



DOI: 10.32768/abc.20218129-36

## COX-2 Expression in Carcinoma of the Breast and Surrounding Non-neoplastic Breast Tissue

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## ARTICLE INFO

**Received:**  
17 November 2020  
**Revised:**  
01 December 2020  
**Accepted:**  
12 December 2020

**Key words:**

Autocrine effect,  
breast Cancer,  
carcinogenesis,  
COX-2 expression,  
paracrine effect

## ABSTRACT

**Background:** Breast carcinoma is the most common malignant tumor and leading cause of cancer related death in women worldwide. Apart from traditional markers, estrogen receptor, progesterone receptor and Her-2neu, which are important for prognostication and staging purposes, a novel marker cyclooxygenase-2 (COX-2) is being studied extensively. We intend to study the spectrum of COX-2 expression in normal breast tissue, ductal carcinoma in situ (DCIS) adjacent to invasive cancer, and in invasive cancer and compare COX-2 expression with histological prognostic parameters and hormone receptor status.

**Methods:** The present study is a prospective study that was conducted in the department of Pathology, SGT Medical College and Hospital, Gurugram (2019-2020). Fifty patients, aged between 21 and 70, suffering from primary breast cancer constituted the study group. Various histological prognostic parameters were assessed. Immunohistochemical profile of the tumor was assessed. COX-2 score was correlated with various clinicopathologic parameters.

**Results:** Among the total of 50 patients suffering from invasive breast carcinoma, 94 percent (47/50) of cases showed the same COX-2 expression level in normal breast epithelium and corresponding tumor areas and this correlation was statistically significant. The correlation between the level of COX-2 expression in tumor and DCIS was highly significant.

**Conclusion:** Inhibition of COX-2 may represent a potential target for preventing breast cancer oncogenesis and as an adjuvant treatment following surgery to reduce local recurrence.

**Introduction**

Breast carcinoma is the most common malignant tumor and leading cause of cancer related death in women worldwide.<sup>1</sup> Its incidence in India is rising and has replaced cancer of cervix as the leading site of cancer.<sup>2</sup> Prognostic factors constitute important tools for the individualization of breast cancer therapy to provide efficient treatment and to spare patients with

excellent low-risk profiles from unwanted side effects of overtreatment.<sup>3</sup>

Apart from traditional markers, estrogen receptor (ER), progesterone receptor (PR) and Her-2neu, which are important for prognostication and staging purpose, a novel marker called cyclooxygenase-2 (COX-2) is being studied extensively. Two isoforms of COX gene have been described: COX-1, a house keeping gene and COX-2, an inducible gene, stimulated by mitogenic and inflammatory causes. COX-2 can be stimulated by oncogenes, growth factors, cytokines and tumor promoters. COX-2 is upregulated in a number of human malignancies: colon, lung, gastric and oesophageal adenocarcinomas.<sup>4</sup>

The role of COX-2 in breast carcinoma has been linked to increased prostaglandin synthesis which

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increases aromatase activity in breast and fat tissue leading to increased estradiol synthesis and development of breast cancer.<sup>5</sup> On the basis of various epidemiologic studies on COX-2 expression, strong evidence has been linked to the use of COX-2 inhibitors as chemo-preventive agent in breast cancer and DCIS lesions. We intend to study the spectrum of COX-2 expression in normal breast tissue, ductal carcinoma in situ (DCIS) adjacent to invasive cancer, and in invasive cancer and compare COX-2 expression with histological prognostic parameters and hormone receptor status.

### Methods

The present study is a prospective study that was conducted in the Department of Pathology, SGT Medical College and University, Gurugram (2019-2020). The ethical approval was waived by institutional review board (SGT IB) as MRM specimens were routinely sent for histopathology and nothing special was done here. Fifty cases of primary breast cancer that underwent radical or modified radical mastectomy constituted the study group. Patients with breast cancer other than primary invasive ductal carcinoma such as lymphoma, sarcoma, stromal tumor, metastases were excluded from the study. Specimens were examined grossly for tumor size, consistency, margin and cut surface along with axillary lymph node status.

Representative blocks were prepared from tumor, normal tissue, area adjacent to tumor, tumor margins, overlying skin, deepest resection margin and axillary lymph nodes. Histopathological diagnosis was established on routine Haematoxylin and Eosin (H&E) stain and various histological prognostic parameters including histologic type, grade and lymph node metastases were assessed. Histologic grading was done by Modified Bloom-Richardson system (MBR) taking into account the scores for tubule formation, nuclear pleomorphism and mitotic count. Histologic grade was assessed by adding up the scores of the three parameters. Lymph node stage in each case was assessed. Using size, MBR histologic grade and lymph node stage, Nottingham prognostic index (NPI) was calculated.

Immunohistochemical profile of the tumor was assessed by subjecting one section each from a representative block of tumor to ER, PR, HER2/neu and COX-2. Immunohistochemical quantification was performed using light microscopy at 400X magnification. IHC was performed by peroxidase-antiperoxidase method. Positive and negative controls were run with each batch of IHC stain.

### *The Interpretation of Immunohistochemical Stains*

#### *ER/PR staining*

Brown diffuse or grainy nuclear staining was taken as positive for ER/PR and assessed by Quick

scoring based on assessment of proportion and intensity.

Score for proportion (PS):

- 0 = no staining
- 1 = <1% nuclei stained
- 2 = 1-10% nuclei stained
- 3 = 11-33% nuclei stained
- 4 = 34-66% nuclei stained
- 5 = 67-100% nuclei stained

Score for intensity (IS):

- 0 = no staining
- 1 = weak staining
- 2 = moderate staining
- 3 = strong staining

The scores were summed to give a maximum of 8. Patients with tumors scoring 2 or less were regarded as ER/PR negative.

#### *HER2/neu staining*

Uniform, intense brown membrane staining of >10% of the tumour cells was taken as positive for HER2/neu.

#### *COX-2 Staining*

Positive cases showed brown cytoplasmic stain. The IHS (Immunohisto-chemical Score) was calculated by combining an estimate of the percentage of immunoreactive cells (quantity score) with an estimate of the staining intensity (staining intensity score), as follows:

- Quantity Score was rated on a scale of 0 to 4, with
- Score 0: 0-5% of cells stained
- Score 1: 6-25% of cells stained
- Score 2: 26-50% of cells stained
- Score 3: 51-75% of cells stained
- Score 4: 76-100% of cells stained

Staining intensity was rated on a scale of 0 to 3, as follows:

- 0: Negative
- 1: Weak
- 2: Moderate
- 3: Strong

When there were multifocal immunoreactivity and significant differences in staining intensities between foci, the average of the least intense and most intense staining was recorded. The raw data was converted to the IHS by multiplying the quantity and staining intensity scores. The scores theoretically ranged from 0 to 12.

Interpretation of IHS scoring was as follows:

- 0 to 3: Negative
- 4 to 8: Moderate
- 9 to 12: Strong Brown

Diffuse or grainy nuclear staining was taken as positive for ER/PR and assessed by Quick scoring



based on assessment of proportion and intensity. Brown membranous staining of Her 2 neu was taken as positive. Immunohistochemical analysis showing uniform, intense membrane staining of >10% of the tumour cells was taken as positive.

COX-2 score was correlated with clinicopathologic parameters including age, tumor size, tumor type, histologic tumor grade, axillary lymph node status, DCIS nuclear grade and NPI along with ER, PR and HER2/neu status. The results obtained were interpreted and correlated statistically.

#### Statistical analysis

The results obtained were interpreted and correlated statistically using all the data obtained, analysed statistically using IBM SPSS statistics for windows, version 20.0. (IBM Corp., Armonk, NY). Mean and standard deviations were calculated. When the data was qualitative, a chi-square test was used to assess the association between these parameters. A p-value <0.05 was taken as significant (S) and p-value <0.01 was taken as highly significant (HS) whereas the p-value of more than 0.05 was taken as non-significant. Correlation of COX-2 IHS with clinicopathological parameters and different areas (normal breast, DCIS and Invasive Carcinoma) was calculated by Spearman rank correlation ( $r_s$ ). It gave a value of ' $r_s$ ' between -1 and +1. The significance of correlation was evaluated using critical values table for Spearman's coefficient of correlation (statistically significant with a  $P \leq 0.05$ ).

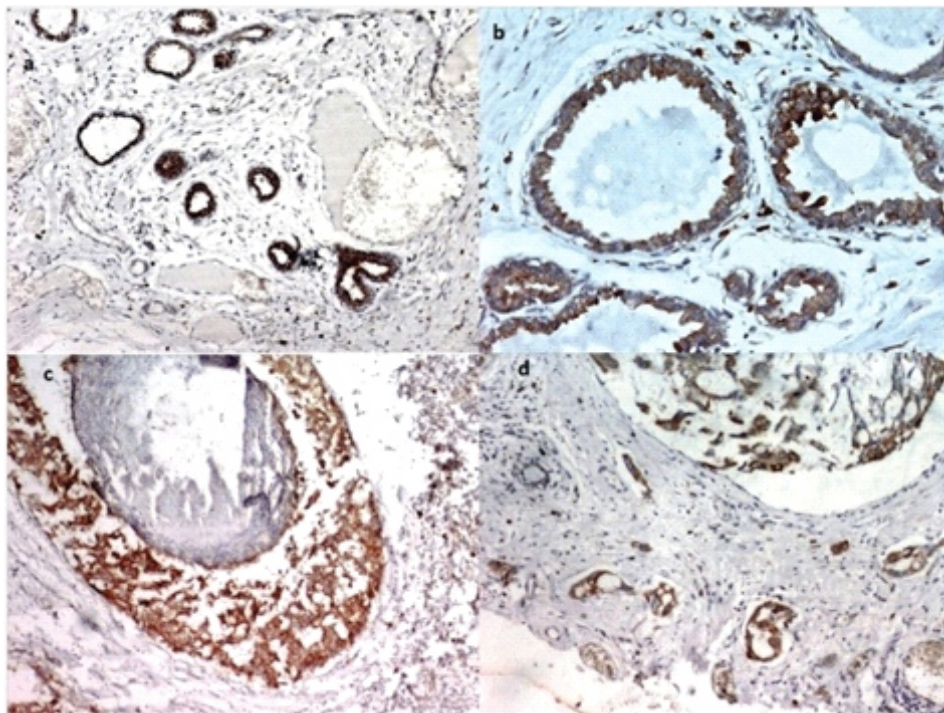
#### Results

A total of 50 patients aged from 21 to 70, suffering

from invasive breast carcinoma participated in the study. Mean age at presentation was 48.22 years. Premenopausal and postmenopausal cases were 38% and 62% respectively. The patients were divided into three groups depending on size (TNM Classification) i.e. < 2cm, 2-5 cm and >5 cm. Seventy eight percent (78%) of cases belonged to 2-5 cm size group.

Histologically, all the patients were infiltrating duct carcinoma (IDC-NOS type) who were graded using Modified Bloom Richardson grading system. Grade II constituted 54% of the cases followed by grade I (32%) and grade III (14%). Lymph node involvement as an important prognostic variable was assessed in all cases and staging was done based on the number of lymph nodes involved. In 42% of the cases, lymph node involvement was not seen (N0), while 30% of the cases were in N1 and 28% of the patients had four or more lymph nodes involvement falling under N2. Fifty six percent of the patients were in moderate prognostic group, 28% in poor and 16% in good prognostic group, respectively.

ER, PR and Her 2 neu status was assessed. Sixty percent of the cases were ER positive and 52% were PR positive. Forty percent of the cases were both ER/PR negative. Only 24% cases had Her 2 neu positivity. COX-2 IHS was separately calculated for normal breast epithelium (10mm away from tumor), DCIS (wherever possible) and tumor tissue. In invasive carcinoma 66% of the cases were moderately positive and 34% were negative for COX-2 expression. None of the cases revealed strong positivity. COX-2 IHS was moderately positive in 72% of normal breast epithelial tissue. DCIS



**Figure 1.** COX-2 expression in normal breast tissue (score-4, intensity-2, IHS-moderate); a) (10X) and; b) (20X); c) COX-2 expression in DCIS. (Score-4, intensity-3, IHS-strong) (10X); d) COX-2 expression in normal breast tissue (score-4, intensity-2, IHS-moderate) and DCIS. (Score-4, intensity-3, IHS-strong) (10X).

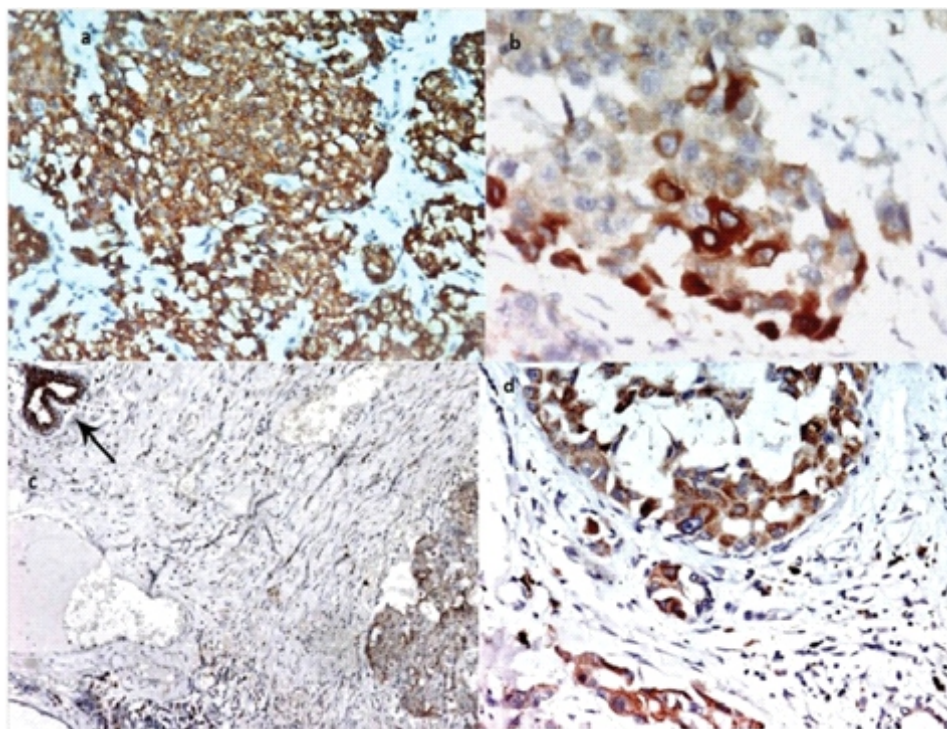


Figure 2. COX-2 expression in invasive breast carcinoma; a) score-4, intensity-1, IHS-moderate (10X) and; b) score-3, intensity-2, IHS-moderate (40X); c) COX-2 expression in invasive breast carcinoma (score-3, intensity-2, IHS-moderate) and normal breast tissue (arrow). (Score-4, intensity-3, IHS-strong) (10X); d) COX-2 expression in invasive breast carcinoma (score-2, intensity-3, IHS-moderate) and DCIS (Score-4, intensity-3, IHS-strong) (20X).

component was seen in 23 cases. Moderate Positive COX-2 IHS score was present in 86% of the DCIS component, while it was negative in 14% of cases.

Ninety four percent (47/50) of cases showed the same COX-2 expression level as normal breast epithelium (Figure 1) and corresponding tumor areas (Figure 2) and this correlation was statistically significant. ( $P < 0.001$ ,  $r_s = 0.869$ )

In our study, 23 cases had both DCIS and Invasive Carcinoma. In 3 cases with negative COX-2 expression in DCIS, the paired invasive cancer lesion was also negative. Conversely, 90% (18/20) of DCIS lesions with moderate COX-2 expression were matched by a similar expression level in paired invasive cancer samples. Only 2 cases with moderate COX-2 expression in DCIS showed negative expression in the corresponding tumor area. The correlation between the level of COX-2 expression in tumor and DCIS was highly significant. ( $r_s = 0.735$ ,  $P < 0.001$ ). In all 23 cases with a DCIS component, COX-2 IHS between normal tissue and DCIS was similar and this correlation was highly significant. ( $P < 0.01$ ,  $r_s = 1.0$ ).

COX-2 IHS was compared with different clinicopathological parameters including age, menopausal status, tumor size, histopathological grade, nodal status, NPI scoring and hormonal receptor status (Table 1). COX-2 expression was statistically insignificant in normal, tumor and DCIS area in relation to age groups, menopausal status, lymph nodal status and hormonal status. COX-2 expression was stronger in T2 pathologic stage rather

than in T3. No significant correlation was seen between COX-2 expression in tumor and DCIS with size of tumor. Positive COX-2 expression was higher in grade I and II groups in tumor and DCIS area ( $P = 0.098$ ). COX-2 expression was statistically significant in DCIS areas and tumor tissue in relation to histopathological grades. COX-2 expression was higher in good and moderate prognostic groups of NPI ( $p$  value = 0.045). However, in poor prognostic group, COX-2 expression was poor. COX-2 expression in tumor was statistically significant in various prognostic groups of NPI while it was insignificant in DCIS areas.

### Discussion

Elevated expression of COX-2 has been established to be a feature of breast cancer. There has been inconsistency in literature regarding the precise significance due to paucity of data on COX-2 expression in normal breast tissue and on the changes in COX-2 expression from normal tissue via ductal carcinoma in situ (DCIS) lesion to invasive cancer. Some studies have found no clinicopathological relevance at all, while others have concluded that COX-2 expression is an important biomarker in invasive breast cancer and pre-cancerous lesions, correlating with poor prognostic features.<sup>6-10</sup> The aim of our study, therefore, was to investigate the significance of COX-2 expression in normal breast tissue, DCIS and invasive breast cancer samples from the same patients.

COX-2 was moderately positive in 66% of the

**Table 1.** Correlation of COX-2 IHS with various clinicopathologic parameters

Clinicopathologic parameters	COX-2 Expression			P(r)=T/N/DCIS
	Tumor(%)	Normal(%)	DCIS(%)	
<b>Tumor size</b>				
<2 cm	12	11	1	0.098(0.237)/0.048(0.281)/0.157(0.305)
2-5 cm	80	83	85	
>5 cm	28	6	14	
<b>Histologic grade</b>				
Grade I	39	38	45	0.098(0.237)/0.048(0.281)/0.011(0.962)
Grade II	51	48	40	
Grade III	10	14	15	
<b>Lymph node status</b>				
N0	45	48	45	0.251(0.166)/0.142(0.211)/2.42(0.182)
N1	33	30	25	
N2	22	22	30	
<b>NPI</b>				
Good	18	20	20	0.045(0.285)/0.0245(0.319)/0.239(0.290)
Moderate	62	60	55	
Poor	20	20	25	
<b>ER</b>				
Positive	63	58	50	0.332(-0.140)/0.971(0.005)/0.610(0.112)
Negative	37	42	50	
<b>PR</b>				
Positive	60	55	50	0.051(-0.278)/0.258(-0.163)/0.610 (0.112)
Negative	40	45	50	
<b>Her 2neu</b>				
Positive	21	22	25	0.53(0.091)/0.067(0.645)/0.305(0.157)
Negative	79	78	75	

cases of tumor, 72% of adjacent normal breast epithelial tissue and 86% of DCIS component. There was no significant difference in COX-2 expression in these groups.

In present study, out of 36 cases with COX-2 positivity in normal tissue, positive COX-2 expression was detected in 33 cases of corresponding tumor areas. Fourteen cases with negative COX-2 expression in normal tissue also showed negative COX-2 expression in corresponding tumor areas. Thus, 94% of cases investigated showed similar COX-2 expression level in normal breast epithelium and the corresponding tumor area in the same patient. The extent of COX-2 expression in normal breast epithelium correlated significantly with that in invasive breast cancer of the same patient. ( $r_s = 0.869$ ,  $P < 0.001$ ).

Published data regarding COX-2 expression in normal breast tissue are conflicting.<sup>6, 8, 11</sup> Consistent with our study, Leo et al. found that in 83% of cases with a negative COX-2 expression in normal breast epithelium, the paired invasive breast cancer lesions were also negative.<sup>8</sup> Conversely, in 95% of cases with a moderate or strong COX-2 expression in normal breast epithelium, this was matched by a moderate or strong COX-2 expression in the invasive breast cancer of the same patient.

However, some studies have reported different results. Half et al. found COX-2 expression in 81% of benign adjacent tissue and described it to be of similar or reduced intensity relative to the malignant tissue within the same tissue sections.<sup>11</sup> Half et al. used reverse transcriptase polymerase chain reaction to detect COX-2 messenger RNA (mRNA). Ranger et al. did not find any COX-2 immunoreactivity in normal breast and adjacent non-cancerous tissue (ANCT).<sup>6</sup> This discrepancy can be partly explained by the paucity of ductal units in normal breast tissue as compared with malignant breast tissue or due to different methods used in the evaluation of the results in different studies (RT-PCR, Immunoblotting).

In a study by Leo et al., there was a statistically significant correlation between the COX-2 expression in DCIS and invasive breast cancer.<sup>8</sup> In 85% of the cases with a negative COX-2 expression in DCIS, the paired invasive cancer lesions were also negative. Conversely, 94% of DCIS lesions with moderate or strong COX-2 expression were matched by a similar expression level in the paired invasive breast cancer samples.

Half et al. showed that within the same tissue sections, COX-2 expression in invasive breast tumors and adjacent DCIS were highly correlated ( $p=0.019$ ).<sup>11</sup> Ranger et al. studied 30 patients with



invasive breast cancer and a significant statistical association was observed between invasive carcinoma and concomitant DCIS lesions ( $p=0.007$ ).<sup>6</sup> Shim et al. studied 64 cases of breast cancer of which 4 cases were composed solely of DCIS, whereas 38 cases of invasive ductal carcinoma contained areas of DCIS.<sup>7</sup> Thirty-two of the 42 cases, including pure DCIS cases and the DCIS component of invasive duct carcinoma (76%), demonstrated COX-2 positivity. Of the cases in which DCIS and invasive carcinoma coexisted, 31 cases showed COX-2 over-expression in both DCIS and invasive components.

Given the high frequency of COX-2 in DCIS area, it can be hypothesized that COX-2 over-expression is involved in the progression to invasive cancer and may be an early event in breast carcinogenesis. But this suggestion needs to be confirmed by further studies.

In the present study, all the cases with a negative COX-2 expression in normal breast epithelium were matched by negative expression in DCIS lesion and all cases with a moderate COX-2 expression in normal breast epithelium coincided with a similar expression in paired DCIS areas. Thus, in all the 23 cases of DCIS, we found a significant correlation between COX-2 expression in DCIS and normal breast epithelium. ( $r_s=1.0, p<0.01$ ).

There was a significant correlation between the COX-2 expression levels in normal breast tissue and DCIS lesion of the same patient. This was in concordance with studies done by Leo et al.<sup>8</sup> and Shim et al.<sup>7</sup> and Boland et al.<sup>12</sup> Our observation that COX-2 is up-regulated in the surrounding epithelial tissue raises the strong possibility that the adjacent normal epithelium is part of the disease process in DCIS, which is further supported by the study of Shim et al., who stated that COX-2 intensity in the normal adjacent epithelium is stronger than in the lesion itself and correlated with DCIS nuclear grade.<sup>7</sup>

In the study, COX-2 expression was correlated with various clinicopathologic parameters including age, menopausal status, tumor size, lymph node status, histological grade, NPI and hormone expression. In the present study, correlation of COX-2 expression with patient's age was statistically insignificant and our observation is in line with various other studies in the literature.<sup>8,9,10,11,13</sup>

COX-2 expression in tumor when compared to different tumor sizes was not statistically significant in our study. This could be due to the small sample size in this study. Tumors with a size range of 2-5 cm were associated with higher expression of COX-2 though it was insignificant. Our findings are in agreement with studies by Leo et al.<sup>8</sup> and Ranger et al.<sup>6</sup> although Ristimaki et al. reported a statistically significant association between COX-2 expression and tumor size.<sup>9</sup>

In the current study, we did not observe a

statistically significant correlation between COX-2 expression and MBR grade in tumor areas, ( $p_t=0.098$ ), but it was significant in DCIS areas ( $p_{dcis}=0.011$ ). Small sample size can also explain the insignificance of COX-2 expression in different grades of invasive carcinoma. Leo et al.<sup>8</sup>, Shim et al.<sup>7</sup> and Ranger et al.<sup>6</sup> did not find any significant association between COX-2 expression and Tumor grade; on the contrary, studies by Ristimaki et al.<sup>9</sup> and Takeshita et al.<sup>10</sup> found a statistically significant correlation between COX-2 expression levels and tumor grades.

The discrepancy in the observation can be partly explained by more cases with a higher grade (grade III) in both studies whereas in our study grade III cases constituted the smallest group. Apart from this, other factors which might have influenced the results could be the number of cases studied and the histological type.

In our study, no correlation was seen between COX-2 expression and lymph node status. This could be because of small sample size in our study. Our observation is supported by Shim et al.<sup>7</sup>, but refuted by Ristimaki et al.<sup>9</sup> and Takeshita et al.<sup>10</sup> who found a statistically significant correlation between COX-2 expression and nodal status among tumor areas. The discrepancy could be partly explained by the small number of cases and different histological types included in the study.

The number of cases with positive COX-2 expression was higher in good and moderate prognostic groups; however, in poor prognostic group, we found less COX-2 expression. COX-2 expression in tumor was statistically significant with prognostic groups ( $p=0.045$ ). None of the studies used NPI as a parameter for studying its correlation with COX-2 expression.

In addition, positive COX-2 expression was seen in both ER/PR positive/negative group and Her2neu positive/negative groups, which was not dependent on hormonal receptor status. On statistical analysis, COX-2 expression was not found to be significant in relation to hormonal receptor status, which was in line with various studies except for some studies which are tabulated below in Table 2.

Most of the literature<sup>6,7,8,10,11,14</sup> on the correlation of COX-2 expression among the tumor areas and hormonal status show that there is no correlation except for Ristimaki et al.<sup>9</sup>, Boland et al.<sup>12</sup> and Perrone et al.<sup>13</sup> who found a significant correlation. This discrepancy could be partly explained by the selection of high grade cases and with different histological types.

To the best of our knowledge, the present study is the largest study comparing COX-2 expression in paired samples of DCIS, invasive breast cancer and adjacent normal breast and establishing a significant correlation amongst the 3 categories. These findings signify that:

**Table 2.** Correlation of cox-2 expression with hormonal receptor status in various studies

Studies (year)	No. of cases	COX-2 Expression in			P value		
		ER Positive (%)	PR Positive(%)	Her neu Positive(%)	ER Positive (%)	PR Positive(%)	Her neu Positive(%)
Ristimaki <i>et al</i> (2002)	1576	33	31	50	<0.0001	<0.0001	<0.0001
Half <i>et al</i> (2002)	57	-	-	-	>0.05	>0.05	>0.05
Shim J <i>et al</i> (2003)	64	67	28	ND	0.273	0.542	ND
Shim V <i>et al</i> (2003)	46	-	-	-	>0.05	>0.05	>0.05
Boland <i>et al</i> (2004)	65	50	ND	79	0.005	ND	0.014
Ranger <i>et al</i> (2004)	30	-	-	-	>0.05	>0.05	>0.05
Perrone <i>et al</i> (2005)	49	86	55	100	>0.05	>0.05	<0.0001
Takeshita <i>et al</i> (2005)	30	55	50	ND	>0.05	>0.05	ND
Leo <i>et al</i> (2006)	39	-	-	-	>0.05	>0.05	>0.05
Present Study (2019)	50	70	40	58	>0.05	>0.05	>0.05

ND= Not Done, -= Number not mentioned in the study

1. COX-2 exerts autocrine and paracrine effects, an observation that has been made earlier too by Shim *et al*, who observed diminishing COX-2 expression with increasing distance from the lesion.<sup>7</sup>

2. Another important and possibly more significant conclusion drawn from our study was that COX-2 intensity in the normal adjacent area was stronger than in the lesion itself and correlated with the DCIS nuclear grade.

These observations support the possibility that adjacent normal epithelium is part of disease process in DCIS and this could be an early event preceding the changes in DCIS and tumor areas.

The limitations which we encountered and which could have affected the final outcome of the study were as follows:

1. The histological types in our study solely comprised infiltrating duct carcinoma (NOS) as per WHO classification whereas other studies included different histological types as their study group.

2. Failure to follow up many of our patients and unavailability of significant clinical details in some cases adversely affected our ability to provide correlative data regarding clinical behavior and survival information.

In conclusion, a statistically significant correlation exists between tumor, adjacent normal epithelium and DCIS, suggesting that COX-2 exerts paracrine effect and is involved in early breast cancer carcinogenesis. Since most infiltrating breast carcinomas are believed to originate from DCIS, the available data suggests that inhibition of COX-2 may represent a potential target for preventing breast cancer oncogenesis and as an adjuvant treatment following surgery to reduce local recurrence. But further studies are mandatory to confirm the findings.

#### Conflict of Interest

The authors declare no conflict of interest.

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