

# Fascin Expression in Invasive Ductal Carcinoma of Breast

## İnvaziv Duktal Meme Karsinomlarında Fascin Ekspresyonu

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### ABSTRACT

**Objective:** Fascin is an actin-binding protein that regulates the rearrangement of cytoskeletal elements. It takes part in the formation of cellular membrane protrusions and in cell motility. It is up-regulated in several types of carcinomas.

**Material and Method:** We examined the expression of fascin in the invasive ductal carcinomas whether lymph node negative (n=16) or lymph node positive (n=16) and in metastatic lymph nodes, microinvasion + invasive ductal carcinoma with extensive in situ component (n=9) by the immunohistochemical method using monoclonal antifascin antibody.

**Results:** Fascin immunoreactivity was detected in 4 (44.4%) microinvasion+invasive ductal carcinoma with extensive insitu component, 7 (43.7%) invasive ductal carcinomas with lymph nodes negative, 13 (81%) lymph node positive tumors and 10 (62.5%) metastatic lymph nodes. There was a statistically significant difference between these groups (p=0.044). Fascin immunoreactivity was significantly higher in invasive ductal carcinomas with lymph node positive than lymph node negative group (p=0.033). No statistically significant difference was seen between expressions of invasive ductal carcinomas with lymph node positive group and their metastasis in the lymph nodes. Tumors with high fascin immunoreactivity tended to show more frequent lymphovascular invasion (p= 0.002). Advanced stage and high grade correlated significantly with higher fascin immunostaining (p=0.036, p=0.01). There was no significant association between fascin expression and tumor size, ER/PR and cerb-B2 overexpression.

**Conclusion:** We evaluated the expression of fascin to determine its role in the progression of invasive ductal carcinomas, invasive phenotype and metastatic potential. Our findings suggest that fascin expression plays a role in the metastatic potential of invasive ductal carcinomas.

**Key Words:** Fascin, Breast carcinomas, Metastatic potential

### ÖZ

**Amaç:** Fascin, aktin bağlayıcı protein olup hücre iskeletinin düzenlenmesinde rol oynar. Hücre membranı çıkıntılarının oluşumu ve hücre motilitesinin sağlanmasında görevlidir. Çeşitli karsinom tiplerinde fascin ekspresyonu artar.

**Gereç ve Yöntem:** Bu çalışmada, 16 lenf nodu negatif invaziv duktal karsinom, 16 lenf nodu pozitif invaziv duktal karsinom ve bu gruptaki olguların metataz izlenen lenf nodülleri, 9 mikroinvaziv + yaygın insitu komponent içeren invaziv duktal karsinom olgularında immünohistokimyasal yöntemle monoklonal anti-fascin antikoru kullanılarak fascin ekspresyonu araştırıldı.

**Bulgular:** Fascin mikroinvaziv + yaygın insitu komponent içeren invaziv duktal karsinom olgularının 4'ünde (%44,4), lenf nodu negatif invaziv duktal karsinom olgularının 7'sinde (%43,7), lenf nodu pozitif invaziv duktal karsinom olgularının 13'ünde (%81) ve metastatik lenf nodlarının 10'unda (%62,5) pozitif bulundu. Bu gruplar arasında istatistiksel olarak anlamlı farklılık izlendi (p=0,044). Fascin immün reaktivitesi lenf nodu pozitif invaziv duktal karsinom olgularında lenf nodu negatif invaziv duktal karsinom olgularına göre istatistiksel olarak anlamlı derecede yüksek bulundu (p=0,033). Lenf nodu pozitif invaziv duktal karsinom olguları ile bu grubun metastatik lenf nodlarındaki ekspresyonlar arasında istatistiksel olarak anlamlı farklılık bulunmadı. Yüksek fascin immünreaktivitesi izlenen tümörlerde daha sık lenfovasküler invazyon izlendi (p=0,002). İleri evre ve yüksek grade, yüksek fascin immünorektivitesi ile ilişkili bulundu (p=0,036, p=0,01). Fascin ekspresyonu ile tümör çapı, ER/PR ve cerb-B2 ekspresyonu arasında anlamlı ilişki izlenmedi.

**Sonuç:** İnvaziv duktal karsinom olgularında fascin ekspresyonunu, invaziv fenotip ve metastatik potansiyel üzerindeki etkisini inceleyerek tümör progresyonundaki rolünü değerlendirdik. Bulgularımız fascin ekspresyonunun invaziv duktal karsinomların metastatik potansiyelinde rol oynadığını düşündürmektedir.

**Anahtar Sözcükler:** Fascin, Meme karsinomları, Metastatik potansiyel

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## INTRODUCTION

Malignant neoplasms are one of the most common causes of death and constitute a major public health problem and among them, 85% are carcinomas (1). Most cancer deaths are caused by secondary and metastatic diseases resistant to conventional therapies. Therefore understanding the early event by which carcinoma cells invade local tissue and disseminate through the blood or lymphatic systems to colonise other body sites is a major focus in cancer research. In addition, identification of new molecular markers that could detect more aggressive tumor behaviour is important (2).

Malignant cellular transformation is characterized by many phenotypical alterations such as changes in cell shape, cell rounding, increased cell motility, loss of anchorage dependency and loss of cell-cell contacts (1,3,4,5). Many of these changes are due to the rearrangements of cytoskeletal actin microfilaments and actin cross-linking proteins (1,6,3,7). Among these molecules, fascin is a highly conserved 55-kDa protein that regulates the rearrangement of cytoskeletal elements and play an important role in the organization of several types of actin-based structures such as filopodia, spikes, lamellipodial ribs, dendrites and microvilli (1,8,9,10). In mammals, three subtypes of the fascin family include fascin-1, fascin-2 and fascin-3 (1,11). The gene encoding fascin 1 is located at chromosome 7p22 (1). Normally, fascin is expressed by cells characterized by different types of membrane protrusions (8). Significant expression of fascin was seen throughout the development in neurons, follicular dendritic cells of lymphoid tissue, basal layer cells of stratified squamous epithelia, mesenchyme, and vascular endothelial cells (12, 13). Simple columnar epithelia of the biliary duct, colon, ovary, pancreas, and stomach were all negative for fascin expression (13).

In the literature the absence or low expression of fascin in normal epithelia is dramatically altered in many human carcinomas and overexpression may play an important role in the biologic behaviour of glial astrocytic tumor, oropharyngeal squamous cell carcinoma, colorectal cancer, bile duct carcinoma, renal cell carcinoma, pancreatic carcinoma, lung carcinoma (11,14-26). Fascin expression is also increased in Epstein-Barr virus-transformed B lymphocytes in the Reed-Steinberg cells of Hodgkin's lymphoma (27,28).

We evaluated the expression of fascin by performing immunohistochemistry to determine its role in the progression of invasive ductal carcinomas (IDC), invasive phenotype and metastatic potential and to elucidate its utility as a preoperative novel therapeutic option.

## MATERIAL and METHODS

Cases diagnosed as invasive ductal carcinoma at the Department of Pathology between November 2002 and November 2004 were included in this study. The criteria for microinvasion and invasive ductal carcinoma with extensive in situ component were determined according to WHO classification (29). The expression of fascin in the invasive ductal carcinomas with lymph node negative (IDC+LN) (n=16), lymph node positive (IDC+LN+) (n=16) and in their metastatic lymph nodes (n=16), microinvasive carcinoma + invasive ductal carcinoma with extensive in situ component (IDC with EIC) (n=9) were analysed by immunohistochemical (IHC) method using monoclonal anti-fascin antibody. The clinicopathological data of the patients were retrieved from their medical charts and pathology reports. Surgical staging was performed using TNM criteria.

IHC staining of the tumor sections were carried out by streptavidin biotin peroxidase method using ER (1:100 dilution, RM9101, Neomarker, USA), PR (1:200 dilution, RM9102, Neomarker, USA), c-erbB-2 (1:100 dilution, MS730, Neomarker, USA) and fascin-1 antibody (1:200 dilution, M20, Novacastra, United Kingdom). Briefly, 5 µm tumor sections were deparaffinized and hydrated through graded alcohols to water. The slides were immersed in 0.01M citrate buffer for 20 min in a microwave oven for antigen retrieval. After cooling and washing in PBS, endogen peroxidase was blocked with 3% hydrogen peroxidase. The slides were incubated with primary antibodies and then washed and incubated with linking reagent for 15 min. Staining was visualized using diaminobenzidine. Mayer hematoxylin was used as a counterstain. Positive and negative control slides (according to manufacturer's data sheet of each antibody) were included in every experiment in addition to the internal positive controls (normal breast tissue).

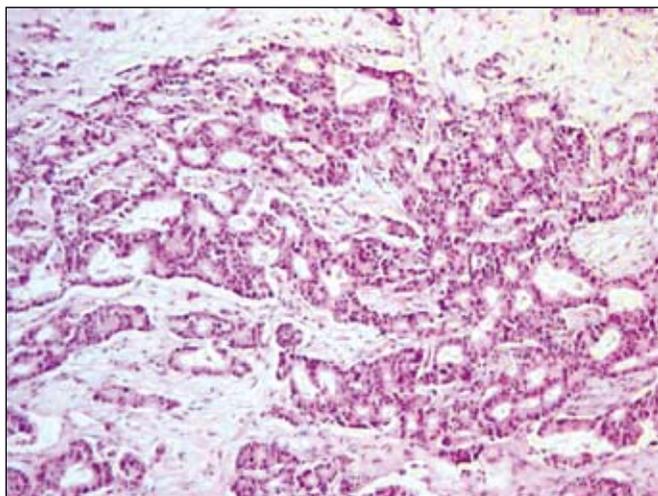
IHC staining was evaluated semiquantitatively as the percentage of positive stained cells and the intensity of the stain (0: no staining, 1: faint positivity, 2: intermediate positivity, 3: strong positivity). Nuclear staining for estrogen receptor (ER) and progesterone receptor (PR), membranous staining for c-erbB-2 and cytoplasmic staining for fascin-1 were evaluated.

For statistical analysis, ER and PR expressions with more than 10% nuclear and strong (+3) staining were regarded as positive. Strong complete membrane staining was regarded as +3 positive for c-erbB-2 and staining of more than 10% of tumor cells was regarded as positive fascin

immunoreactivity. Statistical analysis was performed using the SPSS 10.0 for Windows software package. The Chi-square test was used to examine the association between groups and fascin immunoreactivity, hormone receptors and other variables. All statistical tests were two-sided and  $p \leq 0.05$  was considered significant.

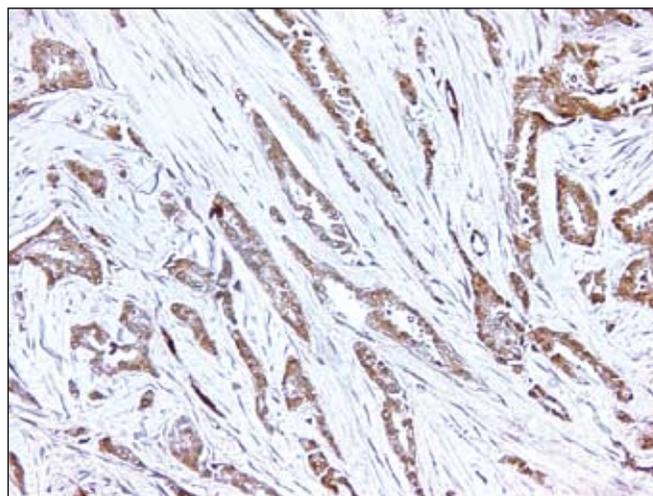
## RESULTS

At diagnosis, the median patient age was 53.73 (range 28-80). Modified radical mastectomy and level I to II axillary dissection were performed in all patients. All patients were pathologically staged according to the guidelines of 2003 TNM classification. One case was T1, 11 cases were T2, 25 cases were T3 and 4 cases were T4. Fifteen patients had stage I disease, 14 had stage II disease, 2 had stage III and 10 had stage IV disease. The majority was T3 in size and ER/PR positivity (63.4% and 56%, respectively), HER2 amplification was detected via immunohistochemistry in 20 (48.7%) cases. Histopathologic grade was determined according to Elston and Ellis method and 4 IDCs were grade 1, 18 were grade 2, 19 were grade 3 (Figure 1).

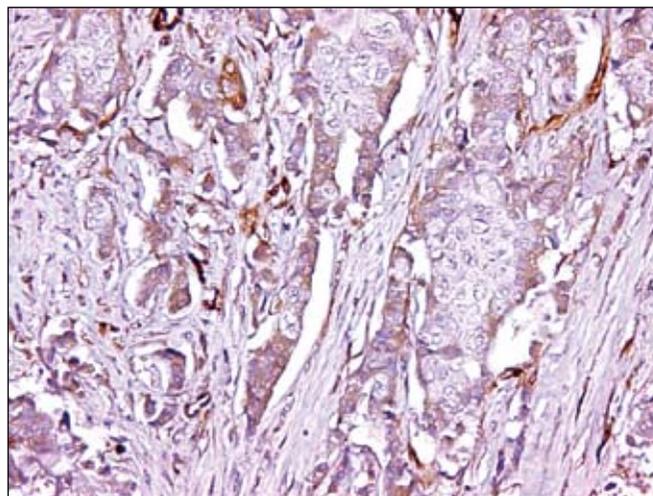


**Figure 1:** Invasive ductal carcinoma, grade 1 (H&E, x100).

Fascin immunoreactivity was detected in 4 (44.4%) microinvasion+IDC with EIC, 7 (43.7%) IDC+LN-, 13 (81%) IDC+LN+ tumors and 10 (62.5%) metastatic LN (Figure 2,3,4) (Table I). There was a significant difference for fascin immunoreactivity in these groups ( $p=0.044$ ).



**Figure 2:** Fascin immunopositivity in low grade invasive ductal carcinoma (DAB, x200).



**Figure 3:** Fascin immunopositivity in high grade invasive ductal carcinoma (DAB, x400).

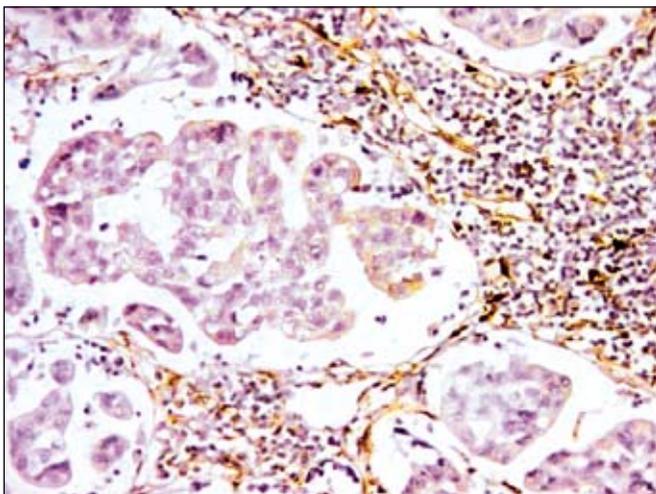
**Table I:** Immunohistochemical fascin expressions of the tumors

	<i>FASCIN</i> (-)	<i>FASCIN</i> (+)	<i>TOTAL</i>
IDC+LN+ *	3	13	16
IDC+LN- **	9	7	16
Microinvasion+IDC with EIC***	5	4	9
<b>TOTAL</b>	17	24	41

\*Invasive ductal carcinomas, lymph node positive.

\*\*Invasive ductal carcinomas, lymph node negative.

\*\*\*Microinvasive carcinoma + invasive ductal carcinoma with extensive insitu component



**Figure 4:** Fascin immunopositivity in metastatic lymph node (DAB, x400).

**Table II:** Correlation of fascin expressions and clinicopathological characteristics of the tumors

Invasive Ductal Carcinoma	Fascin (-) (n=12)	Fascin (+) (n=20)	P value
<b>Grade</b>			
I+II (n=17)	10	7	0,01
III (n=15)	2	13	
<b>Size (cm)</b>			0,454
≥2 (n=23)	8	15	
<2 (n=9)	4	5	
<b>Stage</b>			0,036
≤IIa (n=19)	10	9	
≥IIb (n=13)	2	11	
<b>LVI*</b>			0,002
- (n=18)	11	7	
+ (n=14)	1	13	
<b>ER</b>			0,574
- (n=14)	5	9	
+ (n=18)	7	11	
<b>PR</b>			0,556
-(n=15)	7	8	
+(n=17)	5	12	
<b>c-erb-B2</b>			0,063
- (n=12)	2	10	
+ (n=20)	10	10	

LVI\*: Lymphovascular invasion

Though the expression of fascin was not different between IDC+LN- and microinvasion+IDC with EIC, it was significantly higher in IDC+LN+ than IDC+LN- group ( $p=0.033$ ). No statistically significant difference was seen between IDC+LN+ group and their metastasis in the lymph nodes. Tumors with high fascin immunoreactivity tended to show more frequent lymphovascular invasion ( $p=0.002$ ). Advanced stage and high grade correlated significantly with higher fascin immunostaining ( $p=0.036$ ,  $p=0.01$ ). There was no significant association between fascin expression and tumor size, ER/PR and cerb-B2 overexpression (Table II).

## DISCUSSION

The invasion and metastasis of tumor cells are a major cause of mortality in cancer patients. Loss of cell-cell adhesion, changes in cell shape resulting in membrane protrusions and movement of tumor cells to lymphatic and venous circulation are considered to be necessary steps in metastasis formation (1). Cytoskeletal actin microfilaments and cross-linking proteins are responsible for these changes (1). Fascin, a 55-kDa globular protein, aggregates F actin into parallel bundles to rearrange the cytoskeleton and expressed by cells with different types of membrane protrusions (14).

In the literature, overexpression of fascin is reported in several common types of carcinoma (1,11,14). More than 95% of invasive pancreatic tumors and 89% of non-small cell lung carcinomas express high levels of fascin (1). In another study, fascin expression levels were correlated with histological grade in glial astrocytic tumors and fascin overexpression may play an important role in the prognosis of glioblastoma multiformes (15). Higher immunostaining fascin scores were strongly associated with advanced grades advanced T stages of pancreatobiliary adenocarcinomas (16). In oral and oropharyngeal squamous cell carcinoma, fascin protein was overexpressed in carcinoma cells compared with their non-neoplastic epithelial counterparts (17,19). In addition, expression of fascin in lung, gastric, esophageal carcinoma has correlated with more advanced stage, poor prognosis and or decreased survival time (1,8,30). Pelosi et al. observed fascin expression in 78% of 96 adenocarcinomas of lung and found fascin expression as an independent prognostic factor (8). Zhang et al have reported that fascin up-regulation markedly correlated with cell proliferation and lymph node metastasis in esophageal squamous cell carcinomas (31). In ovarian tumors, the expression of fascin in cultured tumor cells was significantly associated with the ability of these cells to grow intraperitoneally (32). Strong and diffuse expression was seen in a subset of advanced

colorectal adenocarcinomas that correlated with shorter survival in stage III and IV patients. Fascin may have prognostic value as an early biomarker for more aggressive colorectal adenocarcinomas (25). Moreover, patients with the same tumour stages could be stratified in different risk categories for relapse and progression according to fascin expression (23).

In the literature there are a number of studies about fascin expression in breast carcinoma. Yoder et al. found fascin expression in 16% of the invasive breast carcinoma cases and it was correlated with ER negativity, PR negativity, grade 3 and advanced stage and also associated with an aggressive clinical course and poor disease-free and overall survival (12). Similarly, in another study of 58 patients with breast cancer showed that fascin expression correlated significantly with tumor grade, DNA ploidy, and correlated inversely with estrogen receptor and progesterone receptor expression (33). In vitro experiments have shown that hormone receptor negative breast cancer cells have increased cell motility and increased invasiveness (34). These published observations suggest a possible relationship between hormone receptor negativity, enhanced cell motility and fascin expression in human breast carcinoma. These data confirm that there is a common relation with the aggressive tumor behaviour. In the current study, fascin was up-regulated in most (81%) IDC+LN+ tumors which was significantly higher than IDC+LN- group and correlated with more frequent lymphovascular invasion, advanced stage and higher grade but there was no correlation with the ER/PR status. These findings suggest that up-regulation of fascin in tumoral tissue may promote invasion and metastatic potential of IDC.

Regarding to HER2 status and fascin expression, similar to our finding Yoder et al. found no correlation (12). Alternatively, in another study showed that highly increased fascin level were observed in breast cancer cell line overexpressing c-erb B2 (34). Fascin overexpression in these cell line could result from factors including increased transcriptional activity of the fascin gene and or decreased degradation of fascin protein.

These contradictory results could be due to limited population size or an institutional bias. In addition it might reflect the biological complexity of HER2 gene amplification and protein overexpression occurring in vivo.

If fascin is a biomarker for aggressiveness, we would expect to see a high frequency of fascin positive metastasis from fascin positive tumors. In gastric carcinomas, 72% of the metastases of fascin-positive primary gastric carcinomas

were fascin-positive, only 3% of lymph-node metastasis from fascin-negative gastric tumors were fascin-positive (30). Similarly, in our study, fascin immunoreactivity was detected in 13 (81%) IDC+LN+ tumors and 7 of them were fascin-positive in metastatic LN and the primary tumor was fascin negative in only 3 fascin positive lymph node metastases. Finally fascin-positive primary tumors may more rapidly and more frequently metastasize than fascin negative-tumors. A challenging result was observed by Vignjevic et al. who found that expression of fascin1 in primary tumors correlated with the presence of metastases but fascin1 was not expressed in metastases and they stated that the expression of fascin1 was down-regulated when tumor cells reached their metastatic destination (18).

Although metastasis to vital organs is often the cause of mortality, only limited success has been attained in developing effective therapeutics against metastatic disease. Current prognostic factors do not provide sufficient information to allow individual risk of patients with breast cancer. Greater understanding of the molecular and cellular basis of breast cancer phenotypes is important. Our data suggest that fascin expression is related to high metastatic potential. Clearly, more studies should be done for further information about the fascin expression and the regulatory activity in human breast cancer.

We propose that genes involved in cell migration and invasion, such as fascin1, could serve as novel targets for metastasis prevention. If the expression of fascin in human breast cancers and its metastasis are observed in prospective studies, it may represent a potential therapeutic target and down-regulation of tumor specific fascin may become a novel therapeutic strategy.

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