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Emerging Role of COL10A1 in Breast Cancer Pathogenesis and its Potential as a Clinical Biomarker

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Submission Date : 17 Jan 2026
Accepted Date : 19 Feb 2026
Published Date : 30 March 2026
DOI: https://doi.org/10.3329/jrpmc.v11i1.90014

Abstract

Background:
Breast cancer is a leading malignancy worldwide, with high morbidity and mortality among women. Despite advances in therapy, metastasis, recurrence, and resistance remain challenges. Collagen type X alpha-1 (COL10A1) is normally expressed in cartilage but is increasingly implicated in tumorigenesis. Overexpression of COL10A1 in breast cancer correlates with higher grade, invasiveness, and poor prognosis.

Objective:
To evaluate COL10A1 expression in breast cancer and its association with tumor characteristics, receptor status, and potential biomarker utility.

Methods:
A hospital-based cross-sectional study was conducted at department of Surgery, Dhaka Medical College Hospital from July 2022 to June 2023, including 40 breast cancer patients. Data on demographics, clinical features, and reproductive history were collected, and tissue samples were analyzed for COL10A1 expression. Inclusion required histopathological confirmed breast cancer in women ≥40 years. Statistical analysis used SPSS for frequencies, percentages, means, and chi-square tests. Ethical approval and informed consent were obtained, ensuring confidentiality and voluntary participation.

Results:
The study of 40 breast cancer patients revealed a mean age of 47.41 years. The majority had invasive ductal carcinoma (70%), Grade II (50%) or III (35%) tumors, and hormone-sensitive disease (60% ER-positive, 50% PR-positive). HER2-positivity was 25%. Critically, 80% exhibited moderate-to-high COL10A1 expression, which was strongly associated with high-grade tumors, as 10 of 14 Grade III patients showed high expression.

Conclusion:
COL10A1 overexpression correlates with aggressive breast cancer, highlighting its potential as a prognostic biomarker.

Keywords: Breast cancer, COL10A1, Collagen type X alpha-1, Biomarker, Tumor grade

Citation: Roy NR,Narju SP,Hoque F,Barman S.Emerging Role of COL10A1 in Breast Cancer pathogenesis and its Potential as a Clinical Biomarker.J Rang Med Col.2026 Mar;11(1):105-110.doi: https://doi.org/10.3329/jrpmc.v11i1.90014

Introduction:

Breast cancer remains one of the most prevalent malignancies worldwide, with substantial morbidity and mortality, particularly among women.[1] Despite advances in diagnosis and therapy, issues such as metastasis, recurrence, and therapeutic resistance continue to challenge clinical management.[2] Therefore, identification of novel molecular drivers and biomarkers is critical to improve prognosis and guide more precise treatment strategies. One promising candidate is Collagen type X alpha-1 chain (COL10A1), a non-fibrillar collagen normally expressed during cartilage development that has increasingly been implicated in tumorigenesis.[3] Recent bioinformatics analyses have demonstrated that COL10A1 is overexpressed in breast cancer tissues compared to normal breast tissue, and its elevated

expression correlates with unfavorable clinicopathologic variables, including higher grade, nodal involvement, and poorer patient survival.[4] For example, Yang et al showed that COL10A1 promotes breast cancer cell proliferation, migration, and invasion via interaction with prolyl 4-hydroxylase β subunit (P4HB), suggesting a functional, oncogenic role.[5] Knockdown of COL10A1 in in vitro models significantly impairs tumor cell aggressiveness, indicating its potential as a driver of malignancy.[5] Mechanistically, COL10A1 has been linked to several tumor-promoting pathways. A recent review detailed how COL10A1 can activate TGF-β 1/Smad, MEK/ERK, and focal adhesion kinase (FAK) signaling, thereby inducing epithelial–mesenchymal transition (EMT), invasion, and proliferation.[3] Mechanistically, COL10A1 has been shown to interact with the discoidin domain receptor 2 (DDR2), resulting in the phosphorylation of focal adhesion kinase (FAK) and the subsequent enhancement of cell motility.[6] Such interactions not only remodel the extracellular matrix (ECM) but also contribute to a pro-metastatic microenvironment.Beyond breast cancer, elevated COL10A1 has been reported in other malignancies such as gastric, colorectal, pancreatic, and lung cancers, where its expression often correlates with advanced disease and poor prognosis.[7-9] In gastric cancer specifically, COL10A1 overexpression has been shown to activate MAPK/JNK signaling and drive EMT by upregulating mesenchymal markers such as N-cadherin and Snail while downregulating epithelial markers like E-cadherin.[7] In colorectal cancer, COL10A1 is enriched in cancer-associated fibroblasts (CAFs) and is associated with immune cell infiltration, supporting a role in modulating the tumor stroma and immune microenvironment.[8] Given the accumulating evidence, COL10A1 emerges as a potential clinical biomarker in breast cancer: it not only reflects tumor aggressiveness but may also help stratify patients for targeted therapy. However, despite compelling preclinical and bioinformatic data, the precise clinical utility and molecular mechanisms of COL10A1 in breast cancer remain underexplored. This study therefore aimed to investigate the role of COL10A1 in breast cancer pathogenesis, examine its expression in patient samples, and assess its potential as a prognostic or diagnostic biomarker.

Methods:

The hospital-based cross-sectional observational study was conducted in the Department of General Surgery and the Breast Clinic of Dhaka Medical College Hospital (DMCH), Dhaka, Bangladeshfrom July 2022 to June 2023 on 40 breast cancer patients.Data were collected using a structured, pre-tested questionnaire and review of hospital records. After obtaining ethical approval for the study was obtained from the Institutional Review Board (IRB) of Dhaka Medical College Hospital (DMCH) and informed consent, demographic information, reproductive history, clinical features, imaging findings, and histopathological reports were recorded. Tissue samples were collected during biopsy or surgery and processed for the assessment of COL10A1 gene expression using standard laboratory techniques (immunohistochemistry or molecular assays depending on availability). Each participant was followed through diagnostic evaluation to confirm tumor type, grade, and receptor status. All information was obtained directly from patients or their medical records, ensuring accuracy and completeness.

The study included female patients aged 40 and above with newly diagnosed breast cancer confirmed by histopathology, recruited from General Surgery Department and Breast Clinic of Dhaka Medical College Hospital. Patients with previous breast cancer treatment, chemotherapy or radiotherapy before tissue sampling, or incomplete information were excluded to ensure accurate data.

All collected data were entered into a spreadsheet and analyzed using Statistical Package for Social Sciences (SPSS) version 26.0. Descriptive statistics such as frequency, percentage, mean, and standard deviation were calculated to summarize demographic and clinical variables. Associations between COL10A1 expression and tumor characteristics were evaluated using chi-square tests or Fisher's exact test where appropriate. A p-value <0.05 was considered statistically significant. Data were presented in tables and charts for clarity.

Results:

The study involved 40 patients, mainly aged 41–50 years (47.5%), with a mean age of 47.41±2.52 years. Most had a normal BMI (55%), with a mean of 21.07±1.17 kg/m . Nearly half

had higher secondary education (47.5%), lived in urban areas (65%), and were mostly from middle-income families (50%) (Table-I).

Table-I: Demographic characteristics of the study participants (N=40)

Demographic characteristics	no (%)
Age Group (years)	
≤40	12(30.0)
41–50	19(47.5)
>50	9(22.5)
Mean Age±SD (years)	47.41±2.52
Body Mass Index (BMI)	
Normal (18.5–24.9)	22(55.0)
Overweight (≥25.0)	18(45.0)
Mean BMI±SD (kg/m)	21.07±1.17
Educational Level	
Primary or below	7(17.5)
Secondary	14(35.0)
Higher Secondary & above	19(47.5)
Residence	
Urban	26(65.0)
Rural	14(35.0)
Socioeconomic Status	
Lower	11(27.5)
Middle	20(50.0)
Upper	9(22.5)

Among 40 breast cancer patients, 30% had a family history, and 70% did not. Early menarche was reported by 60% at or before 13 years, while 35% used contraceptives. Most patients were multiparous (80%) (Table-II).

Table-II: Distribution of reproductive and clinical history (n=40)

Variable	no (%)
Family history of Breast Cancer	
Present	12(30.0)
Absent	28(70.0)
Age at Menarche	
≤13 years	24(60.0)
>13 years	16(40.0)
Contraceptive Use	
Yes	14(35.0)
No	26(65.0)
Parity	
Multipara	32(80.0)
Primipara	8(20.0)

(IDC) was the most common tumor, present in 70% of cases, followed by invasive lobular carcinoma (ILC) at 15%, and mixed carcinoma (10%) (Figure-1)

Half of the tumors were Grade II (moderately differentiated) in 20 patients. Grade III (poorly differentiated) tumors were in 14 patients, and Grade I (well-differentiated) tumors in 6 patients. Most had moderate to high aggressiveness (Figure-2)

Out of 40 patients, 24 were estrogen receptor-positive, 20 were progesterone receptor-positive, and 10 were HER2/neu positive, showing more hormone-sensitive breast cancer subtypes (Table-III)

In the study of COL10A1 expression, 45% of patients showed high levels, 35% moderate, and 20% low or no expression.Overall, a significant proportion (80%) had either moderate or high expression, suggesting that COL10A1 may play a biologically relevant role in breast cancer tissue changes (Table-IV).

High COL10A1 expression linked to aggressive tumors; 10 Grade III patients and 8 Grade II patients showed high expression, while Grade II had 10 moderate and Grade I had 4 low expressions (Table-V).

Table-III: Hormone receptor positivity status of participants

Receptor positivity Status	Positive no.(%)
ER (Estrogen Receptor)	24(60.0)
PR (Progesterone Receptor)	20(50.0)
HER2/neu	10(25.0)

Table-IV: COL10A1 expression levels (based on tissue analysis)

Expression Category	no.(%)
High Expression	18(45.0)
Moderate Expression	14(35.0)
Low/Negative Expression	8(20.0)

Table-V: Association between COL10A1 expression and tumor grade

COL10A1 Expression	Grade I (no.)	Grade II (no.)	Grade III (no.)
High	0	8	10
Moderate	2	10	2
Low/Negative	4	2	2

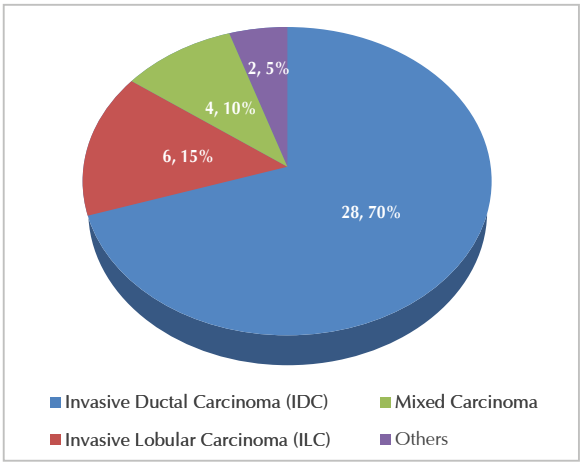

Figure-1: Tumor characteristics (Histopathology)

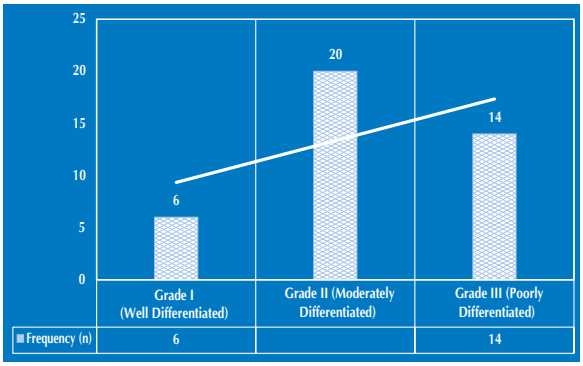

Figure-2: Tumor grade distribution

Discussion:

The present study provides a comprehensive clinicopathological and molecular profile of 40 breast cancer patients. Our analysis revealed that a significant majority of the study population presented with moderate to high-grade tumors and hormone receptor-positive disease, with a notable overexpression of COL10A1, a potential marker of tumor aggressiveness. First, the demographic profile of our cohort, with a mean age of 47.41 years and the largest proportion (47.5%) in the 41-50 year age group, aligns with the global pattern of breast cancer being a disease of middle-aged women, particularly in developing nations where the peak incidence occurs a decade earlier than in Western countries.[9] This underscores the significant health burden of breast cancer in the economically productive age group. Regarding histopathological types, our finding that Invasive Ductal Carcinoma (IDC) was the most prevalent (70%) is consistent with the established literature, which reports that IDC constitutes approximately 70-80% of all breast cancers, making it the most common histological subtype worldwide.[10] This reaffirms the representative nature of our study sample in the broader context of breast cancer pathology.The distribution of tumor grades in our study, with 50% being Grade II and 35% Grade III, indicates a preponderance of moderately to poorly differentiated tumors. This is a critical finding as it correlates with a more aggressive disease course and a potentially worse prognosis. A similar study by[11] also reported a high frequency of Grade II and III tumors in their cohort, highlighting a common clinical challenge in managing these aggressive variants.Our molecular subtyping data showed that 60% of patients were Estrogen Receptor (ER)-positive and 50% were Progesterone Receptor (PR)-positive, while HER2/neu positivity was observed in 25% of cases. This pattern, where hormone-sensitive subtypes are most common, is well-documented. For instance, a large population-based study confirmed that the Luminal A and B subtypes (which are ER/PR-positive) collectively account for the majority of breast cancer cases, which is in direct agreement with our receptor status findings.[12] The most significant finding of our study pertains to the expression of COL10A1. We observed that 80% of the patients exhibited moderate to high expression of this protein. This high prevalence suggests that COL10A1 is not an isolated phenomenon but may play a widespread and biologically relevant role in the tumor microenvironment of breast cancer. This aligns with the growing body of evidence implicating aberrant extracellular matrix remodeling in cancer progression.[13] Furthermore, our data established a strong association between high COL10A1 expression and aggressive tumor characteristics, specifically Grade III tumors. Among the 14 patients with Grade III disease, 10(71.4%) showed high COL10A1 expression. This finding is strongly supported by a study by,[14] which demonstrated that COL10A1 is a key mediator of tumor invasion and metastasis, and its upregulation is a hallmark of poorly differentiated carcinomas across multiple cancer types.The role of COL10A1 in promoting a more aggressive phenotype can be explained by its function in the tumor microenvironment. It is primarily produced by cancer-associated fibroblasts and facilitates tumor cell migration,

invasion, and epithelial-mesenchymal transition. Research by[15] provided mechanistic insight, showing that COL10A1 secretion activates integrin-mediated signaling pathways in cancer cells, ultimately leading to enhanced metastatic potential.The correlation between COL10A1 and high-grade tumors also suggests its potential utility as a prognostic biomarker. Patients with elevated COL10A1 expression may be at a higher risk for disease recurrence and progression. A prior investigation by[16] found that high serum levels of COL10A1 degradation products were independently associated with reduced overall survival in breast cancer patients, reinforcing its prognostic value.From a therapeutic perspective, the overexpression of COL10A1 in aggressive tumors presents a potential novel target. While direct targeting of collagen proteins is challenging, understanding its upstream regulators and downstream effectors could unveil new therapeutic avenues. Preclinical models have shown that silencing COL10A1 expression can significantly reduce tumor growth and metastasis, as evidenced in the work of.[17]

Limitations:

This study has limitations, including a small sample size and a design that cannot assess long-term outcomes such as disease recurrence, metastasis, or survival or causal relationships.

Conclusion:

The present study highlights the emerging role of COL10A1 in breast cancer pathogenesis. The findings suggest that COL10A1 is frequently overexpressed in breast cancer tissues and that its expression is closely associated with tumor aggressiveness and histopathological grade. These observations indicate that COL10A1 may serve as a valuable biomarker for diagnosis and prognosis, providing insight into tumor behavior and potentially guiding personalized therapeutic strategies.

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