importance of this kind of studies and the need for more of such studies to help in treatment selection especially among node-negative breast cancer patients.

5.CONCLUSION

In conclusion, our study shows that ADAM17 protein may be involved in human breast cancer initiation, progression and distant metastasis, considering its expression from “no to strong” in both node-negative and node-positive breast cancer. Also its prognostic impact could be independent of conventional prognostic factors upon further studies. Though we were not able to prove ADAM17 prognostic impact on individual survivorship and patient outcome it could be possible that, ADAM17 may be a risk assessment biomarker, capable of determining individuals who may be at high risk. This is due to the fact that in other studies, it was reported that the levels of ADAM17 expression were significantly associated with uPA, and its high level was significantly associated with poor outcome in patients with breast cancer [38,52]. Further studies with ADAM-17 inhibitors or blocking ADAM17 could be a target for breast cancer treatment and management.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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