

Stromal Caveolin-1 Levels Predict Early Ductal Carcinoma in Situ Progression to Invasive Breast Carcinoma

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Introduction

With the increased use of screening mammography, the incidence of ductal carcinoma in situ (DCIS) has increased substantially and it currently accounts for 20–30% of newly diagnosed breast carcinomas in United States. Breast conserving therapy with or without radiotherapy is the accepted treatment for most cases of DCIS. However, the local recurrence rate with such therapy ranges from 10 to 40% with half of these patients developing invasive carcinoma. Tamoxifen, used as an adjuvant systemic therapy for DCIS, does not increase overall survival and data on reduction of local recurrence rates are conflicting.

The current classification for DCIS based on nuclear grade, architectural differentiation and presence of necrosis, does not adequately predict the likelihood of recurrence after breast conserving therapy. Therefore, there is a critical need to identify novel predictors of DCIS progression and potential targets for therapy.

Recently, we showed that an absence of stromal (caveolin 1) Cav-1 expression in human breast cancers is a powerful single independent predictor of early disease recurrence, metastasis and poor clinical outcome. However, it remains unknown whether stromal Cav-1 levels play any role in the progression of DCIS. The aim of this study was to evaluate the stromal expression of Cav-1 in a cohort of DCIS patients treated with wide-excision and close follow-up and examined the association between stromal Cav-1 expression and clinicopathological variables, DCIS recurrence or progression to invasive breast cancer.

Material and Methods

DCIS breast tissues were obtained from the Surgical Pathology files at the Thomas Jefferson University. Seventy-eight cases for which histologic slides and blocks were available were included in the study. Clinical and treatment information was extracted by chart review. All patients were treated by the same surgeon (Gordon F. Schwartz, M.D.), undergoing surgical excision only, and all had negative margins (\leq or $>$ 10 mm) at the conclusion of surgical excision or re-excision. None of the patients underwent radiation therapy, or were given tamoxifen. The median follow-up time for these patients was 146.8 months (12.23 years). For each case, histologic pattern (solid, cribriform, papillary, micropapillary, comedo), nuclear grade, presence of necrosis and inflammation were recorded. Cav-1 expression in the tumor stroma was assessed by a standard immunoperoxidase method (anti-caveolin-1 IgG, BD Biosciences, San Jose, CA; 1:50 dilution). The staining was scored semi-quantitatively as negative (0; no staining), weak (1; either diffuse weak staining or strong staining in less than 30% of stromal cells) and strong (2; defined as strong staining of 30% or more of the stromal cells). All hypothesis testing was performed using the Fisher exact test or the Kruskal-Wallis test, depending on the discrete or continuous nature of the other factors.

Results

Sixteen DCIS patients underwent some form of recurrence: 8 recurred to DCIS, while the other 8 recurred with progression to invasive breast cancer. Nearly ninety percent of DCIS patients (7/8) that underwent recurrence to invasive breast cancer had reduced or absent levels of stromal Cav-1. Representative examples of Cav-1 immunostaining are shown in (Figure 1). The absence of stromal Cav-1 (score = 0) was specifically associated with early disease progression to invasive breast cancer, with reduced time to recurrence and higher recurrence rate. All DCIS patients with an absence of stromal Cav-1 underwent some form of recurrence (5/5) and the majority (4/5) underwent progression to invasive breast cancer (Figure 2). This represents an overall cumulative incidence rate of 100% for recurrence and 80% for progression. An absence of stromal Cav-1 in DCIS lesions was also specifically associated with the presence of inflammatory cells. Inflammation (the presence of lymphocytes and/or macrophages) was specifically associated with DCIS progression to invasive breast cancer (Figure 3) however this effect was strictly dependent on stromal Cav-1 levels. Conversely, ninety-seven percent of DCIS patients with high levels of stromal Cav-1 (score = 2) did not show any invasive recurrence over the duration of follow-up (4–208 mo), and 89% of such patients are estimated to remain free of invasive recurrence, even after 15 y.

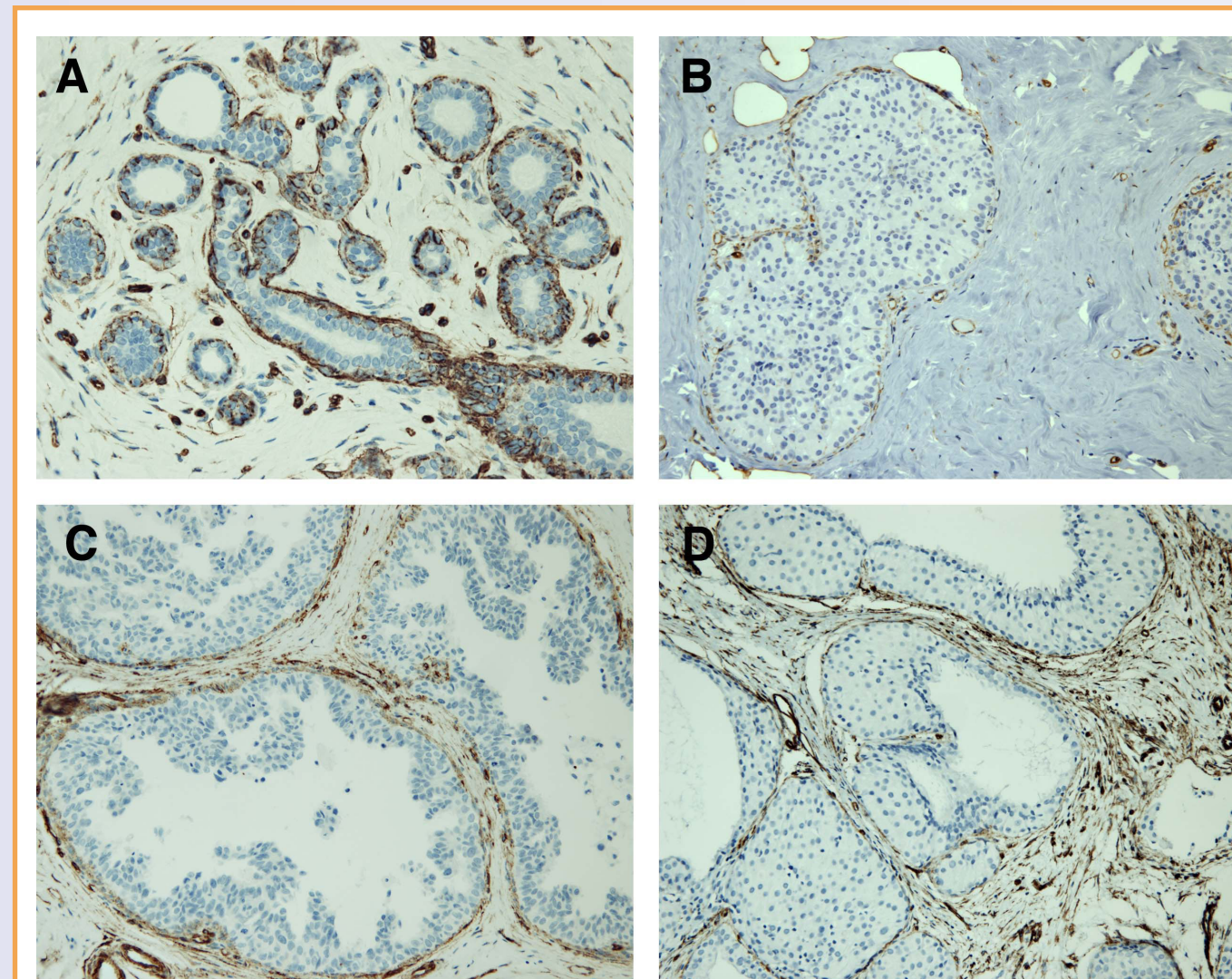


Figure 1 Cav-1 immunohistochemical staining in normal breast and ductal carcinoma in situ (DCIS). A, Focal weak staining in stromal fibroblasts in the terminal duct lobular unit. B, Score 0 (no staining) in DCIS. C, Weak expression of stromal Cav-1 (score 1) in DCIS. D, Strong diffuse staining in stromal fibroblasts representing score 2. In all panels myoepithelial and endothelial cells exhibit strong staining. (original magnification 400X (panel A) and 200X (panels B-D))

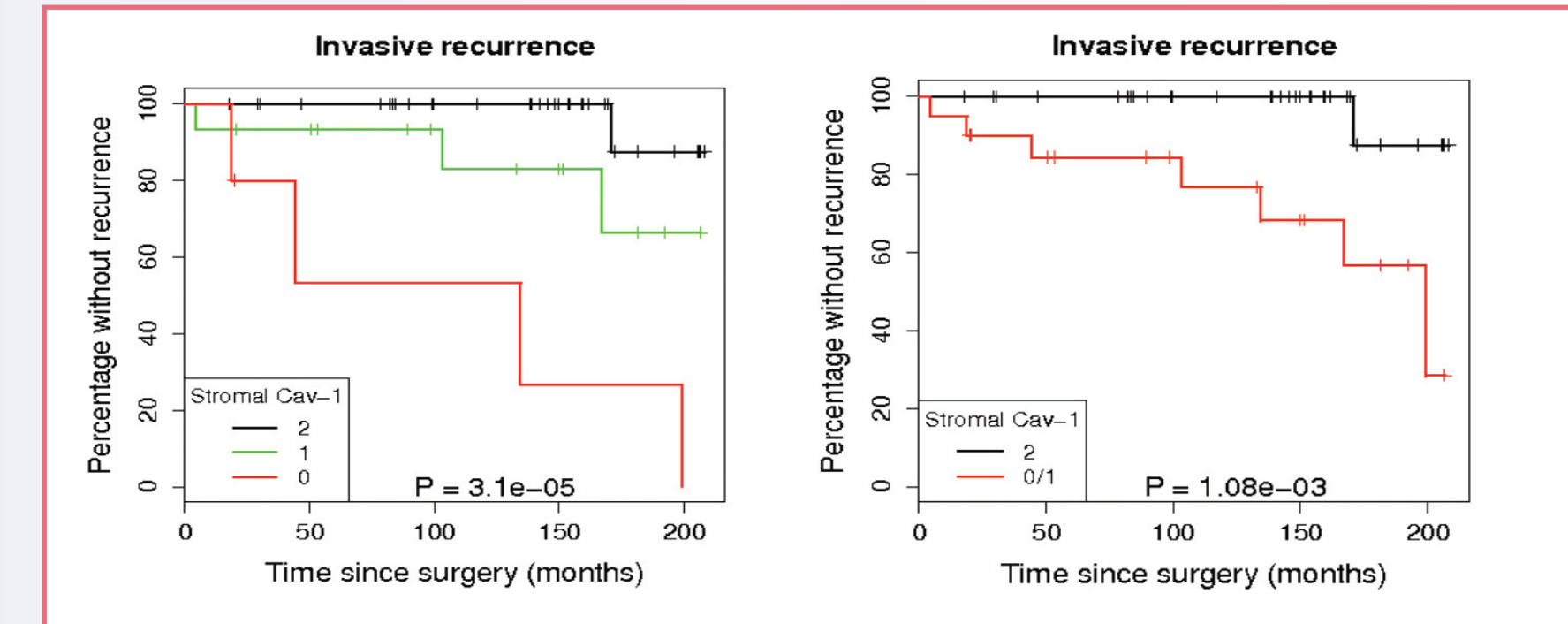


Figure 2. Kaplan-Meier curves for stromal Cav-1 status and time to overall recurrence among DCIS patients. Note that an absence or reduction of stromal Cav-1 is strongly associated with an increase in progression to invasive breast cancer. On the left, patients were stratified into three different groups. On the right, patients with low or absent Cav-1 were considered as a single group. p values (log rank test) are as shown.

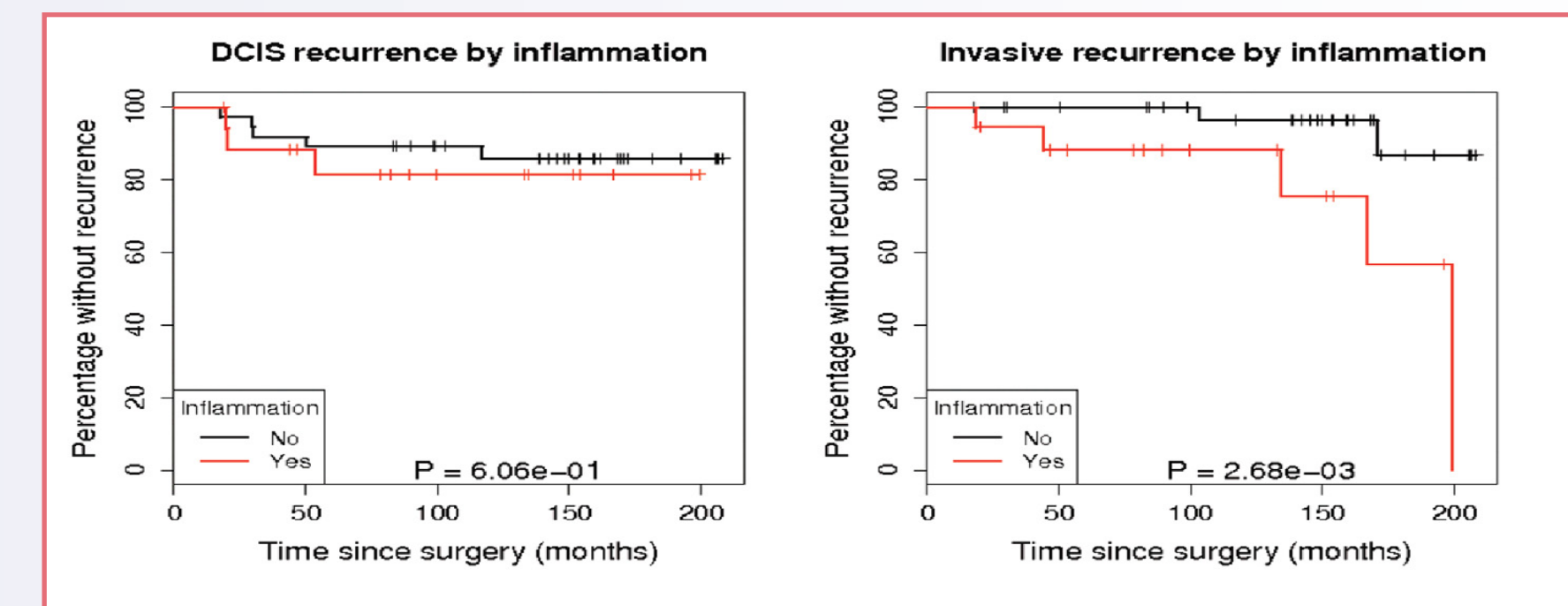


Figure 3. Kaplan-Meier curves for inflammation and time to DCIS recurrence and invasive recurrence among ER(+) DCIS patients. Note that inflammation is associated with an increase in progression to invasive breast cancer, but not simple DCIS recurrence. p values (log rank test) are as shown.

Conclusions

Stromal Cav-1 may represent a valuable new biomarker for dividing DCIS patients into high-risk and low-risk groups at diagnosis, facilitating their treatment stratification.