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Original Research

Kaiso Expression in Triple Negative Breast Cancer in a Tertiary Hospital in Ghana.

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Abstract

Background: Breast cancer has produced more lost disability-adjusted life years (DALYs) than any other type of cancer. The prevalence of the disease, especially triple negative breast cancer (TNBC) in Africa is on the rise, with poor survival rates. With the great advancements in treatments of breast cancers, that of TNBC is still a challenge due to its narrowed treatment options and poor disease prognosis. This research seeks to explore the expression of kaiso in Ghanaian breast cancer and how they may modulate clinicopathological features, and disease prognosis.

Methodology: A cross-sectional retrospective study was conducted on formalin-fixed paraffin-embedded (FFPE) breast cancer tissues retrieved from the archives of the pathology unit of Komfo Anokye Teaching Hospital (KATH). Immunohistochemistry assessment was performed on haematoxylin and eosin-stained slides selected for tissue microarray construction. Data were analysed using SPSS version 28 and Microsoft excel 2013.

Result: 55.3% of the cases tested negative to progesterone receptor (PR), oestrogen receptor (ER), and human epidermal growth receptor 2 (HER2). There were significant associations between menopausal status and molecular subtype (p=0.010), Kaiso expression and histological diagnoses (<0.001) and Kaiso against lymphovascular invasion (0.050). However, there were no significant associations between Kaiso localization and the clinicopathological features although 63.9% of the expression was seen in the nucleus.

Conclusion: The study indicates that Kaiso is highly expressed in Ghanaian TNBC and likely associated with worse outcomes in aggressive tumour types.

Keywords: Kaiso expression; TNBC; Tissue microarray; Immunohistochemistry.

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Introduction

For a very long time, the breasts have not only remained an identification tool but also, the most salient and appealing feature of the female sexual organ. The female breasts are not for sexual pleasure only but serve an important function of sustaining young offspring (1). Unfortunately, there has been an increase in the number of young women losing their breasts or parts of it as a result of breast cancer (2,3). The disease has proven to be a key obstacle to the advancement of life expectancy with approximately 2.3 million new cases diagnosed and a corresponding 685,000 deaths globally in 2020. Breast cancer is the most commonly diagnosed cancer in women worldwide, representing 1 in 4 cancers (4).

Some parts of the world have seen a decline in breast cancer mortality and this has been associated to the advancement in treatment and early detection (5). Unfortunately, Africa is not a member of this subset. Low and middle-income nations account for half of all breast cancer patients, with these countries experiencing about 58% of the deaths (6-8). The current aggregated incidence of breast cancer per 100,000 women in Central (27.9), Eastern (29.9), Western (37.3), and Southern Africa (46.2) has death rates reported at 15.8, 15.4, 17.8 and 15.6 respectively. This challenge is magnified by issues linked with access to quality healthcare, diagnosis, treatment and management of the disease (9,10). According to a recent review by (11), the prevalence of breast cancer in Africa is on the rise and is expected to double by the year 2050.

The fact that African breast cancer has different molecular features from those of Caucasians is crucial to the issues confronted in the treatment and management of breast cancer in Africa (12–14). Generally, African women are known to have the greatest percentage of breast cancers that are receptor-negative or triple-negative (14–18). As a result, a large proportion of breast cancer cases in Africa are not able to fully benefit from the available treatment options owing to the negative status for ER, PR and HER-2 hence have worse prognosis. This to an extent has contributed to the lower survival rate in Africa, Ghana included, compared to other developed countries; >40% against 80% as reported by (6). It has become necessary that more research is done to uncover predictive/prognostic markers that could lead to better treatment options.

Kaiso, a ubiquitous protein that has high affinity for both the Kaiso binding site (KBS; TCCTGCNA) and methylated CpG dinucleotides (19,20) has been implicated in several disparate human cancer and also the regulation of tumour suppressive miRNA (21,22). Most of the supposed Kaiso target genes have been linked to tumour onset, proliferation, progression and metastasis (23,24). Kaiso is a member of POZ-ZF family of transcription factors and was first recognized as a binding partner of the E-cadherin catenin cofactor—p120-catenin (p120ctn). It has most often been characterized as a transcriptional repressor, but some studies indicate that Kaiso can also function as a transcriptional activator (19). Recent research has discovered a link between nuclear expression of Kaiso and African Americans' poor overall survival compared to their Caucasian counterparts. Its depletion has been shown to attenuate metastatic activity of cancer cells (14). This study would provide novel information on the expression of Kaiso in Ghanaian TNBC cases as no study has been conducted in Ghana pertaining to Kaiso. It would also inform the exploration of Kaiso as a potential therapeutic target/prognostic marker for Ghanaian TNBC patients.

This study aims to determine the expression of Kaiso, establish its predictive/prognostic importance and how it may modulate the clinicopathological features of breast cancer using cases from a Ghana tertiary hospital in Kumasi.

Methodology

Following ethical approval from the Committee on Human Research, Publication and Ethics (CHRPE) of the Kwame Nkrumah University of Science and Technology (KNUST), archived FFPE breast cancer tissue blocks from 2008 to 2017 were obtained from KATH. The FFPE blocks were submitted to the Department of Pathology at the KNUST School of Medicine and Dentistry for histological evaluation. After excluding cases with inconclusive diagnosis, destroyed FFPE blocks, unmatching and or missing data, a total of 150 samples out of which 84 were TNBC hence the working sample.

Three microns thin section slides were made from the eligible blocks using a microtome. The sections were deparaffinized using xylene and subsequently differentiated and rehydrated by immersion in a series of alcohol solution with decreasing grades (95%-70%). The slides were stained and counterstained with haematoxylin and eosin respectively using the regressive method. Two experienced pathologists reviewed the H&E slides independently for histological characterization after which tumour representative areas were marked for TMA construction. 1mm cylindrical cores of tumour foci were extracted from mapped FFPE blocks (donor blocks) and introduced into the TMA recipient paraffin blocks that were constructed with Micatu MicaArray Gen. 4. Two cores were used to represent each case. The recipient blocks were gently heated under an incandescent lamp. The same procedure employed for the preparation of the H&E slides was used for the TMA slides. The TMA slides were incubated overnight at 37℃ awaiting immunohistochemistry.

TMA slides were placed in a citrate buffer and incubated in a pressure cooker for 20 minutes at 97℃ to expose epitopes for antibody binding. After, they were treated with 3% H_2O_2 diluted with methanol for 10 minutes and washed with Tris Buffered Saline (TBS) to block background staining. Nonspecific antibody binding was prevented by incubating the slides in casein solution and washed again with TBS. Drops of mouse monoclonal primary antibodies were introduced and incubated overnight at 37℃ (Table 1). An auxiliary antibody formed with peroxide and anti-peroxide (DAKO) was added and allowed to sit for 30minutes. Sections were developed with 3,3-diaminobenzidine tetrahydrochloride (DAB), counterstained with alum haematoxylin, differentiated in 1% acid alcohol for 15 minutes and washed with distilled water. The sides were then mounted using DPX mountant. The immunoreactivity during incubation revealed the expression of the antigens under study; ER, PR, HER 2 and Kaiso. Negative controls were prepared by substituting the primary antibody with TBS. Slides were interpreted and scored using the standard scoring protocols for each antibody. Membrane staining was used for HER2 according to the ASCO/CAP guidelines (25). The IHC scoring was done according to ASCO/CAP guidelines (25,26) by two pathologists independently. Four molecular subtypes were classified based on the works of (27,28). Data were entered and analysed using Excel 2016 and SPSS version 28. The Chi-square test was used for estimation of associations between categorical variables. A p-value <0.05 at the 95% confidence interval was considered statistically significant.

Results

A total of 150 breast cancer cases were used for initial investigations using their representative sections from Formalin Fixed Paraffin Embedded blocks. After which samples were then restricted to TNBC cases. As indicated in Figure 1, the ages ranged from 17 to 92 years old, with cohort 40-49 years having the highest occurrence and mean age 49.68 years. Invasive Carcinoma NST was the most prevalent histological diagnosis (82.0%). About 51.2% of the cases with data on lymphovascular invasion were positive. In about two-third of the cases, high grade cancers were found (70.0%). The descriptive statistics for the TMA cases are shown in Table 2.

Kaiso was expressed in 98.8% (82 out of 83) of the TNBC cases. Kaiso expression was seen in the cytoplasm and nucleus of cancerous cells however, there was a higher nuclear expression (63.7%) compared to cytoplasmic expression (Table 3). The cases were classified into the breast cancer molecular

subtypes based on the expression ER, PR and HER2. Triple negative was the most dominant with 55.3% as presented in Table 3. Figures 1 and 2 show IHC photomicrographs of antibodies used for this study.

The chi-square test showed association between Kaiso, grade and lymphovascular invasion. A p-value of < 0.05 was considered significant. There was a significant association between Kaiso expression, histological diagnosis, lymphovascular invasion and subcellular localization ($p<0.001$, $p=0.050$ and $p<0.001$ respectively). In addition, there was a significant association between the menopausal status of women and molecular subtypes ($p=0.010$) as shown in figure 5. Figure 6 shows Kaiso subcellular localization within the histologic grades.

Table 1: Information on Antibodies Used

Antibody	Clone	Pretreat	Dilution	Control	Company	Address
ER	1D5	ER1/20	1:50	Breast CA	BioCare Medical	Concord CA
HER2	CB11	ER1/20	RTU	Breast CA	DAKO	Carpinteria CA
PR	PgR 636	ER1/10	1:400	Endo/Myome	DAKO	Carpinteria CA
Kaiso	6F		1:10000	CSML0	DAKO	Carpinteria CA

Table 2: Descriptive Statistics and Histological features of TMA cases

Age distribution	Mean/Years	Standard deviation/Years
	49.68	14.02
Histological diagnoses	Invasive carcinoma NST	123 (82.00)
	Ductal carcinoma in situ	6 (4.00)
	Metaplastic carcinoma	5 (3.33)
	Invasive lobular carcinoma	5 (3.33)
	Mucinous carcinoma	5 (3.33)
	Medullary carcinoma	2 (1.33)
	Others*	4 (2.67)
Histological grade	Low grade	12 (7.89)
	High grade	105 (70.00)
	Unknown	33 (22.00)
Lymphovascular invasion	Positive	21 (13.82)
	Negative	20 (13.16)
	Unknown^	111 (73.03)

**Others refer to diagnosis described as clinically insignificant by the WHO*
^Result was inconclusive

Table 3: Immunohistochemistry Features of the Cases

Antibody	Frequency	Percentage Expressed (%)
ER		
Positive	44	30.14
Negative	102	69.86
Total	146	

PR		
Positive	18	12.59
Negative	125	87.41
Total	143	
HER2		
Positive	109	77.86
Negative	31	22.14
Total	140	
Molecular Subtype		
Luminal A	27	18.00
Luminal B	16	10.67
HER2 overexpression	24	16.00
Triple negative	83	55.33
Kaiso		
Nuclear	53	63.86
Cytoplasmic	29	34.94
Negative	1	1.20

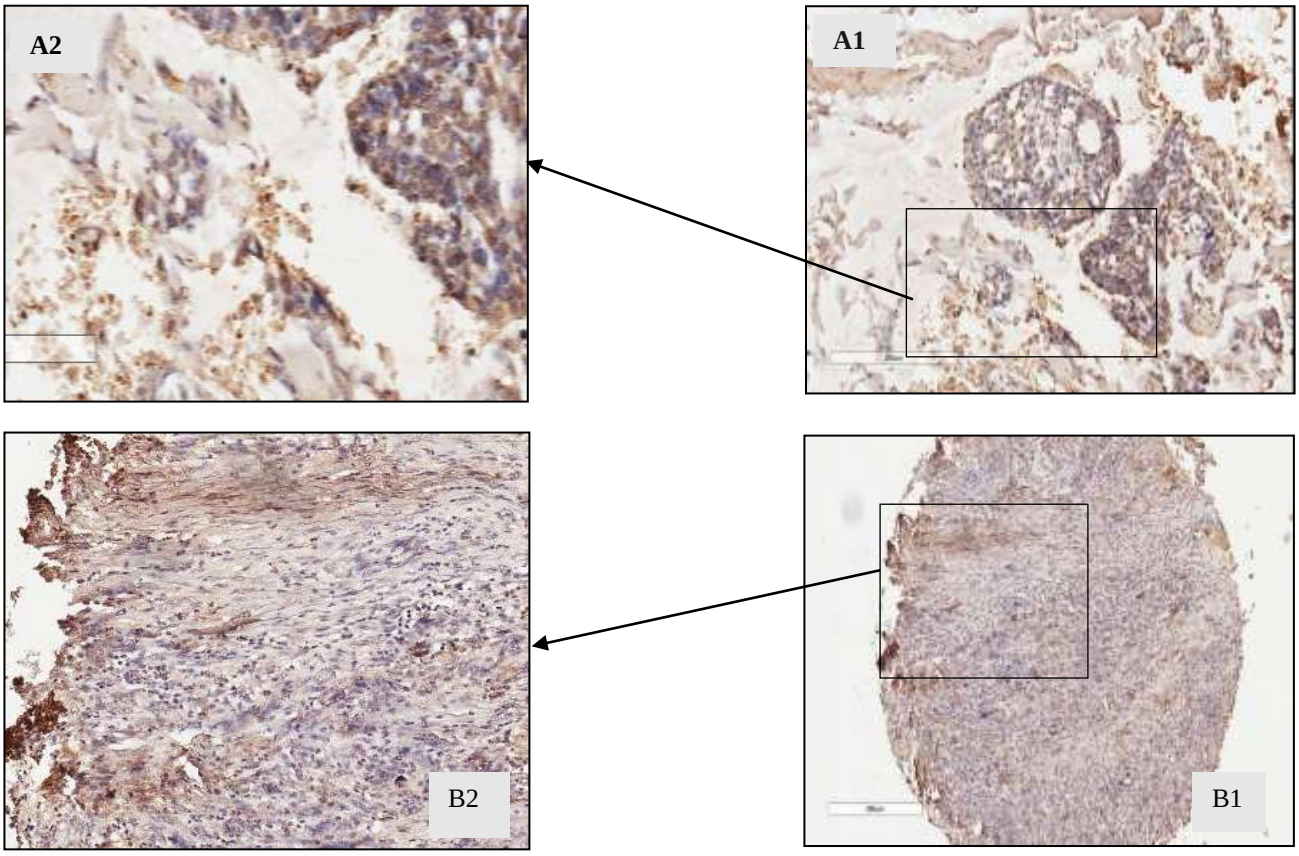

Figure 1: Photomicrographs of breast cancer cases positive for Kaiso in the nucleus (A1) and Kaiso in the cytoplasmic (B2) with A2 and B2 focusing on enlarged parts. The golden-brown areas signify positive tumour staining.

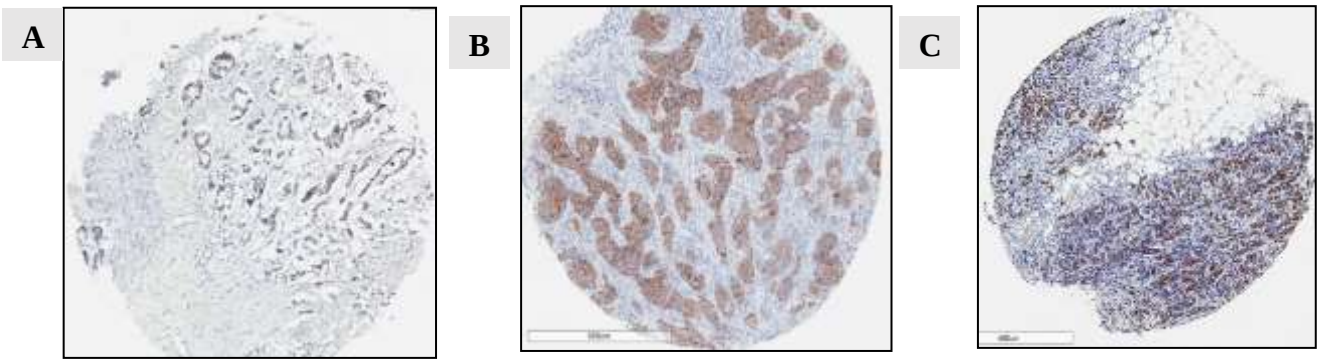

Figure 2: Photomicrographs of breast cancer cases positive for ER (A); B. HER 2 (B) and PR (C). The golden-brown areas signify positive tumour staining.

Table 4: Expression of Kaiso in TNBC against Clinicopathological Characteristics

Clinicopathological Exotics	**Kaiso Positive**	**X^2**	**P-value**
Histological diagnosis			
Invasive NST	70		
Ductal Carcinoma in situ	2		
Invasive Lobular	2	83.000	**<0.001**
Metaplastic	2		
Mucinous	2		
Others	4		
Histological grade			
Low grade	5	0.095	0.954
High grade	64		
Lymphovascular invasion			
Positive	11	5.989	**0.050**
Negative	11		
Kaiso localization			
Cytoplasmic	29	83.000	**<0.001**
Nuclear	53		

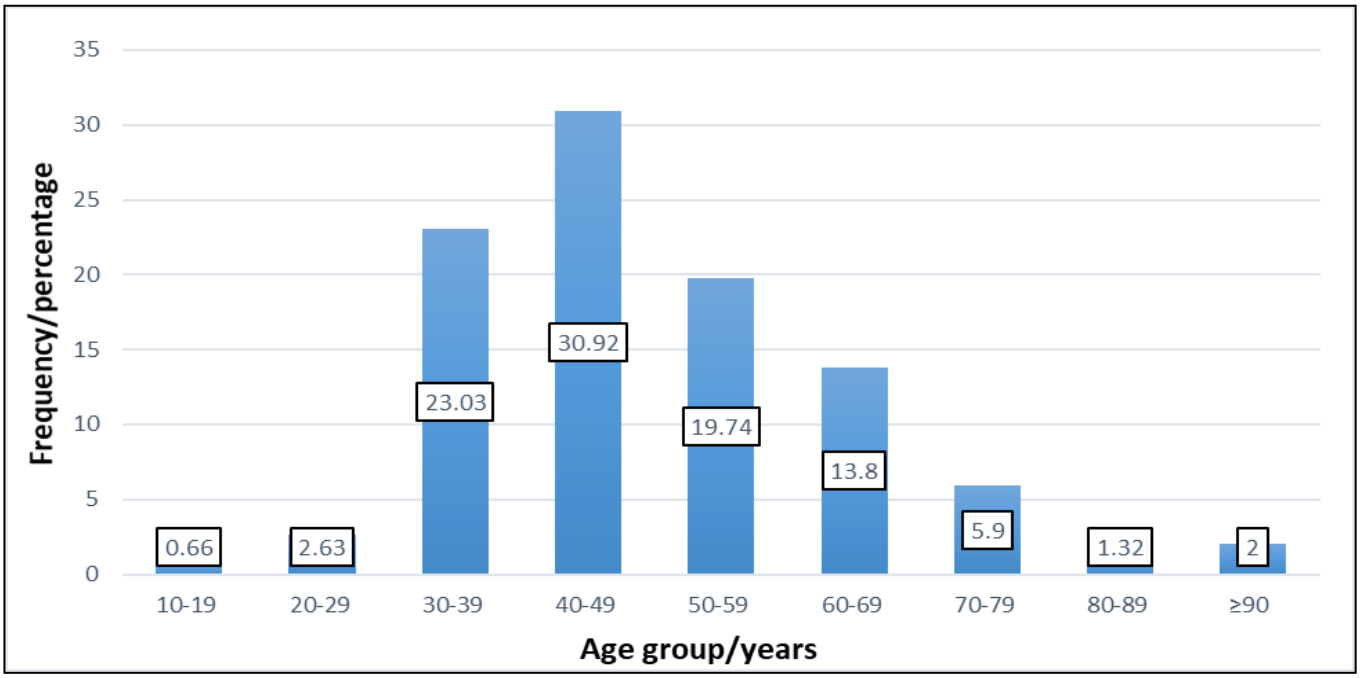

Figure 3: Age Group Distribution Breast Cancer

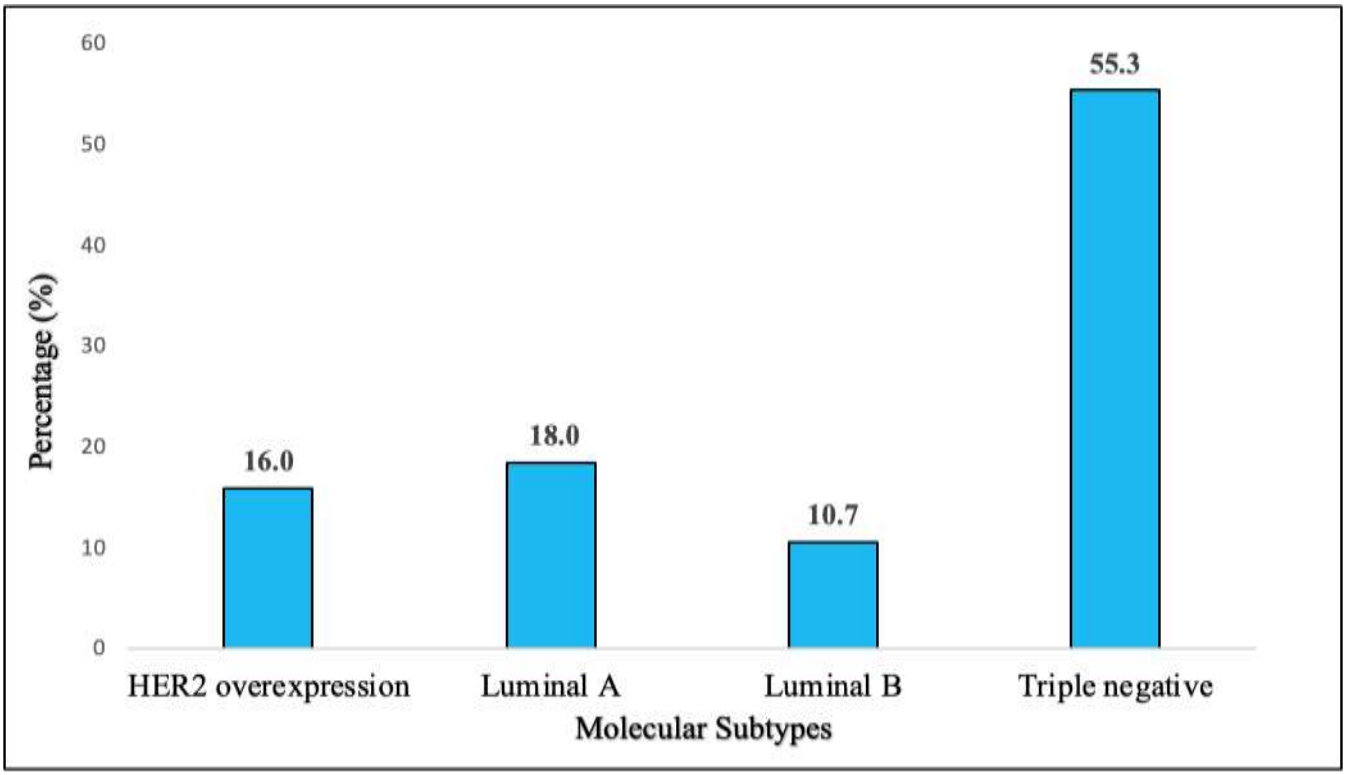

Figure 4: Distribution of Breast Cancer Molecular Subtypes in Ghana

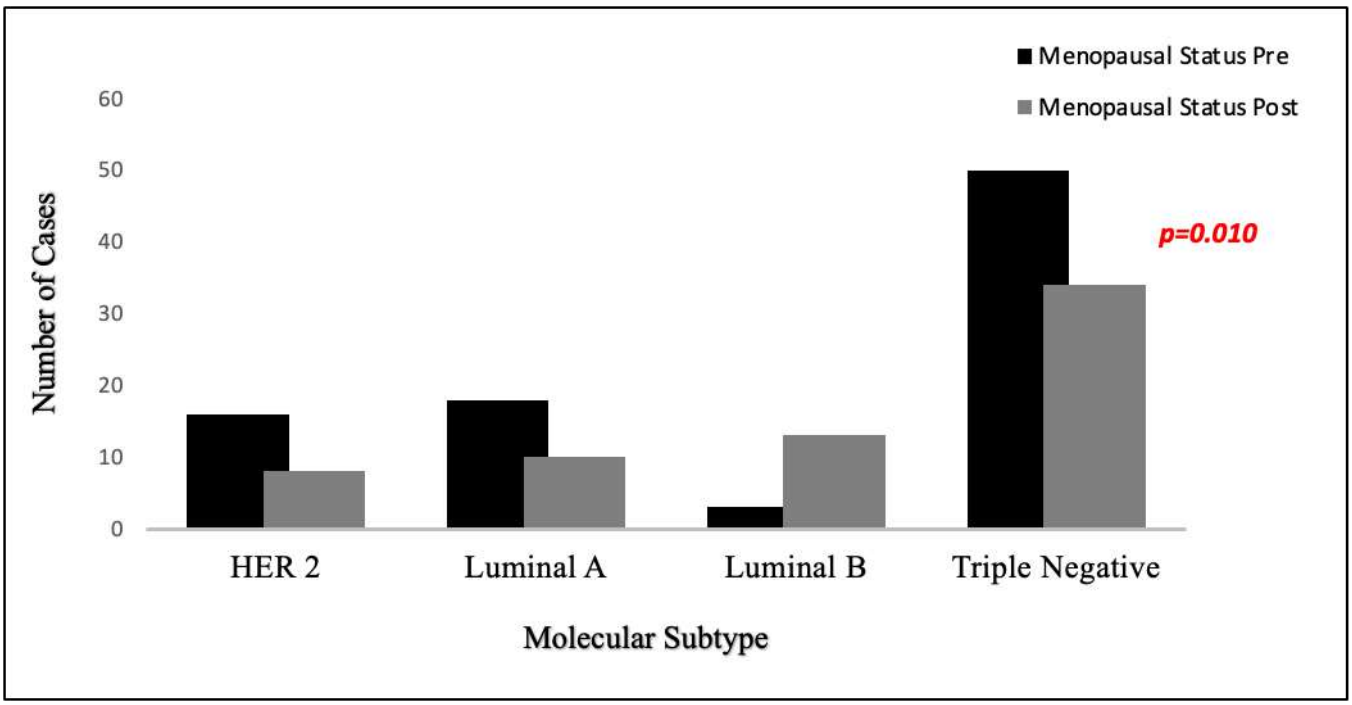

Figure 5: Association of Molecular Subtypes with Menopausal Status

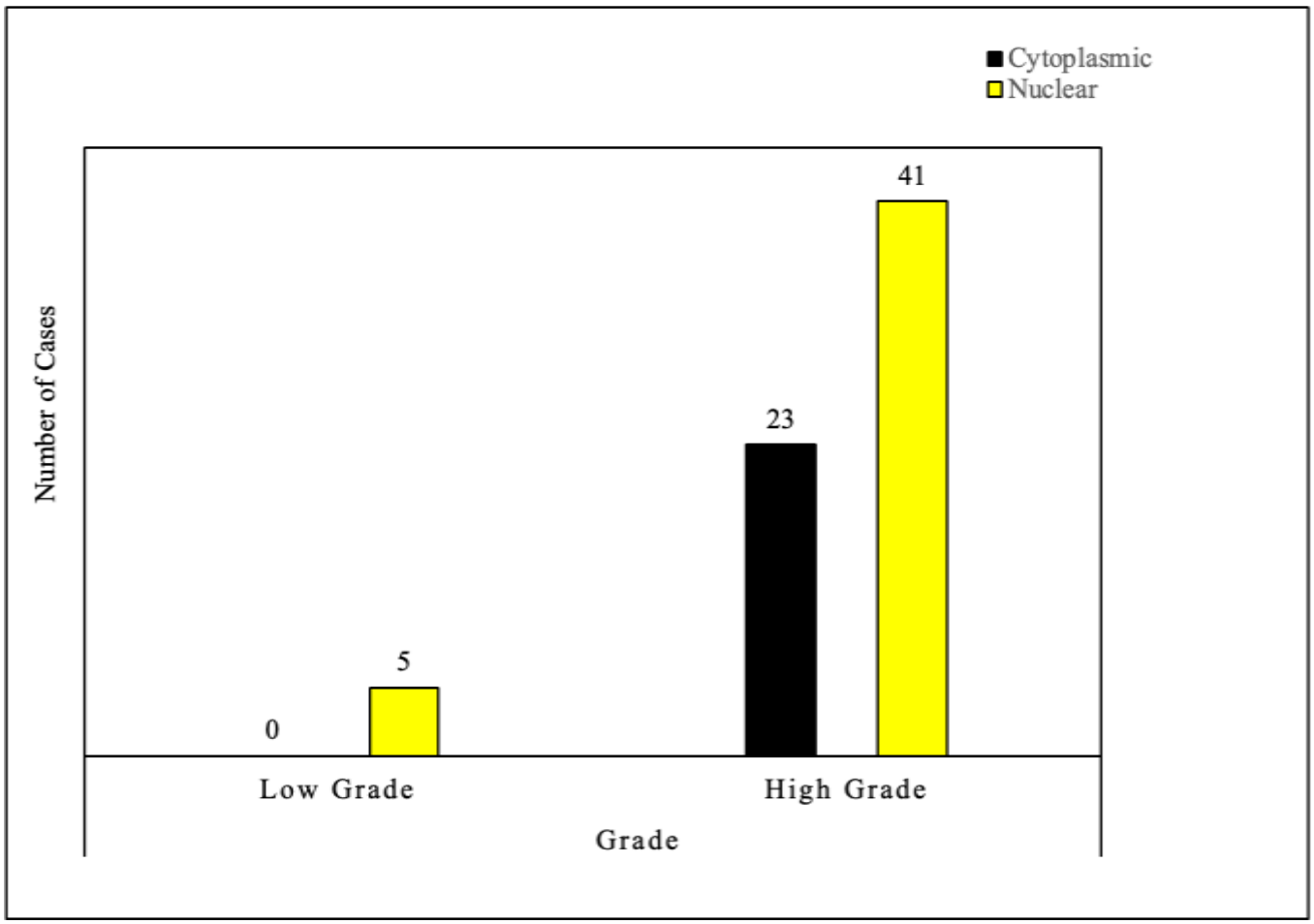

Figure 6: Distribution of Kaiso Localization against Tumour Grade

Discussion

Treatment of breast cancer is highly dependent on the molecular markers present in the cancer. Therefore, the evaluation of biomarkers is relevant to projecting the response to treatment. It has become noticeable from studies (18,20,29,30) that Kaiso can mediate several of the vital tumour-acquired capabilities which include invasion, metastasis, apoptosis, cell proliferation, and inflammation. This study therefore sought to explore the prognostic and or predictive significance of Kaiso as a biomarker for Ghanaian breast cancers as none of such study has been carried out in the country.

From the results, majority (55.3%) of the cases are TNBC. This agrees with, although slightly higher than prior studies conducted in Ghana with regards to molecular subtypes (5,31,32). This confirmed that more than half of all breast cancer cases in Ghana do not express ER, PR and HER 2. Studies from Nigeria (12,33) also reported TNBC as the predominant molecular, however, some studies from the Eastern African countries reported TNBC second to luminal A (34,35). This suggests that breast cancer presentation is not the same across sub regions. The percentage of TNBC cases recorded is higher than observed in studies conducted among the western counterparts (36,37), again emphasizing the differences between breast cancer in Ghana and by extension African, and other ethnicities.

Consistent with other studies, this study found that breast cancer in Ghana is significantly higher *(p=0.010, Fig.3)* in premenopausal women (Ameh-Mensah et al., 2021; Atta Manu et al., 2020; Quayson et al., 2014). This solidifies the assertion that breast cancers in African women are more prevalent in the reproductive ages (35,39,41). The reason could be due to many factors but mainly the relatively younger age of menarche in women of African descent (42). Scientists have explained that breast cancer aetiology comprises several pathways, one of which relates to hormones such as oestrogen which increases cell proliferation thereby increasing the chance of mutations occurring during DNA replication. This pathway suggests that the timing of puberty could potentially affect breast cancer risk because it is a time of substantial changes in the hormonal environment (43). The mean age, 49.3 (17-92) recorded from this study is lower compared to those in other parts of the world (44,45) further proving that there is disparity in breast cancer presentation in different populations.

A higher number of the cases were high grade tumours and associated with lymphovascular invasion. This could reflect a surrounding tumour microenvironment that predicts underlying aggressive tumour and worse prognosis. It also indicates that majority of cases in this study may have worse survival outcomes (46). With about 98.8% of the cases expressing Kaiso, it can be said that Kaiso is highly expressed in Ghanaians and also supports the notion that Kaiso is highly expressed in women of Africa descent (14). It is noteworthy that all the low-grade cancers that tested positive to Kaiso had the expression in the nucleus. This suggests that those cancers could proceed to become very aggressive since nuclear localization of Kaiso has an influence on the degree of aggressiveness (19). Kaiso binds to both methylated CpG dinucleotides and the KBS consensus sequence. It has been found that its interaction with wild type p53 activates the transcription of proapoptotic genes whiles its interaction with mutant p53 potentially represses transcription of the proapoptotic genes (47). This may explain Kaiso's association with high aggressiveness in Ghanaian breast cancer as most cases express mutant p53 as put forward by Ameh-Mensah et al (38). Most of the TNBC cases showed a higher nuclear Kaiso expression compared to cytoplasmic expression agreeing with the report of Jones et al (48). It has been suggested that the high expression of Kaiso in the nucleus positively correlates with local invasion, poorer overall survival and lymph node metastases (47).

Conclusion

From the findings, it could be said that most of the breast cancers in Ghana are triple negative in nature and of high histologic grade. Almost all the cases expressed Kaiso with more than half showing nuclear expression. Significant associations were seen between Kaiso expression, Kaiso localization and lymphovascular invasion. This suggests that Kaiso is highly expressed in Ghanaian TNBC, associated with worse outcomes in patients with aggressive tumour types and hence may be considered as a potential prognostic marker for TNBC.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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