

Cadherin Expression in the Nigerian and United Kingdom Breast Cancer Cases: A Comparison of Clinicopathological and Prognostic Characteristics

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Abstract

Background: The expression of the cadherins have been shown to have both clinicopathological and prognostic significance in breast cancer from different ethnic populations. However, the clinicopathological and prognostic significance of the cadherins expression in Nigerian breast cancer (BC) have hitherto not been determined. The aim of this study was therefore to describe the expression patterns of E- and P-cadherin in Nigerian and United Kingdom (UK) BC cases and to compare the clinicopathological and prognostic significance of the cadherins between the two cohorts.

Methods: Tissue microarray of about 266 formalin-fixed paraffin-embedded Nigerian and 301 UK BC samples with well-characterized clinicopathological indices were subjected to immunohistochemical staining for E- and P-cadherins and other biomarkers. These biomarkers were correlated with the patients' clinicopathological and prognostic data using the appropriate statistical tests on SPSS. A p value of < 0.05 was taken as statistically significant.

Results: A lower rate of E-cadherin expression was found in the Nigerian cohort (29.2%) compared to their UK counterparts (54.8%). However, the rate of P-cadherin expression was similar in both Nigerian (53.4%) and UK (52.9%) series. While E-cadherin expression showed no pathological significance in the Nigerian cases, it was associated with favourable clinicopathological features in the UK cohort. P-cadherin on the other hand was associated with adverse clinicopathological features, including the triple-negative and basal-like BC subtype in both BC populations. However, we found no prognostic significance for either E-cadherin or P-cadherin in both BC cohorts.

Conclusion: While P-cadherin expression is high in both the Nigerian and UK BC cohorts and might therefore function as a biomarker for the basal-like BC, E-cadherin expression was associated with favourable clinicopathological indices in UK, but not in the Nigerian, cohorts.

Keywords: Nigerian and United Kingdom breast cancer; E-cadherin; P-cadherin; Clinicopathological

Abbreviations: BC: Breast Cancer; EMT: Epithelial Mesenchymal Transition; NOS: Not Otherwise Specified; BCSS: Breast Cancer-Specific Survival; DFI: Disease-Free Interval; CK: Cytokeratin; EGFR: Epidermal Growth Factor Receptor; ER: Oestrogen Receptor; PR: Progesterone Receptor; BRCA1: Breast Cancer Antigen 1; HER2: Human Epidermal Growth Receptor 2

Introduction

Tumour cell invasion and metastases are facilitated by the epithelial mesenchymal transition (EMT) which is in turn associated with changes in expression of the different isoforms of cadherin cell adhesion molecules [1-3]. These isoforms which include E-cadherin, N-cadherin, P-cadherin, amongst others, have specific normal tissue expressions [1-3]. For example, E-cadherin is normally expressed in epithelial tissues where it mediates cell-cell adhesions, limits cell motility and establishes apico-basal polarity [1]. N-cadherin is expressed in mesenchymal tissues where it mediates focal adhesion of mesenchymal cells with the extracellular matrix components and cell motility [1,2]. P-cadherin is expressed by myoepithelial cells in which it maintains the myoepithelial cell undifferentiated state which is necessary for orderly differentiation of glandular structures [1,3].

In malignant epithelial tumours such as breast cancer, the EMT is characterized by down-regulation of E-cadherin expression and up-regulation of N-cadherin, or aberrant co-expression of P- and E-cadherins [1-3]. The expression patterns of the cadherins have been shown to have both clinicopathological and prognostic significance in breast cancer from different ethnic populations [1-9]. Specifically, E-cadherin loss in primary breast cancer is associated with high grade tumour and positive lymph node status and confers shorter survival characteristics

on patients [4-8]. Such poor prognostic indices have also been observed in breast cancers with high expression of N- and P-cadherins [1-3,9]. However, the implications of the aberrant expression of the cadherins in the Nigerian breast cancer population have yet to be investigated.

The aim of this study is to determine the clinicopathological and prognostic significance of the cadherin switch in Nigerian women with breast cancer compared to their United Kingdom counterparts. We investigated the expression of E-cadherin and P-cadherin using Tissue Microarray and Immunohistochemistry and compared the clinicopathological features and survival characteristics of E- and P-cadherin expression between the Nigerian and the United Kingdom cases.

Materials and Methods

The Reporting Recommendations for Tumour Markers Prognostic Studies criteria were followed in this study [10]. Ethical approval was obtained both from the Medical Advisory Committee of the Olabisi Onabanjo University Teaching Hospital and by the Nottingham Research Ethics Committee 2.

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Received June 09, 2016; **Accepted** June 19, 2016; **Published** June 25, 2016

Citation: Agboola AO, Ebili HO, Iyawe VO, Banjo AAF, Salami BS, et al., (2016) Cadherin Expression in the Nigerian and United Kingdom Breast Cancer Cases: A Comparison of Clinicopathological and Prognostic Characteristics. *Surgery Curr Res* 6: 271. doi:[10.4172/2161-1076.1000271](https://doi.org/10.4172/2161-1076.1000271)

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Patients

The Nigerian and United Kingdom cohorts used in this study comprised those that were described in previous studies [11-14].

Tissue microarray construction

Tissue microarray was constructed from formalin-fixed, paraffin-embedded breast cancer samples as previously described [11-14].

Immunohistochemical methods

Immunohistochemical staining of the tissue microarray slides followed previously described methods [11,12]. The immunohistochemical expression of the EMT biomarkers E- and P-cadherin was sought in the Nigerian breast cancer cases. The basal phenotype markers, Ki-67, p53 and BRCA1 were included to study their association with the cadherins. Positive and negative controls for each marker were included in the experiments. A proportion of UK grade-matched cases were used to compare the cadherin expression in the Nigerian series.

The E-cadherin was scored following the semi-quantitative Histochemical score (H-score) method which was described by McCarty et al. [15], where the intensity of staining and percentages of the stained cells were taken into consideration, with a minimum of zero and maximum of 300 scores. In addition, the scoring of the BRCA1, p53, Ki-67, other components of basal phenotype was as done in the previous studies [11-14].

Statistical analyses

Statistical Analyses was performed using SPSS version 16. The association between the cadherin markers expression and categorical clinicopathological variables was examined using the chi-square test. Analysis of survival characteristics of the cadherin biomarkers was analysed using Kaplan–Meier and Log-rank tests. Multivariate analysis was performed using Cox Regression Analysis. A two-sided P-value of <0.05 was considered to be statistically significant.

Results

Staining characteristics of E- and P-cadherin

The expressions of E- and P-cadherins were mainly detectable in the cytoplasm with some membranous staining of the invasive tumour cells (Figure 1). Based on the histogram distributions of scores, an H-score of ≥ 100 was taken as positive staining for E-cadherin, while a score of ≥ 10 was considered positive for P-cadherin expression. Using these cut off points 66/226 (29.2%) and 165/301 (54.8%) of the Nigerian and UK breast cancer cases respectively showed positive expression of E-cadherin, while 142/266 (53.4%) and 138/261 (52.9%) showed positive expression of P-cadherin in the Nigerian and UK cohorts respectively.

Clinicopathological and prognostic significance of E- and P-cadherin expression in the Nigerian versus the United Kingdom breast cancer cases

The expression of E- and P-cadherin was compared between the Nigerian breast cancer cohorts and their United Kingdom counterparts. The results showed that the UK cases significantly had more cases expressing E-cadherin than the Nigerian cohorts (54.8% vs 29.2%; $p < 0.001$). However, there was no significant difference in P-cadherin expression between the two cohorts.

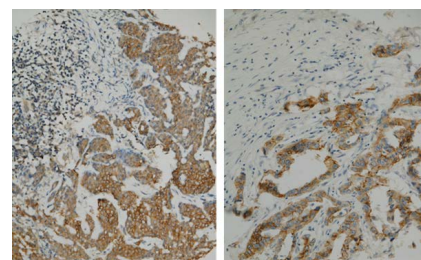


Figure 1: Photomicrograph of breast cancer section showing E-cadherin (A) and P-cadherin (B) immunoreactivity. Magnification x20.

Furthermore, while there was no significant association between the clinicopathological features and E-cadherin in the Nigerian cohorts, P-cadherin expression was significantly associated with menopausal status ($p = 0.04$) and tumour tubular differentiation ($p = 0.02$) (Tables 1 and 2).

In the UK series, the tumours that expressed E-cadherin were more of lobular histological type ($p < 0.001$), were smaller than 2cm in diameter ($p < 0.003$), had reduced tendency for vascular invasion ($p < 0.02$) and better differentiated tubules compared to those with reduced or loss of E-cadherin expression ($p < 0.001$). However, there was no significant correlation between the age of the women, menopausal status, lymph node involvement, vascular invasion, tumour size and E-cadherin expression (Table 1). P-cadherin-expressing tumours were more likely invasive ductal carcinoma NOS ($p = 0.02$), had poorer tubule formation ($p < 0.001$) and marked nuclear pleomorphism ($p = 0.006$) than tumours with reduced or no P-cadherin expression (Table 2).

E- and P-cadherin expression did not individually show any associations with breast cancer-specific survival (BCSS) or disease-free interval (DFI) in both the Nigerian and British cohorts (Figure 2).

Relationship between E- and P-cadherin and other biomarker expression

E-cadherin expression in the Nigerian breast cancer cohort did not show any associations with the tested biomarkers, including CK5/6, CK 14, EGFR, ER, PR, PIK3CA, p53, MUC1, BRCA1 and Ki-67 (Table 3). Furthermore, E-cadherin expression showed no association with P-cadherin ($p = 0.23$). P-cadherin expression was associated with BRCA 1 loss ($p = 0.005$), CK5/6 expression ($p = 0.007$), EGFR expression (0.02), ER loss (0.004), PR loss ($p = 0.004$), basal-like phenotype ($p = 0.025$), PIK3CA expression ($p = 0.02$), p53 over-expression ($p = 0.01$) and MUC1 expression ($p = 0.02$) (Table 4).

In the UK series, E-cadherin expression had a direct association with ER ($p = 0.02$) and HER2 ($p = 0.03$) expression and the Luminal A molecular subtype ($p < 0.001$) of breast cancer and an inverse association with the triple-negative subtype ($p = 0.002$) (Table 3). P-cadherin expression show significant direct associations with CK 5/6 ($p < 0.001$), CK 14 ($p = 0.008$) and EGFR ($p < 0.001$) expression as well as basal-like ($p < 0.001$) and triple-negative ($p < 0.001$) breast cancer subtypes; and an inverse association with ER and PR expression. Like in the Nigerian series, P- and E-cadherin expression showed no association ($p = 0.58$) (Table 4).

E-cadherin and P-cadherin subsets revealed no new clinicopathological or biomarker expression information

We hypothesized that stratifying the breast cancer cases into cadherin expression subsets (Ecad-low, Ecad-high, Pcad-low and

Nigerian BC cohort					UK BC cohort				
Variables	E-cadherin expression		X ² value	p_value	Variables	E-cadherin expression		X ² value	p_value
	Negative	Positive				Negative	Positive		
Age (years) ≤ 50 > 50	106 (66.7) 53 (33.3)	43 (65.2) 23 (34.8)	0.048	0.82	Age (years) ≤ 50 > 50	45 (33.1) 91 (66.9)	51 (31.1) 113 (68.9)	0.135	0.713
Menopausal Pre Post	111 (69.8) 48 (30.2)	42 (63.6) 24 (36.4)	0.817	0.36	Menopausal Pre Post	53 (39.0) 83 (61.0)	60 (36.6) 104 (63.4)	0.180	0.671
Sizes (cm) ≤ 2 > 2	12 (7.5) 147 (92.5)	7 (10.6) 59 (89.4)	0.564	0.45	Sizes (cm) ≤ 2 > 2	53 (39.0) 83 (61.0)	93 (56.4) 72 (43.6)	9.029	0.003
Lymph node involvement Negative Positive	12 (2.5) 147 (92.5)	5 (7.6) 61 (92.4)	0.001	0.99	Lymph node involvement Negative Positive	83 (61.0) 53 (39.0)	97 (58.8) 68 (41.2)	0.156	0.693
Vascular Invasion Negative Positive	126 (79.2) 33 (20.8)	49 (74.2) 17 (25.8)	0.675	0.41	Vascular Invasion Negative Positive	50 (36.8) 86 (63.2)	83 (50.6) 81 (49.4)	5.775	0.02
Tumour Type Typical medullary Atypical medullary Tubular Lobular Ductal /NST Mucinous Tubulolobular Lobular mixed Tubular mixed	0 (0.0) 0 (0.0) 2 (1.3) 3 (1.9) 134 (84.3) 5 (3.1) 1 (0.6) 2 (1.3) 12 (7.5)	6 (1.5) 2 (3.0) 0 (0.0) 1 (1.5) 60 (90.9) 0 (0.0) 0 (0.0) 0 (0.0) 2 (3.0)	13.182	0.10	Tumour Type Typical medullary Atypical medullary Tubular Lobular Ductal NST Tubulolobular Lobular mixed Tubular mixed Mixed NST Others	6 (4.5) 0 (0.0) 32 (25.4) 57 (42.5) 1 (0.7) 11 (8.2) 11 (8.2) 2 (1.5) 9 (6.7) 3 (2.2)	2 (1.2) 3 (1.8) 5 (3.0) 113 (68.9) 1 (0.6) 3 (1.8) 32 (19.5) 0 (0.0) 3 (1.8) 2 (1.2)	62.788	< 0.001
Mitotic Figure Low Moderate High	101 (63.5) 37 (23.3) 21 (13.2)	41 (62.1) 13 (19.7) 12 (18.2)	1.069	0.58	Mitotic figure Low Moderate High	57 (42.9) 33 (24.8) 43 (32.3)	56 (33.9) 53 (32.1) 56 (33.9)	2.965	0.227
Nuclear pleomorphism Small regular uniform cells Moderate increase in size and variability Marked variability	1 (0.6) 58 (36.5) 100 (62.9)	0 (0.0) 22 (33.3) 44 (66.7)	0.649	0.72	Nuclear pleomorphism Small regular uniform cells Moderate increase in size and variability Marked variability	0 (0.0) 74 (55.6) 59 (44.4)	2 (1.2) 66 (40.0) 97 (58.8)	8.374	0.02
Tubule Formation > 75% 10-75% < 10%	1 (0.6) 8 (5.0) 150 (94.3)	0 (0.0) 4 (6.1) 62 (93.9)	0.509	0.77	Tubule Formation > 75% 10-75% < 10%	0 (0.0) 28 (21.1) 105 (78.9)	6 (3.6) 71 (43.6) 87 (52.7)	23.887	< 0.001

Table 1: Clinicopathological features of E-cadherin expression in Nigerian and UK BC cases.

Pcad-high) may show subset(s) with new clinicopathological and prognostic information in the Nigerian BC cases compared to their UK counterparts. However, in each of the subsets defined no new information was revealed with respect to the previously found difference in clinicopathological and molecular features between Nigerian and UK breast cancer cases. E- and P-cadherin expressions did not define clinically useful subsets of breast cancer cases.

Discussion

To the best of our knowledge this is the first study that has investigated the clinicopathological significance of the cadherin expression in Nigerian breast cancer cases in comparison to UK cases. While the 54.8% E-cadherin expression rate in the UK cases falls within the 46-75.3% rate that has been found in other studies, the 29.2% rate found in the Nigerian cohort is significantly lower [4-8,16]. This perhaps is a reflection of the fact that over 90% of the Nigerian breast cancer cases in this study are in the advance stage as adjudged by lymph node metastases. E-cadherin loss has previously been associated with advance stage breast cancer [8]. In contrast, the proportion of the UK cases in advance stage is only 40%.

P-cadherin, on the other hand, is expressed in 20-71% of invasive breast cancer, within which the 52.9% and 53.4% rates we found for our cohorts fall [1,3,9]. We also found no association between the expressions of E- and P-cadherin, an indication that their expressions do not have mutually exclusivity in breast cancer progression and that the cadherin switch includes intermediate states with complex expression patterns of the cadherins [1,3,9].

E-cadherin loss in breast cancer has been associated with adverse clinicopathological characteristics in breast cancer from several populations studied [4-6]. We found this to be the case in our UK cohort of breast cancer in which E-cadherin loss was associated with larger tumours, increased tendency for vascular invasion and poor tubular differentiation. However, E-cadherin expression was not associated with any clinicopathological feature in the Nigerian breast cancer series, although the number of breast cancer cases with lymph node involvement, higher nuclear pleomorphism, larger size and poor tubular differentiation were higher in the E-cadherin-negative than the E-cadherin-positive groups. Similar to our finding, Brzozowska et al. and Younis et al. in their studies found no association between E-cadherin loss and clinicopathological indices [7,8]. It is worthy

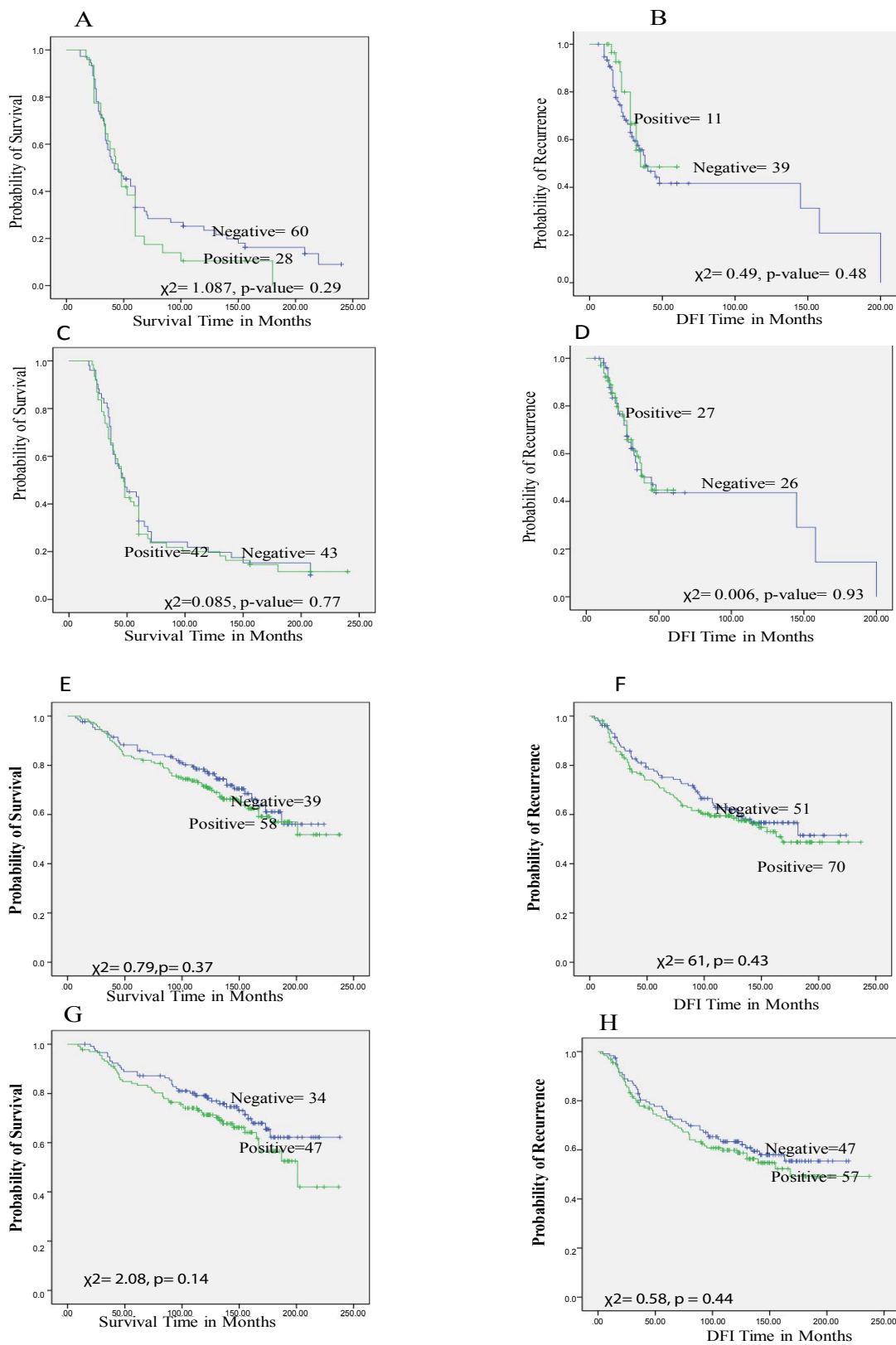


Figure 2: A and B. E-cadherin expression in relation to BCS and DFI in Nigeria series **C and D.** P-cadherin expression in relation to BCS and DFI in Nigeria series **E and F.** E-cadherin expression in relation to BCS and DFI in the UK series **G and H.** P-cadherin expression in relation to BCS and DFI in in UK series.

Nigerian BC cohort					UK BC cohort				
Variables	P-cadherin expression		X ² value	p_value	Variables	P-cadherin expression		X ² value	p_value
	Negative	Positive				Negative	Positive		
Age (years) ≤ 50 > 50	65 (63.7) 37 (36.3)	79 (65.3) 42 (34.7)	0.05	0.80	Age (years) ≤ 50 > 50	30 (24.6) 92 (75.4)	54 (39.1) 84 (60.9)	6.26	0.01
Menopausal Pre Post	63 (61.8) 39 (38.2)	90 (74.4) 31 (25.6)	4.09	0.04	Menopausal Pre Post	42 (34.4) 80 (65.6)	57 (41.3) 81 (58.7)	1.29	0.25
Sizes (cm) ≤ 2 > 2	12 (11.8) 90 (88.2)	7 (5.8) 114 (94.2)	2.53	0.11	Sizes (cm) ≤ 2 > 2	64 (52.0) 59 (48.0)	60 (43.5) 78 (56.5)	1.90	0.16
Lymph node involvement Negative Positive	12 (11.8) 90 (88.2)	9 (7.4) 112 (92.6)	1.21	0.27	Lymph node involvement Negative Positive	72 (58.5) 51 (41.5)	82 (59.4) 56 (40.6)	0.02	0.88
Vascular Invasion Negative Positive	73 (71.6) 29 (28.4)	91 (75.2) 30 (24.8)	0.37	0.54	Vascular Invasion Negative Positive	58 (47.5) 64 (52.5)	58 (42.0) 80 (58.0)	0.79	0.37
Tumour Type Atypical medullary Tubular Lobular Ductal /NST Mucinous Tubulolobular Lobular mixed Tubular mixed Mixed NST Others	1 (1.0) 1 (1.0) 2 (2.0) 88 (86.3) 3 (2.9) 1 (1.0) 0 (0.0) 6 (5.9) 0 (0.0) 0 (0.0)	1 (0.8) 1 (0.8) 1 (0.8) 109 (90.1) 0 (0.0) 0 (0.0) 3 (2.5) 6 (5.0) 0 (0.0) 0 (0.0)	8.01	0.33	Tumour Type Atypical medullary Tubular Lobular Ductal NST Mucinous Tubulolobular Lobular mixed Tubular mixed Mixed NST Others	1 (0.8) 3 (2.5) 22 (18.0) 61 (50.0) 1 (0.8) 6 (4.9) 18 (14.8) 1 (0.8) 7 (5.7) 0 (0.0)	7 (5.1) 0 (0.0) 10 (7.2) 91 (65.9) 1 (0.7) 5 (3.6) 17 (12.3) 1 (0.7) 4 (2.9) 2 (1.4)	21.95	0.02
Mitotic Figure Low Moderate High	66 (64.7) 24 (23.5) 12 (11.8)	75 (62.0) 24 (19.8) 22 (18.2)	1.91	0.38	Mitotic figure Low Moderate High	4 (3.3) 45 (37.2) 72 (59.5)	2 (1.5) 41 (29.9) 94 (68.6)	2.787	0.248
Nuclear pleomorphism Small regular uniform cells Moderate increase in size and variability Marked variability	0 (0.0) 37 (36.3) 65 (63.7)	0 (0.0) 37 (30.6) 84 (68.4)	0.81	0.36	Nuclear pleomorphism Small regular uniform cells Moderate increase in size and variability Marked variability	2 (1.7) 66 (54.6) 53 (43.8)	0 (0.0) 52 (38.0) 85 (62.0)	10.128	0.006
Tubule Formation > 75% 10-75% < 10%	0 (0.0) 1 (1.0) 101 (99.0)	2 (2.5) 9 (7.4) 108 (90.1)	8.14	0.02	Tubule Formation > 75% 10-75% < 10%	56 (46.3) 37 (30.6) 28 (23.1)	40 (29.2) 32 (23.4) 65 (47.4)	16.822	< 0.001

Table 2: Clinicopathological features of P-cadherin expression in Nigerian and UK BC cases.

of note that the cohorts used in the aforementioned studies, like our Nigerian cohort, had disproportionate amounts of E-cadherin-positive cases – 75.3% and 72% respectively- and small sample sizes; and these could have precluded meaningful statistical analyses and obscured the actual significance of E-cadherin loss in these BC populations.

P-cadherin expression, on the other hand, was found to be associated with features of high tumour grades in both the Nigerian and UK breast cancer cohorts; and with and postmenopausal status in the Nigeria cohort and invasive ductal carcinoma NOS in the UK cohort. P-cadherin expression has similarly been reported by other studies to show an association with high tumour grades, age at diagnosis and tumour histological subtype [1,3,9]. Other clinicopathological indices which have been shown to correlate with P-cadherin expression but which we did not find in either of our breast cancer cohorts include lymph node metastases [1,3,9].

With respect to biomarker expression, while E-cadherin expression showed no association with any of the biomarker tested in the Nigerian cohort, it shows associations with ER and HER2 expression and the

Luminal A and the triple-negative molecular subtype of breast cancer in the UK breast cancer series. The association between breast cancer subtypes biomarkers and E-cadherin expression in the UK cohort is in concordance findings in other studies, but contrasts with the absence of any associations in the Nigerian series, as well as the Brzozowska et al. and Younis et al. studies [5,7,8]. This lack of pathobiological significance of E-cadherin expression in the Nigerian series may represent another difference in tumour biology between Nigerian and UK breast cancer cases. On the other hand, it may be reflective of the disproportionate representation of E-cadherin-positive tumor in the Nigerian cohort (only 29%) used in this study. Further studies in which E-cadherin-positive and -negative are about equally represented in the sample cohort are probably needed to clarify the significance of E-cadherin expression in the Nigerian breast cancer cases.

P-cadherin expression has been associated with the features of basal-like subtype of breast cancer, including ER loss, PR loss, EGFR expression and CK 5/6 and CK14 expression, p53 over-expression

Nigerian BC cohort					UK BC cohort				
Variables	E-cadherin expression		X ² value	p_value	Variables	E-cadherin expression		X ² value	p_value
	Negative	Positive				Negative	Positive		
BRCA1 Negative Positive	104 (81.9) 23 (18.1)	37 (68.5) 17 (31.5)	3.93	0.05	BRCA1 Negative Positive	23 (20.0) 92 (80.0)	20 (14.4) 119 (85.6)	1.409	0.235
CK5/6 Negative Positive	85 (63.4) 49 (36.6)	29 (55.8) 23 (44.2)	0.92	0.33	CK5/6 Negative Positive	116 (86.6) 18 (13.4)	147 (89.6) 17 (10.4)	0.669	0.413
CK14 Negative Positive	76 (58.9) 53 (41.1)	32 (60.4) 21 (39.6)	0.03	0.85	CK14 Negative Positive	119 (91.5) 11 (8.5)	150 (92.0) 13 (8.0)	0.023	0.880
Classification Basal HER-2 Lum A Lum B Uncl	32 (20.1) 20 (12.6) 28 (17.6) 5 (3.1) 14 (8.8)	18 (27.3) 11 (16.7) 12 (18.2) 3 (4.5) 6 (9.1)	4.42	0.49	Classification Basal HER-2 Lum A Lum B Uncl	15 (11.3) 5 (5) 97 (72.9) 3 (2.3) 13 (9.8)	12 (7.5) 9 (5.6) 125 (78.1) 13 (8.1) 1 (0.6)	19.21	< 0.001
ER Negative Positive	110 (75.3) 36 (24.7)	43 (69.4) 19 (30.6)	0.80	0.37	ER Negative Positive	35 (25.9) 100 (74.1)	24 (14.7) 139 (85.3)	5.83	0.02
EGFR Negative Positive	88 (68.8) 40 (31.2)	30 (62.5) 18 (37.5)	0.61	0.43	EGFR Negative Positive	105 (86.8) 16 (13.2)	121 (80.1) 30 (19.9)	2.11	0.14
HER_2 Negative Positive	116 (81.7) 26 (18.3)	45 (73.8) 16 (26.2)	1.63	0.20	HER_2 Negative Positive	127 (94.1) 8 (5.9)	141 (86.5) 22 (13.5)	4.67	0.03
KI_67 Negative Positive	20 (14.5) 118 (85.5)	14 (24.6) 43 (75.4)	2.84	0.09	KI_67 Negative Positive	40 (38.1) 65 (61.9)	42 (30.2) 97 (69.8)	1.66	0.19
Mucin1 Negative Positive	60 (48.4) 64 (51.6)	22 (47.8) 24 (52.2)	0.004	0.94	Mucin1 Negative Positive	15 (12.7) 103 (87.3)	12 (8.9) 123 (91.1)	0.96	0.33
P_cad Negative Positive					P_cad Negative Positive	52 (45.2) 63 (54.8)	71 (48.6) 75 (51.4)	0.30	0.58
PGR Negative Positive	95 (76.0) 30 (24.0)	42 (75.0) 14 (25.0)	0.02	0.88	PGR Negative Positive	54 (40.0) 81 (60.0)	62 (37.8) 102 (62.2)	0.15	0.69
p53 Negative Positive	40 (34.8) 75 (65.2)	22 (37.3) 37 (62.7)	0.10	0.74	p53 Negative Positive	104 (77.0) 31 (23.0)	117 (72.2) 45 (27.8)	0.89	0.34
Triple Negative No Yes	61 (50.4) 60 (49.0)	33 (55.0) 27 (45.0)	0.33	0.56	Triple Negative No Yes	106 (78.5) 29 (21.5)	150 (91.5) 14 (8.5)	10.07	0.002

Table 3: Correlation E-cadherin and other biomarker expression in Nigerian and UK BC cases.

and BRCA1 loss [1,3]. Furthermore, it has been demonstrated that P-cadherin expression is a more sensitive marker for the basal-like breast cancer subtype than CK 5/6 and EGFR [3]. In line with the strong association between P-cadherin and basal-like breast cancer subtype this study demonstrated an association between the basal-like breast cancer and ER and PR loss, CK 5/6, CK14, p53 and EGFR expression in both the Nigerian and UK breast cancer cohorts. Furthermore, we demonstrated that P-cadherin was associated with BRCA1 loss in the Nigerian, but not in the UK, breast cancer cohort. This is probably due to the significantly higher rate of BRCA 1-deficient basal-like cancer in the Nigerian cohort relative to the UK cases [11,17].

P-cadherin has also been associated with the invasive potentials of breast cancer. For example, P-cadherin has been demonstrated to induce increased motility and invasiveness of breast cancer cells in association with the epithelial mesenchymal transition [1,3,9]. In this study we showed an association between P-cadherin and MUC1 expression, in the Nigerian series, but not in the UK cohort. Schroeder et al. reported that MUC1 expression is associated with breast cancer cell invasion and metastasis. In that study it was shown that MUC1 interacts with β -catenin both *in vitro* and in clinical breast cancer to promote cell

invasion and metastases [18]. The association between P-cadherin and MUC1 expressions in the Nigerian cohort suggests that MUC1 expression may be important in cellular invasion and metastases in at least a subset of P-cadherin-positive Nigerian breast cancer cohort.

In contrast to many other studies, we did not find any prognostic significance for both E-cadherin and P-cadherin expression either in the Nigerian or the UK cases [1,3,5-7,9]. Furthermore, we did not find any association between prognostic marker Ki-67 and either P-cadherin or E-cadherin in both breast cancer populations [12].

The high rate of P-cadherin expression in both breast cancer populations may have therapeutic significance. Albergaria et al. showed that P-cadherin silencing in breast cancer cells inoculated in mice inhibited the growth of cancer *in vivo* [3]. Furthermore, a novel and highly selective human monoclonal antibody (PF-03732010) has been developed against P-cadherin and has demonstrated remarkable anti-tumour and anti-metastatic activities against P-cadherin-expressing tumours in preclinical trials [19]. Such therapy may be especially important in the triple-negative breast cancer subtype which currently lack targeted therapy.

Nigerian BC cohort					UK BC cohort				
Variables	P-cadherin expression		X ² value	p_value	Variables	P-cadherin expression		X ² value	p_value
	Negative	Positive				Negative	Positive		
BRCA1 Negative Positive	53 (70.7) 22 (29.3)	91 (87.5) 13 (12.5)	7.85	0.005	BRCA1 Negative Positive	18 (16.4) 92 (83.6)	24 (18.3) 107 (81.7)	0.15	0.69
CK5/6 Negative Positive	58 (68.2) 27 (31.8)	54 (49.1) 56 (50.9)	7.18	0.007	CK5/6 Negative Positive	118 (97.5) 3 (2.5)	113 (81.9) 25 (18.1)	16.34	< 0.001
CK14 Negative Positive	36 (51.4) 34 (48.6)	59 (59.6) 40 (40.4)	1.11	0.29	CK14 Negative Positive	117 (96.7) 4 (3.3)	120 (87.6) 17 (12.4)	7.12	0.008
Classification Basal HER-2 Lum A Lum B Uncl	18 (17.6) 9 (8.8) 21 (20.8) 5 (4.9)	40 (33.1) 15 (12.4) 17 (14.0) 2 (1.7)	10.07	0.07	Classification Basal HER-2 Lum A Lum B Uncl	1 (0.8) 2 (1.7) 107 (88.4) 8 (6.6)	26 (19.1) 8 (5.9) 86 (63.2) 5 (3.7)	33.53	< 0.001
ER Negative Positive	57 (63.3) 33 (36.7)	91 (81.3) 21 (18.7)	8.20	0.004	ER Negative Positive	6 (4.9) 116 (95.1)	47 (34.3) 90 (65.7)	34.24	< 0.001
EGFR Negative Positive	58 (76.3) 18 (23.7)	60 (59.4) 41 (40.6)	5.5	0.02	EGFR Negative Positive	109 (90.8) 11 (9.2)	108 (78.3) 30 (21.7)	7.59	0.006
HER_2 Negative Positive	71 (83.5) 14 (16.5)	82 (79.6) 21 (20.4)	0.47	0.49	HER_2 Negative Positive	112 (91.8) 10 (8.2)	124 (90.5) 13 (9.5)	0.13	0.71
KI_67 Negative Positive	19 (22.4) 66 (77.6)	17 (15.2) 95 (84.8)	1.66	0.19	KI_67 Negative Positive	32 (32.7) 66 (67.3)	33 (28.9) 81 (71.1)	0.34	0.56
Mucin1 Negative Positive	44 (57.1) 33 (42.9)	39 (39.4) 60 (60.6)	5.50	0.02	Mucin1 Negative Positive	9 (8.0) 104 (92.0)	17 (13.3) 111 (86.7)	1.76	0.18
E_cad Negative Positive	57 (74.0) 20 (26.0)	57 (65.5) 30 (34.5)	1.395	0.23	E_cad Negative Positive	52 (42.3) 71 (57.7)	63 (45.7) 75 (54.3)	0.30	0.58
PGR Negative Positive	53 (66.3) 27 (33.7)	83 (84.7) 15 (15.3)	8.31	0.004	PGR Negative Positive	32 (26.0) 91 (74.0)	71 (51.8) 66 (48.2)	18.04	< 0.001
p53 Negative Positive	29 (43.3) 38 (56.7)	24 (24.7) 73 (75.3)	6.22	0.01	p53 Negative Positive	108 (90.0) 12 (10.0)	83 (60.1) 55 (39.9)	29.75	< 0.001
Triple Negative No Yes	45 (56.3) 35 (43.7)	41 (44.6) 51 (55.4)	2.34	0.13	Triple Negative No Yes	118 (96.7) 4 (3.3)	101 (73.2) 37 (26.8)	26.99	< 0.001

Table 4: Correlation P-cadherin and other biomarker expression in Nigerian and UK BC cases.

In conclusion, we have shown for the first time that while P-cadherin is associated with the basal-like breast cancer in both Nigerian and UK breast cancer cases, E-cadherin expression was associated with the luminal A and HER2 breast cancer subtypes in the UK cases but showed no pathobiological significance in the Nigerian cohorts.

Acknowledgement

The authors wish to acknowledge the efforts of the technical staff of the Histopathology Department, Olabisi Onabanjo University Teaching Hospital Sagamu, Nigeria, and University of Nottingham City Hospital towards the completion of this study.

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Citation: Agboola AO, Ebili HO, Iyawe VO, Banjo AAF, Salami BS, et al., (2016) Cadherin Expression in the Nigerian and United Kingdom Breast Cancer Cases: A Comparison of Clinicopathological and Prognostic Characteristics. *Surgery Curr Res* 6: 271. doi:[10.4172/2161-1076.1000271](https://doi.org/10.4172/2161-1076.1000271)

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