

## Expression of P53 and PTEN in Correlation with some Clinical and Pathological Features in Breast Cancer of Sudanese Patients

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### Abstract

**The goal** of our study was to determine the expression and phosphorylation of PTEN at residues Ser380/Thr382/383, as well as the nuclear expression of p53 in Sudanese patients with breast cancer in association with clinicopathological aspects of breast cancer.

**Methods and Results:** This retrospective, descriptive study was carried out in Wad-Madani, Gezira state in Sudan, from January 2015 to August 2016. A total of 179 biopsies were taken at random from patients with breast lesions. Two blocks were obtained for each patient. One came from a malignant lesion (Group A), whereas the other came from the margin adjacent to healthy tissue (Group B). Immunohistochemistry and immunofluorescent histochemistry were performed on two separate slides. We found a statistically significant difference in the frequency of immunohistochemical expression of p53 and phosphorylation of PTEN between the cancerous breast tissue and adjacent normal tissue. P53 and PTEN exhibited a significant relationship with each other and the grade of tumor, indicating their importance in the aggressiveness of breast lesions. It should also be emphasized that there is an association between p53 expression and lymph node metastasis, which indicates the involvement of p53 mutation in the metastasis of breast cancer. (**International Journal of Biomedicine. 2023;13(1):62-68.**)

**Keywords:** PTEN • p53 • breast cancer • immunohistochemistry

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### Abbreviations

**DFS**, dermatofibrosarcoma; **DCI**, ductal carcinoma in situ; **FHC**, fibrous histiocytoma; **IDC**, invasive ductal carcinoma; **ILC**, invasive lobular carcinoma; **PD**, Paget's disease.

### Introduction

Breast cancer<sup>(1)</sup> is the most common female malignancy and the second leading cause of mortality in women worldwide. In addition to its heterogeneity, BC incidence is increasing

globally, putting a financial strain on both developed and developing countries.<sup>(2,3)</sup> Many risk factors, including genetic predisposition, have been linked to the etiology of breast cancer,<sup>(4)</sup> including previous history of breast tumors in the same person or in his/her family<sup>(5)</sup> or even malignancies other

than breast tumors,<sup>(6)</sup> as well as levels of hormones over a lifetime (e.g., estrogen increase and decrease cycle, hormone replacement treatment),<sup>(7)</sup> which are raising the possibility of breast cancer. Moreover, physical inactivity, obesity, and alcohol drinking all contribute to an elevated risk of breast cancer.<sup>(8,9)</sup>

Economically developing countries, like Sudan, account for over 60% of all breast cancer fatalities worldwide.<sup>(10)</sup> Breast cancer is a serious issue in Sudan, where it is characterized by early onset, late presentation, and poor resources. However, screening for high-risk individuals is inexpensive.<sup>(11)</sup>

The tumor protein p53 (p53) is the primary regulator of human genome stability through cell cycle regulation. The most common genetic alteration in breast cancer is mutations of the *TP53* gene.<sup>(12,13)</sup> Immunohistochemical staining for p53 is used as a surrogate for mutational analysis in the diagnostic workup of carcinomas of multiple sites. Strong and diffuse immunopositivity of p53 is generally interpreted as likely indicating a *TP53* gene mutation.<sup>(14)</sup> Phosphatase and tensin homolog (*PTEN*) is a tumor-suppressor gene, and phagocytosis mutations in the *PTEN* gene have been linked to various malignancies, including breast cancer.<sup>(15,16)</sup> It has been demonstrated in a mouse model that a 20% reduction in the *PTEN* expression can result in high penetrance breast cancer.<sup>(17)</sup> Yang et al. found that phosphorylation of PTEN at residues Ser380/Thr382/383 resulted in the loss of phosphatase activity and tumor-suppressor function.<sup>(18)</sup>

The goal of our study was to determine the expression and phosphorylation of PTEN at residues Ser380/Thr382/383, as well as the nuclear expression of p53 in Sudanese patients with breast cancer in association with clinicopathological aspects of breast cancer.

## Materials and Methods

This retrospective, descriptive study was carried out in Wad-Madani, Gezira state in Sudan, from January 2015 to August 2016. A total of 179 biopsies (fixed in a 10% neutral buffered formalin) were taken at random from patients with breast lesions. Two blocks were obtained for each patient. One came from a malignant lesion (Group A), whereas the other came from the margin adjacent to healthy tissue (Group B). Histologically, malignant samples were classified as ductal carcinoma in situ (DCI), invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), sarcoma, and others. The histology sections had been previously diagnosed for all breast lesions in the Research Laboratory of the Faculty of Medicine at the University of Gezira.

Three serial sections (4 mm thick) were taken from each of the 179 biopsies using a Leica RM2125 RT rotary microtome. Immunohistochemistry and immunofluorescent histochemistry were performed on two separate slides.

### *P53 immunohistochemistry technique*

We used CONFIRM anti-p53 (DO-7) Primary Antibody ((IgG1, kappa). Catalog Number: 800-2912. Species: Mouse. Localization: Nuclear. Regulatory Status: IVD. Ventana Medical System, Inc. 1910E, Tucson, Arizona, USA.

### *PTEN immunofluorescent histochemistry technique*

We used PTEN pSer380/pThr382/383 rabbit polyclonal antibody, Aff – Purified (Cat. # AP02355PU-N). OriGene Technologies, Inc. Rockville, MD, USA.

Statistical analysis was performed using statistical software package SPSS version 23.0 (Armonk, NY: IBM Corp.). Group comparisons were performed using chi-square test with Yates correction. Inter-group comparisons were performed using Student's t-test. A probability value of  $P < 0.05$  was considered statistically significant.

Ethical approvals were obtained from the research center at Faculty of Medical Laboratory Sciences, University of Gezira (Wad Madani, Sudan). The data was only used for study purposes without individual details identifying the participant.

## Results

For this retrospective, descriptive study, the 179 histological biopsies were obtained from patients with breast lesions. The ages of the patients (174/97.2% females and 5/2.8% males) ranged from 13 to 95 years, with a mean age of 50.2 years (Table 1). Our sample population was divided as follows: 120(67.0%) samples were obtained in 2015 and 59(33.0%) in 2016. From 179 biopsies, 68(38.0 %) lesions were from the right breast, 63(35.0%) from the left breast, 1(0.6%) from both sides, and the remaining 47(26.3%) without indication of the affected side.

**Table 1.**

**The age distribution of the study population.**

Age group	Frequency	Percent	Valid Percent	Mean age
<30 years	11	6.1%	6.3%	50.20
31-40	46	25.7%	26.4%	
41-50	52	29.1%	29.9%	
51-60	26	14.5%	14.9%	
>61	39	21.8%	22.4%	
Missing	5	2.8%	-----	
Total	179	100%	100%	

All tissue specimens had previously been histopathologically identified as having either malignant or benign pathological conditions. We took histopathological sections from two blocks in each sample, one from the lesion and the other from the normal part of the tissue. All specimens were then immunohistochemically examined for P53 and PTEN.

The 179 breast lesions were all malignant tumors: DCI (10/5.6%), IDC (151/84.4%), ILC (6/3.4%), sarcoma (9/5.0%), and others (3/1.7%). In terms of malignancy grade, there was Grade I (4/2.2%), Grade II (74/41.3%), and Grade III (69/38.5%), and 1(0.6%) was the anaplastic case. Furthermore, 31(17.3%) cases had no determined grade mentioned.

In terms of infiltration, 165(92.2%) were infiltrating malignancies, and 14(7.8%) were in situ malignancies. Metastasis of malignancy to lymph nodes was detected in only 18(10.1%) cases. In terms of histological sites, we found the following: ducts (150/83.8%), lobules (17/9.5%), nipples (PD) (2/1.1%), and medullary carcinoma (7/3.9%). Basal cell carcinoma was detected in only 1(0.6%) case, fibrous histiocytoma in only 1(0.6%) case, and dermatofibrosarcoma (DFS) protuberans also in 1(0.6%) case.

Regarding histological form, we found the following: papillary (4/2.2%), mucinous (5/2.8%), cribriform (3/1.7%), phyllodes tumor (6/3.4%), and nonspecific histological form (161/89.9%). Our cases were divided into four types of cancerous cells: carcinoma (138/77.1%), adenocarcinoma (37/20.7%), sarcoma (3/1.7%), and lymphoma (1/0.6%) (Table 2). As shown in Table 3, there was an increase in the expression of p53, phosphorylation of PTEN, and Nuclear PTEN expression (Nuclear PTEN) in Group A, compared to Group B. There were statistically significant differences between Group A and Group B for all three parameters studied (PTEN, P53, and Nuclear PTEN) (Table 4).

**Table 2**

*The demographic data and BC characteristics.*

Sex		Total				
Female	Male					
174	5					
Year						
2015		2016				
120		59				
Grade						
Grade I	Grade II	Grade III	Anaplastic	No Grade		
4	74	69	1	31		
Lymph node metastasis						
Absent		Present				
161		18				
Histological site						
Ductal	Lobular	Nipple	Medullary	Basal cell	FHC	DFS protuberans
150	17	2	7	1	1	1

**Table 3.**

*Expression of nuclear p53, PTEN, and Nuclear PTEN.*

	Group A			Group B		
	PTEN	p53	Nuclear PTEN	PTEN	p53	Nuclear PTEN
Negative	16	20	3	69	87	56
Positive	163	159	176	110	92	123
Total	179					

**Table 4.**

*T-test for Groups A and B.*

Variables	Groups	T	P-value
PTEN	Group A - Group B	12.654	0.000
p53	Group A - Group B	12.948	0.000
Nuclear PTEN	Group A - Group B	11.568	0.000

We found that phosphorylation of PTEN at residues Ser380/Thr382/383 was increased in Group A in association with the histopathological grade of breast cancer ( $P=0.005$ ) and the histological site of the lesion ( $P=0.026$ ). However, there was no significant relationship between PTEN mutation in cancerous tissue and the following variables: year of sample collection, sex, patient's age group, and metastasis to lymph nodes (Table 5).

The same analysis was performed for p53 expression in cancerous tissue (Group A). A significant relationship was found only between the presence of p53 expression and the metastasis to lymph nodes ( $P=0.037$ ). However, there was no significant relationship between P53 expression and the following variables: year of sample collection, sex, patient's age group, the histopathological grade of breast cancer and the histological site of the lesion (Table 6).

Our analysis revealed the relationship between the type of breast cancer diagnosis and sex ( $P=0.001$ ), age group ( $P=0.037$ ), grade of lesions ( $P=0.000$ ), and histological site ( $P=0.000$ ) (Table 7).

## Discussion

Breast cancer is the leading cause of cancer morbidity and mortality among women in developing countries.<sup>(19)</sup> Breast cancer remains the most common type of cancer in Sudan, despite the fact that it accounted for only 22.9% of all cancers in Sudan in 1959, when the first report about cancer in Sudan, "Malignant epithelial tumors in the Sudanese," was published by Hickey<sup>(20)</sup> following a lecture presented to the Royal College of Surgeons, England on 13 March 1958.

Due to a lack of adequate awareness and screening programs,<sup>(21-22)</sup> Sudanese women are still suffering from advanced stages of breast cancer. The average age ranged from 41 to 50 years. The majority of cases within our study were ductal lesions at the later stages (Grade III) with metastasis to lymph nodes. Most patients in this study were of menopausal age, and the clinical course of the disease at that time appeared to be similar to that of European women.<sup>(22)</sup> However, a recent study found possible differences in breast cancer between Sudanese women in Central Sudan and women in Northern Italy.

Our findings are nearly consistent with previous research, which found that Sudanese patients were premenopausal in age, had larger tumors at more advanced stages and grades, and were frequently positive for nodal metastases, when compared

to Italian patients. The expression of estrogen receptors varied between the two groups, with most Sudanese patients' tumors

expressing no receptors. These clinicopathological and patient characteristics are now widespread in Sudan.<sup>(22)</sup>

**Table 5.**  
*The relationship between PTEN mutation in Group A and demographic data*

Variables		PTEN (Group A)			P-value
		Negative	Positive	Total	
Year	2015	8	112	120	0.070
	2016	8	51	59	
	Total	16	163	179	
Sex	Female	15	159	174	0.458
	Male	1	4	5	
	Total	16	163	179	
Age group	<30 years	3	8	11	0.418
	31-40	3	43	46	
	41-50	6	46	52	
	51-60	2	24	26	
	>61	2	37	39	
	Total	16	163	174	
Lymph node metastasis	No Lymph Node Metastasis	15	146	161	0.712
	Lymph Node Metastasis	1	17	18	
	Total	16	163	179	
Grade	Grade I	0	4	4	0.005
	Grade II	5	69	74	
	Grade III	4	65	69	
	Anaplastic	0	1	1	
	No Grade	7	24	31	
	Total	16	163	179	
Histological site	Ductal	13	137	150	0.026
	Lobular	1	16	17	
	Nipple (Paget's disease)	0	2	2	
	Medullary	1	6	7	
	Basal cell	0	1	1	
	Fibrous Histiocytoma	1	0	1	
	DFS protuberans	0	1	1	
	Total	16	163	179	

**Table 6.**  
*The relationship between p53 expression in Group A and demographic data*

Variables		P53 (Group A)			P-value
		Negative	Positive	Total	
Year	2015	13	107	120	0.945
	2016	7	52	59	
	Total	20	159	179	
Sex	Female	20	154	174	0.705
	Male	0	5	5	
	Total	20	159	179	
Age group	<30 years	2	9	11	0.676
	31-40	3	43	46	
	41-50	8	44	52	
	51-60	1	25	26	
	>61	6	33	39	
	Total	20	154	174	
Lymph node metastasis	No Lymph Node Metastasis	19	142	161	0.037
	Lymph Node Metastasis	1	17	18	
	Total	20	159	179	
Grade	Grade I	1	3	4	0.102
	Grade II	11	63	74	
	Grade III	4	65	69	
	Anaplastic	0	1	1	
	No Grade	4	27	31	
	Total	20	159	179	
Histological site	Ductal	19	131	150	0.148
	Lobular	0	17	17	
	Nipple (Paget's disease)	0	2	2	
	Medullary	0	7	7	
	Basal cell	1	0	1	
	Fibrous Histiocytoma	0	1	1	
	DFS protuberans	0	1	1	
	Total	20	159	179	

**Table 7.**  
**The relationship between the type of BC diagnosis and demographic data.**

Variables		Diagnosis						P-value
		DCI	IDC	ILC	Sarcoma	Other	Total	
Year	2015	4	104	5	6	1	120	0.214
	2016	6	47	1	3	2	59	
	Total	10	151	6	9	3	179	
Sex	Female	10	149	5	8	2	174	0.001
	Male	0	2	1	1	1	5	
	Total	10	151	6	9	3	179	
Age group	<30 years	0	10	0	1	0	11	0.037
	31-40	5	37	0	2	2	46	
	41-50	4	43	0	5	0	52	
	51-60	1	23	1	1	0	26	
	>61	0	33	5	0	1	39	
	Total	10	146	6	9	3	174	
Lymph node metastasis	No Lymph Node Metastasis	10	135	6	8	2	161	0.456
	Lymph Node Metastasis	0	16	0	1	1	18	
	Total	10	151	6	9	3	179	
Grade	Grade I	1	3	0	0	0	4	0.000
	Grade II	3	66	4	1	0	74	
	Grade III	1	65	1	1	1	69	
	Anaplastic	0	0	0	1	0	1	
	No Grade	5	17	1	6	2	31	
	Total	10	151	6	9	3	179	
Histological site	Ductal	9	135	0	6	0	150	0.000
	Lobular	0	8	6	1	2	17	
	Nipple (PD)	1	0	0	0	1	2	
	Medullary	0	7	0	0	0	7	
	Basal cell	0	1	0	0	0	1	
	FHC	0	0	0	1	0	1	
	DFS Protuberans	0	0	0	1	0	1	
	Total	10	151	6	9	3	179	

The current study found a difference that is statistically significant in mutation frequency for p53 and phosphorylation of PTEN between the cancerous breast tissue and adjacent normal tissue, and this was applied to all parameters studied. Our results are consistent with findings in previous studies performed by Gang et al.<sup>(23)</sup> for P53, and Miao et al.<sup>(24)</sup> and Alam et al.<sup>(25)</sup> for PTEN and Nuclear PTEN.

We discovered a statistically significant relationship between PTEN phosphorylation and tumor grade due to PTEN inactivation. This is supported by Al-Subhi et al.<sup>(26)</sup> and Khan et al.<sup>(27)</sup> We did not detect a significant relationship between p53 expression in cancerous breast tissue and such factors as sex, age group, tumor grade, or histological site of the breast lesion. These findings were consistent with the data of Pan et al.<sup>(28)</sup> However, we found a link between p53 expression and lymph node metastasis, indicating an aggressive form of breast cancer. This was consistent with Payandeh et al.<sup>(29)</sup>

The current study found a significant correlation between breast cancer diagnosis and patient gender. It goes without saying that breast cancer is more inherent in women. Breast cancer diagnosis was statistically strongly correlated with tumor grade and histological site. We also found that most cases were Grade II and ductal lesions, which was consistent with Fu et al.<sup>(30)</sup> We also discovered a statistically significant relationship between diagnosis and age group. This is supported by Efirid et al.<sup>(31)</sup> So, among women >65 years of age, 75% had well or moderately differentiated tumors and only 16% had lymph node invasion. Most tumors in this age group were  $\leq 2$  cm (67%). Approximately 17% of older women had the more aggressive triple-negative breast cancer (HR-/HER2-).<sup>(31)</sup> At the same time, there was no statistically significant link between breast cancer diagnosis and lymph node metastasis. However, Yun et al.<sup>(32)</sup> found that the presence of symptoms, triple-negative breast cancer subtype, larger size mass on breast ultrasonography (>10 mm), and higher Breast Imaging Reporting and Data System category on breast ultrasonography ( $\geq 4c$ ) were positively associated with axillary lymph node metastasis.

P53 and PTEN can be used as breast cancer diagnostic and prognostic markers. We advocate for a comprehensive national program of breast cancer awareness and screening for the entire Sudanese population, as well as the creation of a freely accessible dataset portal for all cancers. Given the sociological, cultural, and educational considerations discussed above, screening and surveillance protocols may be appropriate, but they must be designed with great care and sensitivity.

## Conclusion

We found a statistically significant difference in the frequency of immunohistochemical expression of p53 and phosphorylation of PTEN between the cancerous breast tissue and adjacent normal tissue. P53 and PTEN exhibited a significant relationship with each other and the grade of tumor, indicating their importance in the aggressiveness of breast lesions. It should also be emphasized that there is an association between p53 expression and lymph node



metastasis, which indicates the involvement of p53 mutation in the metastasis of breast cancer.

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## Competing Interests

The authors declare that they have no competing interests.

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