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A retrospective analysis suggests PTEN expression is associated with favorable clinicopathological features of breast cancer

Leonard Derkyi-Kwarteng[1], Frank Naku Ghartey[2]✉, Eric Aidoo[3], Ernest Addae[1], Emmanuel Gustav Imbeah[1], Ato Ampomah Brown[3] & Samuel Acquah[4]

The phosphatase and tensin homolog (PTEN) gene acts as a tumor suppressor by regulating the PI3K/AKT pathway, crucial for cell growth and survival. Mutations or loss of PTEN are common in breast cancer, leading to uncontrolled cell growth. Understanding PTEN's role is vital for targeted therapies. 276 formalin-fixed paraffin-embedded (FFPE) breast cancer tissue blocks from 2012 to 2016 were analyzed for PTEN expression. Immunohistochemistry was performed to identify and assess tumor related clinicopathological characteristics as well as patient demographics. These were statistically matched with PTEN expression. Only 27.5% of the breast cancer tumors were PTEN-positive. PTEN expression correlated significantly with smaller tumor size, lower tumor grade, positive estrogen and progesterone receptor status, and favorable/unfavorable Ki67 status ($p < 0.001$). No significant association was found with vascular invasion, histologic type, age, HER2 status, staging, or lymph node involvement ($p > 0.05$). The study confirms PTEN's association with favorable clinicopathological features in breast cancer, supporting its role as a prognostic marker. These findings underscore the importance of PTEN in breast cancer biology and its potential as a therapeutic target. Furthermore these findings confirm the prevalence of advanced stage and aggressive breast cancer tumors in Ghana.

Keywords PTEN expression, Retrospective analysis, Clinicopathological characteristics, Breast carcinoma, Favorable prognosis, Archival samples

The phosphatase and tensin homolog (PTEN) gene is a tumour suppressor gene located on chromosome 10q23 and has been found to be mutated in different cancers[1]. This protein has been shown to have a dual-specificity phosphatase with lipid and protein phosphatase activity which functions as a negative regulator of PI3K/AKT oncogenic pathway. This is frequently mutated or deleted in human carcinogenesis. The antagonisation of the PI3K/AKT pathway is through the dephosphorylating PIP3, which results in decreased translocation of AKT to the cellular membrane.[2–5].

The activation of PTEN can be done through several different mechanisms including mutation, deletion, epigenetic silencing, transcriptional repression, microRNA regulation disruption of competitive endogenous RNA network, posttranslational modifications and aberrant PTEN localisation[4,6,7].

The PI3K/AKT is one of the potent signalling pathways promoted by HER 2 overexpression which affects cell cycle progression and inhibit apoptosis[3]. The heterodimer molecule, PI3K is composed of a regulatory subunit (p85) and a catalytic subunit (p110). When PI3K is activated by tyrosine kinase receptor, it phosphorylates PIP2 to produce PIP3[3,8].

The PIP3 mobilises the serine/threonine kinase, AKT to the plasma membrane. With the phosphorylation of Ser 473 of AKT, several kinases are activated, which includes the mammalian target of rapamycin (mTOR), a molecule that regulates cell growth through p21 and p27, with other molecules that inhibit apoptosis such as Bad and caspase proteins[3,9–11]. The PI3K/Akt/mTOR pathway, found to be frequently overactive in human

[1]Department of Pathology, School of Medical Sciences, University of Cape Coast, Cape Coast, Ghana. [2]Department of Chemical Pathology, School of Medical Sciences, University of Cape Coast, Cape Coast, Ghana. [3]Department of Anatomy and Cell Biology, School of Medical Sciences, University of Cape Coast, Cape Coast, Ghana. [4]Department of Medical Biochemistry, School of Medical Sciences, University of Cape Coast, Cape Coast, Ghana. ✉email: f.ghartey@uccsms.edu.gh

cancers, plays a significant role in various processes including cell growth, proliferation, survival, metabolism, and immune response regulation[12].

In the context of breast cancer, PTENplays a crucial role as a tumor suppressor gene. PTEN is involved in regulating cell growth, proliferation, and survival by inhibiting a signalling pathway that promotes cell division and survival. Its main function is to negatively regulate the PI3K/AKT/mTOR pathway[13].

When PTEN is mutated or inactive, the PI3K/AKT/mTOR pathway becomes over activated, leading to uncontrolled cell growth and survival. This dysregulation is commonly observed in various cancers, including breast cancer[14].

Specifically in breast cancer, loss or inactivation of PTEN has been associated with more aggressive tumor behavior, resistance to certain therapies, and a poorer prognosis. Additionally, alterations in the PI3K/AKT/mTOR pathway are often implicated in hormone receptor-positive and HER2-positive breast cancers.

Understanding the role of PTEN in breast cancer is crucial for developing targeted therapies that aim to modulate this pathway, offering potential avenues for more effective treatment strategies. Until now, changes in this gene and or protein expression have been considered as significant molecular features that can impact clinical decision-making[15]. Loss or modification of PTEN function has been detected in a wide range of neoplasms, and is regarded as a foundational genetic occurrence in the development and progression of tumors[16].

Aim

The aim of this study is to investigate the association between PTEN expression and favorable clinicopathological characteristics in archival breast cancer specimens through a retrospective analysis.

Objectives

1. To evaluate the level of PTEN expression in archival breast cancer specimens.
2. To assess the clinicopathological characteristics of breast cancer specimens, such as tumor grade, stage, and hormone receptor status.
3. To determine the relationship between PTEN expression and clinicopathological features.
4. To analyze the impact of PTEN expression on prognosis and patient outcomes in breast cancer.

Scientifically, these objectives are important as they help to elucidate the potential role of PTEN expression in predicting clinicopathological characteristics and prognosis in breast cancer. Understanding these associations can provide valuable insights for personalized treatment strategies and improving patient outcomes.

Methodology

From a collection of 735 formalin-fixed paraffin-embedded (FFPE) tissue blocks containing breast cancer specimens obtained from the archival tissue bank at Korle-Bu Teaching Hospital, Ghana's foremost and largest teaching hospital, a subset of 276 cases from the years 2012 to 2016 was chosen for analysis. Initially, 3 µm-thick sections of FFPE blocks from the selected cases were prepared using a microtome, and these sections were then transferred onto silane-coated slides. The mounted tissue slides underwent deparafinization using xylene and ethanol, followed by a stepwise washing process with water.

Deparafinization

The slides were immersed in three changes of xylene each for 5 min. Rehydration was carried out by immersing the slides two consecutive times in 100% alcohol each for 10 min. The process was repeated in; 95% alcohol, 70% alcohol and 50% alcohol. The slides were then placed in two changes of distilled water for 5 min each. Tissues were then prepared for heat retrieved stage using digital water bath at a temperature of 97 °C for 45 min which was initially pre-warmed at a temperature of 85 °C followed by antibody treatment in the following stepwise method.

Heat retrieval

The tissue slides were transferred into a water bath containing 1.5L distilled water and warmed to a pre-boiling temperature of 97 °C. The slides were then placed in a pre-warmed staining dish containing the ImmunoDNA retrieved in the steamer. It is then covered and left to steam for 60 min. The slides were then transferred into immunoDNA retriever with citrate for 20 min after heat treatment. The slides were then washed in 3 changes of IHC wash buffer. The tissue slides were processed further and covered with the primary antibody using pre-diluted ER, PR, HER-2 and Ki 67 antibodies for 60 min and washed in three (3) washes of IHC buffer. The tissue slides were then covered with polydetector plus link and incubated for 15 min. They were subsequently washed again in 3 washes of IHC buffer and covered with polydetector HRP label and incubated for 15 min. Following that, they were repeatedly washed in 3 changes of IHC buffer. DAB was prepared by adding polydetector DAB buffer and then mixed. The tissue slides were covered with the DAB substrate-chromogen solution and incubated for 5 min. They were finally rinsed with 3 washes of IHC buffer and counterstained with Meyer's haematoxylin and subsequently dehydrated and cover slipped.

Dehydration and mounting of slides

The slides were dehydrated, cleared and mounted using the following steps. Dehydrated was done by moving slides through 2 washes of 95% alcohol each for 10 min then immersed in two washes of 100% alcohol for 10 min

and then immersed in 3 changes of xylene each for 5 min. Finally, these processed tissue slides were mounted with DPX and cover slipped.

Slide reporting

Slides with tumours that showed strong or weak staining for PTEN were said to be positive while those with no staining were said to be negative. Reading and scoring of slides were done by two independent experienced pathologists. A third pathologist was engaged to resolve a few instances where there was disagreement. These were approximately 7% of the cases studied (Table 2). ***BioSB prediluted antibodies, ready for use were applied for Immunohistochemical assessment of ER, PR, AR and PTEN in archival breast cancer tissue blocks.***

Ethical review

The research methodology was reviewed by Cape Coast Teaching Hospital Ethical Review Board (CCTHERB) although we did not need ethical clearance for archival tissue samples per our institutional protocol. All samples were archival samples from the tissue archives. No new tissue samples were procured for analysis. De-Identification of the cases were done.

Results

Highlights of findings

276 parrafin embedded tissue blocks of breast cancer cases were analyzed for PTEN expressivity; 27.5% were positive, 72.5% negative. Smaller tumors tend to be positive ($p < 0.001$). Among Invasive ductal carcinoma histological types: 28.3% were positive; among mucinous carcinoma histological types: none were positivity. Lymphovascular invasion and tumor grade showed trends. Age and hormonal receptors exhibited significant findings. Luminal A and B tumors were positive for PTEN, but HER2 and triple-negative cases were negative. These findings are presented with more details in Table 1.

Discussion

The results of the study provide valuable insights into the association between PTEN expression and various clinicopathological characteristics of breast cancer specimen analyzed.

A detailed discussion of the key findings

PTEN Expression

In this study 72.5% of the archival BC specimen did not show PTEN expressivity and it represents one of the highest ever reported since that by[17], reported 48% loss of PTEN, 29.5% was also reported by[3] This high loss of PTEN among our patients might be due to late tumor presentation. Previous studies have also reported loss of PTEN in sporadic breast cancer and 72% in familial breast cancer[18,19]. This high PTEN loss in familial breast cancer might explain the high number of loss of PTEN in this study although that information is not available. The loss of PTEN may also be related to heterozygote or promoter of methylation[18] and from our observation in this study; it is associated with a high prevalence of aggressive late stage BC in Ghana (Table 2).

PTEN expression and tumor size

The study found a significant association between PTEN expression and tumor size. Smaller tumors (≤ 2 cm and > 2 cm– ≤ 5 cm) were more likely to exhibit positive PTEN expression compared to larger tumors (> 5 cm). This suggests that PTEN expression may play a role in tumor growth regulation, with loss of PTEN associated with larger tumor size which in turn suggests late presentation.

PTEN expression and histologic type

While there was no significant association between PTEN expression and specific histologic types of breast cancer, there were some interesting observations. For instance, invasive ductal carcinoma (NOS) showed a higher percentage of positive PTEN expression compared to other histologic types. This suggests that PTEN expression may vary across different subtypes of breast cancer, although further research is needed to confirm these findings.

PTEN expression and lymphovascular invasion

The study did not find a significant association between PTEN expression and lymphovascular invasion. This indicates that PTEN expression may not directly influence the likelihood of vascular invasion in breast cancer. Furthermore, this study has established that there is no association between PTEN and vascular invasiveness, histologic type, and age ($P > 0.05$). This is in line with other similar studies[16,19–21].

PTEN expression and tumor grade

There was a significant association between PTEN expression and tumor grade. Higher tumor grades (II and III) were more likely to exhibit negative PTEN expression compared to lower-grade tumors (Grade I). This suggests that loss of PTEN expression may be associated with more aggressive tumor behavior and higher histologic grade. The study has clearly confirmed that there is an association between PTEN and; tumor grade, tumor size, and Ki67 ($p<0.001$). This is in agreement with studies by[16] but contradict the observation by[22]

PTEN expression and hormone receptor status

The study found a significant association between PTEN expression and estrogen receptor (ER) as well as progesterone receptor (PR) status. Tumors positive for ER and PR were more likely to exhibit positive PTEN expression,

Clinicopathological characteristics	PTEN Expression		Total	*p-value*
	Positive	Negative		
Tumour size (cm)				
≤ 2	3(100.0%)	0(0.0%)	3(100.0%)	**< 0.001**
> 2 ≤ 5	15(78.9%)	4(21.1%)	19(100.0%)	
> 5	58(22.8%)	196(77.2%)	254(100.0%)	
Total	**76(27.5%)**	**200(72.5%)**	**276(100.0%)**	
Histologic type				
Invasive ductal carcinoma (NOS)*	73(28.3%)	185(71.7%)	258(100.0%)	0.444
Mucinous carcinoma	0(0.0%)	3(100.0%)	3(100.0%)	
Papillary carcinoma	0(0.0%)	1(100.0%)	1(100.0%)	
Invasive lobular carcinoma	1(25.0%)	3(75.0%)	4(100.0%)	
Medullary carcinoma	1(33.3%)	2(66.7%)	3(100.0%)	
Intraductal papillary carcinoma	0(0.0%)	1(100.0%)	1(100.0%)	
Spindle cell carcinoma	0(0.0%)	1(100.0%)	1(100.0%)	
DCIS	1(25.0%)	3(75.0%)	4(100.0%)	
Mixed lobular and ductal carcinoma	0(0.0%)	1(100.0%)	1(100.0%)	
Total	**76(27.5%)**	**200(72.5%)**	**276(100.0%)**	
Lymphovascular invasion				
Yes	53(27.6%)	140(72.4%)	193(100.0%)	0.314
No	18(21.9%)	65(78.1%)	83(100.0%)	
Total	**71(25.7%)**	**205(74.3%)**	**276(100.0%)**	
Tumour grade				
I	12(40.0%)	19(60.0%)	31(100.0%)	**< 0.001**
II	57(35.9%)	101(64.1%)	158(100.0%)	
III	13(15.5%)	74(84.5%)	87(100.0%)	
Total	**82(29.7%)**	**194(70.3%)**	**276(100.0%)**	
Age group 50				
< 50	30(28.0%)	78(72.0%)	108(100.0%)	0.943
≥ 50	46(27.1%)	122(72.9%)	168,166(100.0%)	
Total	**76(27.5%)**	**200(72.5%)**	**276(100.0%)**	
ER				
Positive	55(37.7%)	91(62.3%)	146(100.0%)	**<0.001**
Negative	21(16.2%)	109(83.8%)	130(100.0%)	
Total	**76(27.5%)**	**200(72.5%)**	**276(100.0%)**	
PR				
Positive	44(41.1%)	63(58.9%)	107(100.0%)	**<0.001**
Negative	32(18.9%)	137(81.1%)	169(100.0%)	
Total	**76(27.5%)**	**200(72.5%)**	**276(100.0%)**	
HER 2/Neu				
Positive	9(17.6%)	42(82.4%)	51(100.0%)	0.185
Negative	64(30.2%)	148(69.8%)	212(100.0%)	
Equivocal	3(23.1%)	10(76.9%)	13(100.0%)	
Total	**76(27.5%)**	**200(72.5%)**	**276(100.0%)**	
Ki-67				
Favourable	20(35.7%)	36(64.3%)	56(100.0%)	**< 0.001**
Unfavourable	77(41.8%)	107(58.2%)	184(100.0%)	
Borderline	0(0.0%)	36(100.0%)	36(100.0%)	
Total	**97(35.2%)**	**179(64.8%)**	**276(100.0%)**	
Molecular subtype				
Luminal A	43(37.1%)	73(62.9%)	116(100.0%)	**< 0.001**
Luminal B	12(35.3%)	22(64.7)	34(100.0%)	
Her 2 +	0(0.0%)	29(100.0%)	29(100.0%)	
Triple-negative	21(21.6%)	76(78.4%)	97(100.0%)	
Total	**76(27.5%)**	**200(72.5%)**	**276(100.0%)**	

Table 1. Analysis of PTEN Expression in Archival Breast Cancer Specimen Matched with their Clinicopathological Characteristics. **NOS* Not Otherwise Specified (also referred to as No Special Type (NST)), *ER E*strogen receptor, *PR* Progesterone receptor, *HER-2* Human Epidermal growth factor receptor 2. Significant p-values are in [bold fonts].

Proportion score(PS) assigned	Observed stained area for PS (%)	Intensity score (IS) assigned	Observed stain intensity for is
0	None	0	None
1	1	1	Weak
2	1–10	2	Intermediate
3	10–33	3	Strong
4	33–66		
5	66–100		
TOTAL Score		**Interpretation**	
Sum of proportion and intensity scores			
0–2		Negative	
3–8		Positive	

Table 2. Guidelines for interpretation of ER, PR, and PTEN (biomarkers) results by Allred method.

while ER and PR-negative tumors showed a higher percentage of negative PTEN expression. This is demonstrated by significant correlation between PTEN expressivity and ER as well as PR with P<0.001. This is supported by[23], but disagrees with the observation by[19]. These conflicting findings in PTEN expressivity and ER, PR may be due to the small sample size used by the other researchers who employed sample sizes less than 100. The potential link between PTEN expression and hormone receptor signaling pathways in breast cancer is emphasized.

PTEN expression and HER2 status

There was no significant correlation between PTEN and HER2 expressivity ($P > 0.05$) as shown**.** This supports the findings of[24]. This suggests that PTEN expression may not directly influence HER2 expression or signaling in breast cancer. Another study reported some association[25] It can be inferred that; HER2 + breast lesions harbour gene amplifications which will override normal tumor suppression by PTEN whether it is expressed or not.

PTEN expression and Ki67

We found a significant association between PTEN expression and Ki67 proliferation index ($p < 0.001$). Tumors with favorable Ki67 expression exhibit positive PTEN expression as well as tumors with unfavorable Ki67 expression. It can be inferred that the cell proliferation in the latter could be related to HER2 + tumours which overrides PTEN's ability to suppress their growth. This suggests a potential role for PTEN in modulating cell proliferation in breast cancer. An indirect relationship between PTEN expression and Ki67 in breast cancer is implied by findings in a study; which reported loss of PTEN expression and Ki67 positivity correlated with large tumour size and histological grade[26]

PTEN expression and molecular subtypes

This study identified an association between molecular subtypes and PTEN expressivity with $P < 0.001$. This finding supports that of[23]. Luminal A tumors were more likely to exhibit positive PTEN expression, while HER2-positive tumors showed a higher percentage of negative PTEN expression. This suggests that PTEN expression may vary across different molecular subtypes of breast cancer, with potential implications for targeted therapy[27]. The findings regarding PTEN expression in breast cancer outlined in this study are largely consistent with existing scientific evidence and add valuable insights to our understanding of the role of PTEN in breast cancer. PTEN, a tumor suppressor gene, plays a critical role in regulating cell growth, survival, and proliferation by inhibiting the PI3K/Akt signaling pathway. Loss of PTEN function or reduced expression has been implicated in various cancers, including breast cancer, leading to increased cell proliferation and tumor growth. This study's observation of a significant proportion of breast cancer cases being negative for PTEN expression may be a bit on the high side and may not align with previous research indicating that PTEN loss or inactivation occurs frequently in breast cancer, however it agrees it is particularly common in aggressive subtypes. This loss of PTEN function contributes to oncogenesis by promoting cell survival, proliferation, and metastasis. The findings regarding the association of PTEN expression with tumor characteristics such as size, grade, lymphovascular invasion, and molecular subtypes further support the notion that PTEN status can influence breast cancer behavior. For example, the higher prevalence of PTEN positivity in luminal A and B tumors, which are typically less aggressive and hormone receptor-positive, suggests a potential protective role of PTEN in these subtypes. PTEN expression in relation to age, hormonal receptor status, HER2 expression, and Ki67 proliferation index also corroborates existing literature on the complex interplay between PTEN and these factors in breast cancer biology. For instance, the negative correlation between PTEN and HER2 status is well-documented, as the PI3K/Akt pathway is frequently activated in HER2-positive tumors. Overall, our findings contribute to the growing body of evidence supporting the significance of PTEN expression in breast cancer pathogenesis and its potential implications for tumor aggressiveness, treatment response, and patient outcomes. Further research elucidating the functional consequences of PTEN alterations in breast cancer subtypes is essential for advancing personalized treatment strategies and improving clinical outcomes in patients with breast cancer. Finally, PTEN is frequently altered in breast cancer. Examining publicly accessible genomic datasets confirms that the mutational burdens in cancers

align with those seen in PTEN itself.[28]. This appears to inadvertently breed controversies in its reporting and potential clinical application.

Controversies in PTEN reporting for clinical application
A relatively recent review reports that the controversies around PTEN expression in breast cancer stem from; the limited data on MMR deficiency in this type of cancer, the rarity of such deficiencies, the lack of proper diagnostic tools and guidelines, as well as the different patterns of MMR deficiency compared to endometrial and colorectal cancers[28].

Limited information on mismatch repair (MMR) deficiency in breast cancer
The review reports that very little information is available on the specific biology of MMR deficiency in breast cancer. This lack of data makes it challenging to draw concrete conclusions about the role of PTEN expression in this context[29].

Rarity of MMR deficiency in breast cancer
It is reported that genomic scars in the MMR system, which could indicate a deficiency, are rare in breast cancer, occurring in only about 2% of cases. This rarity further complicates the assessment of PTEN expression's relevance in breast cancer[30]

Lack of diagnostic tools and guidelines
Many publications point out the absence of companion diagnostics and tumor-specific guidelines for analyzing MMR in breast cancer. This lack of standardized testing and guidelines contributes to the controversy, as it prevents consistent and reliable assessment of PTEN and MMR status in breast cancer patients[28,30].

Limited applicability of microsatellite instability (MSI)
Unlike in endometrial and colorectal cancers, where MSI is a common feature of MMR deficiency, MSI is only seen in a minority of breast cancers that show MMR protein loss. This difference in the manifestation of MMR deficiency adds another layer of complexity to understanding and utilizing PTEN expression in breast cancer treatment and prognosis[31]. A proposed algorithm to remedy some of these controversies has been reported[28].

Conclusion
Overall, the results of the study highlight the complex relationship between PTEN expression and various clinicopathological characteristics of breast cancer. Loss of PTEN expression appears to be associated with more aggressive tumor behavior, higher histologic grade, and certain molecular subtypes of breast cancer. Further research is needed to elucidate the underlying mechanisms driving these associations and explore the potential therapeutic implications of targeting the PTEN pathway in breast cancer management. These findings further confirm a high prevalence of late stage and aggressive BC cases in Ghana.

Data availability
All data generated or analyzed during this study are available upon request from the corresponding author.

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Author contributions

LDK and FNG—Conceptual framework, data cleaning, data analysis, manuscript writing and review, EA and EGI—data collection and analysis, EA—data collection, lab work and analysis, AAB and SA—manuscript writing and review, All authors contributed significantly to the manuscript writing and review.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to F.N.G.

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