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ABSTRACT

Background: Histological diagnosis is crucial to the management of breast diseases. It determines the kind of disease, the treatment modalities, and the outcome of management. Our department receives breast biopsies from the northern sector of Ghana constituting over 50% of the Ghanaian population. This study aimed at elucidating the pattern of disease and associated traditional prognostic indices of breast cases in our department over a period of 9 years.

Methods: Information on the demographic characteristics and the histological diagnoses made on all breast cases received and processed in the department were accessed and entered into an Excel spreadsheet. Slides were reviewed and IHC was done on suitable cases. Descriptive statistics were generated using IMB-SPSS version 23.

Results: A total of 4276 breast cases were received by the department within the study period, with 97.6% being female. Age ranged (female/male) from 10 to 98/13 to 102 years, with mean ages of 38.2 years (SD ± 16.7) and 41.15 years (SD ± 21.6), respectively. Cases were evenly distributed in both left and right breasts and 4.3% were bilateral. Inflammatory conditions were seen in 7.5% of cases. The most diagnosed benign tumor was fibroadenoma (54%), followed by fibrocystic change (8.1%). Gynecomastia was diagnosed in 66.3% of males. Malignant cases were 38.6%, with invasive carcinoma NST being the most frequent (87.5%). Histological grades were I = 9.4%, II = 41.6%, and III = 49%. Molecular subtypes were luminal A (19.8%), luminal B (9.9%), Her2 (16%), and TNBC (54.3%).

Conclusion: Our findings show an increase in breast cancer cases compared to previous studies in our center, suggesting increased awareness and improved diagnosis. However, this increase is consistent with most studies in sub-Saharan Africa.

1. Introduction

The series of ductal and lobular growth, lactogenesis, and regression that are consequent to response to menstrual cycle-associated estrogen and progesterone as well as pregnancy- and lactation-related hormones predispose the breast to a myriad of disorders. The majority of these disorders present in the form of breast masses, pain, or nipple discharge and may be accompanied by either changes in overlying skin or lymphadenopathy [1–6].

Even though most breast disorders turn out to be benign, a systemic review and meta-analysis have revealed that the risk of breast cancer increases up to twofolds in individuals who present with benign breast diseases without atypia [7]. More importantly, individuals with benign breast disease with atypia have up to a fivefold increased risk of developing breast cancer. Atypical lobular hyperplasia and atypical ductal hyperplasia are well-known pre-malignant conditions that frequently get upgraded to lobular carcinoma *in situ* and ductal carcinoma *in situ*, respectively, following continual pathological assessment [7,8]. This phenomenon therefore stipulates that adequate attention be given to all forms of breast diseases that may be presented at health facilities.

Reporting on the entirety of breast diseases diagnosed is therefore encouraged, in order to provide more information on the pattern of incidence of breast diseases, enhance clinical knowledge, and inform on the best risk assessment models as well as screening and treatment practices. This may further lead to increased research into chemo-preventive therapies to limit the incidence of breast cancer [7]. Accordingly, various reports have been made on the patterns of benign and malignant breast diseases. Through this, it has been realized that there are differences in the commonest types of benign breast diseases as well as the histological and molecular types of the malignant conditions across different populations [9,10].

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⬤ Supplemental data for this article can be accessed here.

This study was therefore conducted to assess the patterns of occurrences of benign and malignant breast diseases presented to the PaThology Department of Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana. Similar studies [11–14] have previously been conducted in the same department, so this study will assess how the patterns seen have changed over time, and how the current patterns compare with other studies elsewhere in Ghana and other countries.

2. Materials and methods

2.1. Samples

Following ethical approval (Ref: CHRPE/AP/417/ 18) from the Research and Development Unit, KATH and the Committee on Human Research, Publication and Ethics (CHRPE)-KNUST, information on all breast biopsies that were presented to the Pathology Department of KATH from 2009 to 2017 were retrieved. KATH serves as the main referral center for the northern sector of Ghana. Within the period, breast biopsies for 4276 cases were received and processed. Data obtained on the cases included patient demographics such as age and sex. Site of biopsy, histopathological diagnoses, and histological grades of malignant conditions were also noted.

2.2. Case review and immunohistochemistry

All consecutive archived tissues in the form of formalin-fixed paraffin-embedded (FFPE) blocks with their corresponding hematoxylin and eosin (H&E)-stained slides were retrieved for subsequent immunohistochemistry on the malignant cases. New H&E slides were made from the available FFPE blocks where necessary. The slides were reviewed, and 203 suitable malignant cases were selected for tissue microarray (TMA) construction and immunohistochemistry. TMA was constructed using a Micatu MicaArray Gen 3.0, after matching corresponding H&E slides and FFPE blocks; two representative cores were taken for each case. Immunohistochemistry was performed using antibodies for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor II (HER 2), and Ki-67, according to the suppliers' specifications. Scoring of immunohistochemistry for ER, PR, and HER2 was performed following the American Society of Clinical Oncology/College of American Pathologists guidelines [15,16]. Ki-67 scoring was performed in accordance with the guidelines outlined by Abubakar et al. [17]. Table 1 shows the details of the antibodies used.

**Table 1.** Patient demographics and histopathological characteristics of breast cases from 2009 to 2017, KATH.

Category	Frequency	Percentage
Gender		
Female	4170	97.6
Male	104	2.4
Age, years		
10–19	519	12.3
20–29	1072	25.4
30–39	754	17.9
40–49	788	18.7
50–59	560	13.3
60–69	294	7.0
70–79	172	4.1
80–89	43	1.0
90and above	12	.3
Site of biopsy		
Left breast	1824	47.2
Right breast	1875	48.5
Both breasts	165	4.3
Tumor status		
Benign	2596	61.4
Malignant	1631	38.6

2.3. Statistical analysis

Patient demographics, histological details, and immunohistochemistry scores were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23. Descriptive statistics were computed for all variables.

3. Results

Of the 4276 cases received and processed, 4170 (97.6%) were from female patients. These cases ranged from 10 to 98 years with a mean age of 38.2 years (SD ± 16.7). The male cases ranged from 13 to 102 years with a mean age of 41.15 years (SD ± 21.6). In all, 1824 (47.2%) cases involved the left breast, while 1875 (48.5%) were from the right breast. Only 165 (4.3%) were bilateral conditions. For histological diagnoses, benign breast disorders, including inflammatory conditions, were commonest, making up 61.4% (2596) of all cases. Malignancies were reported on 1631 (38.4%) cases. Among the malignant cases that were graded histologically, 621 (49%) were grade III, 528 (41.6%) were grade II, while 119 (9.4%) were grade I. Table 1 details a summary of the demographic and histopathological characteristics of the cases. The benign cases were commonly diagnosed in women in the third decade of life (20–29 years), whereas the malignant conditions had a median occurrence in the fifth decade (40–49 years). Figure 1 shows the comparative distribution of the benign and malignant diagnosis among age groups. Fibroadenoma was the modal benign condition, consisting of 1401 cases, making 54% of all benign conditions. Fibrocystic change was the second most frequent benign condition, diagnosed in 209 cases (8.1% of benign cases). Fibrocystic change was followed by
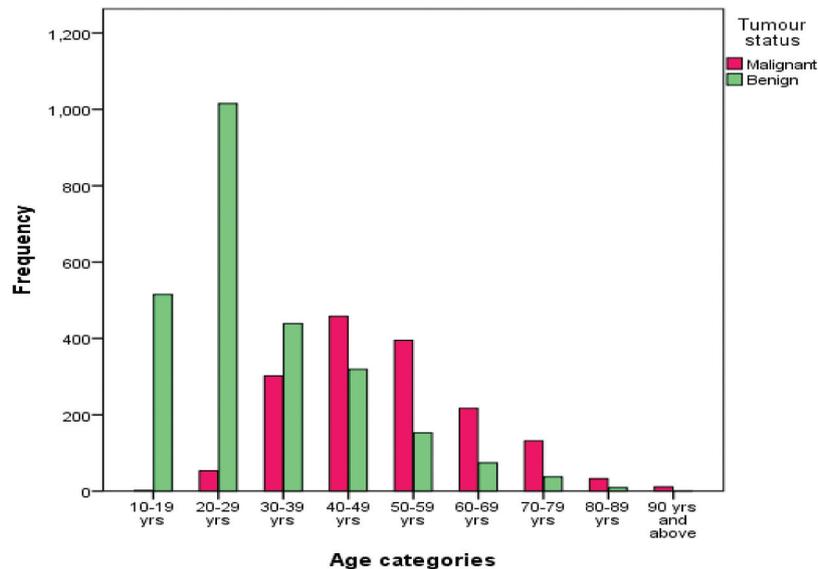
Figure 1. Distribution of benign and malignant cases according to age groups.

Table 2. Histological diagnoses of breast cases from 2009 to 2017, KATH.

| Category	Frequency	Percentage
Histological diagnoses of benign cases		
Fibroadenoma	1401	54.0
Fibrocystic change	209	8.1
Abscess	199	7.7
Mastitis	113	4.4
Gynecomastia	70	2.7
Intraductal papilloma	55	2.1
Fat necrosis	47	1.8
Duct ectasia	40	1.5
Phylloides tumor	39	1.5
Lactating adenoma	37	1.4
Juvenile fibroadenoma	30	1.2
Cyst	27	1.0
Others	329	12.6
Histological diagnoses of malignant cases		
Invasive carcinoma NST	1427	87.5
Ductal carcinoma in situ	60	3.7
Invasive lobular carcinoma	39	2.4
Mucinous carcinoma	32	2.0
Metaplastic carcinoma	24	1.5
Others	49	2.9
Histological grade (of malignant cases)		
Grade I	119	9.4
Grade II	528	41.6
Grade III	621	49

abscess. Gynecomastia was diagnosed in 70 (66.3%) males and made up 2.7% of all benign cases. Of the 2596 malignant cases, invasive carcinoma of no special type (NST) was the most frequent diagnosis, with 1427 cases making up 87.5% of all malignant cases. Ductal carcinoma *in situ* was the second most frequent malignant condition, diagnosed in 60 cases, making up 3.68% of malignant cases. Twenty out of 106 males had malignant diseases within the period. Table 2 shows the details of the histological diagnoses made within the study period. Immunohistochemistry revealed that the majority of the cases (54.3%) were triple negative, followed

by luminal A, with 32 (19.8%) cases. Results of the molecular subtypes are displayed in Figure 2.

4. Discussion

There is a notable degree of fear and anxiety associated with the observation of symptoms of breast diseases due to the potential of diagnosis with breast cancer or pre-malignant lesions that are associated with an increased risk of developing malignancies later in life. An in-depth knowledge of the pattern of occurrence and the predominant age groups mostly implicated in various forms of breast diseases will afford enhanced clinical diagnosis and effective counseling while waiting for terminal pathologic reports [18]. This will further lead to effective, targeted education on breast diseases, to diffuse the fear and anxiety among age groups which frequently present with benign conditions and stress on the need for early reporting among age groups that are most susceptible to malignant conditions [19].

This audit of breast biopsies received and processed at the Pathology Department of KATH from 2009 to 2017 showed that the ages of persons who reported with breast problems ranged from 10 to 102 years. The age range of cases is wider in the current study, and the proportion of cases above 80 years is higher when compared with studies in the same institution from the year 1998 to 2005 [11,12]. This may support the report of an improvement in life expectancy among the general population [20,21]. Females formed the vast majority of cases, with the younger ones (mean age = 30.39 ± 13.6) presenting predominantly with benign breast diseases, while older women (mean age = 50.26 ± 13.59) presented predominantly with malignant diseases (ANOVA p-value <0.001).
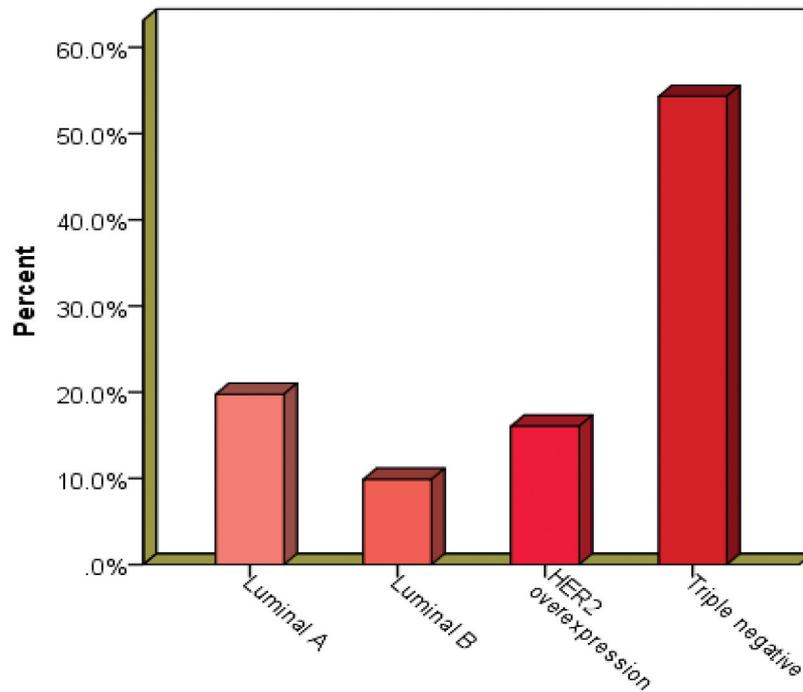
Figure 2. Molecular subtypes of malignant breast cases.

Although this relationship is established in the literature [11,22], the mean age of the benign cases recorded in this study is higher than that reported by other studies in Ghana [23] and Nigeria [10].

In keeping with published data, benign breast diseases were the commonest diagnosis made; this study recorded 61.4% of cases as benign. The percentage of cases in this cohort that had benign conditions is, however, lower than that reported by a previous study in the same department, where benign cases made up about 73.8% of the cohort [11]. Again, it is lower compared to studies in Nigeria [24,25] which reported 71.2%, 72.4%, and 78.7% of cases as benign and another in Tanzania [26] which reported 80.4% as benign cases. Other studies, however, reported lower proportions of benign cases [27,28].

Fibroadenoma was the most frequent benign breast disease seen in our cohort (54% of benign conditions), while fibrocystic change came in second (8.1% of benign conditions). Although some disparities exist in the proportions of fibroadenoma and fibrocystic change across different populations and geographical settings with some few studies reporting higher proportions of fibrocystic change [29], it is widely acknowledged that fibroadenoma is the commonest among black-skinned populations [22] as made evident by numerous other studies [10,-24–27,30]. More so, there is no breast cancer screening program in Ghana, and cases in this study, like other previous studies, are symptomatic breast cases. Most studies on symptomatic breast cases have higher percentages of fibroadenoma than the other

benign breast lesions seen from the screen-detected cases.

The incidence of breast cancer, which is the most common malignancy among females, has been tipped to be on the rise, especially among African populations where incidence was previously low [21,31,32]. Importantly, the breast cancer mortality rates reported among Africans are much higher in comparison to that of Caucasians [33]. Ghana bears its fair share of the low survival rates among breast cancer patients in Africa, with a 5-year survival rate of 47.9% [34]. Consequently, breast cancer is the leading cause of cancer-related deaths among Ghanaian females [35]. This low survival rate/high mortality rate reflects various deficiencies including low levels of education on breast health, delay in health-seeking, delays in diagnosis, high prevalence of aggressive histological and molecular characteristics, and high cost of treatment [19,36–39].

Results from demographic and histological characteristics from this audit generally agree with the literature on African breast cancer. 38.6% of cases in this cohort were diagnosed with various malignant diseases. This figure is notably higher than the 19.9% previously reported by a study on cases presented at the same department in 2005 [11]. Furthermore, it is higher than the 20.9% reported in Accra, Ghana, on cases received from January 2000 to December 2004 [40]. The increase in the proportion of malignant breast diseases in our setting is supportive of an increase in cancer incidence outlined by the rise in age-standardized rates of breast cancer incidence in

Kumasi between 2012 and 2015 [41,42]. The proportion of malignant cases reported in the current study is in agreement with the recent studies in Accra [20,34]. The synchronous increase in the breast cancer incidence in our center and others in Accra could be attributed to a number of factors acting in concert. The principal factors among these are changes in population dynamics that favor population growth and improved life expectancy, obesity, and increased use of hormonal contraceptives [43,44]. The 2010 population statistics of Ghana showed a population growth of 30.4% over the 2000 population figure and an increase in the proportion of persons living beyond 50 years in the same period [45]. An analysis of data from the WHO-Study on global AGEing and adult health (WHO-SAGE) waves 1 and 2, along with numerous other studies on different population groups, also revealed a rapid increase in the prevalence of overweightness and obesity among the Ghanaian adult population [46,47]. Similarly, the Performance and Accountability 2020 (PMA2020) surveys indicate that Ghana has one of the highest annual rates of modern contraceptive uptake in Africa [48].

The mean age of females who presented with malignant diseases was 50.26 years, and invasive carcinoma NST was the predominant malignant disease (87.1%). The age distribution and histological diagnosis are consistent with the published literature on African breast cancer, where invasive carcinoma NST is predominant, and the mean age of malignant female cases was 10–15 years below that of Caucasian women [49]. The majority of the histological types seen among African cases are associated with aggressive phenotypes such as high histological grades. Previous studies made in Ghana [13,14,20,34,50] all reported majority of high-grade carcinomas (grades II and III). In each of these studies, an addition of the proportions of grade II and grade III tumors amounted to more than 80% of cases.

The biological behavior of tumors is inherently dependent on the molecular alterations that drive the tumor characteristics [51]. Disparities have been reported in the molecular characteristics of breast cancer between women of African ancestry and Caucasians, with African and African-American women five times less likely to express estrogen and progesterone receptors. Women of African descent consequently present with triple-negative (lack of ER and PR expression) breast cancer [52]. Epidemiologic and genomic analyses point to genetic differences associated with race/ethnicity as the major reason for this disparity. The results from this study revealed that more than half of the cases (54.3%) were of the triple-negative subtype. Triple-negative breast cancer is known to be associated with aggressive biological behavior, with high rates of proliferation and metastasis. Additionally, a lack of widely recognized and accepted molecular targets as adjuvant therapies leaves cases with this molecular subtype with poor prognosis and unfavorable outcomes [53,54].

Similar to the 54.3% triple-negative cases recorded by this study, a previous study [13] in the same department reported 42.7% as triple-negative cases. On the contrary, other studies [14,55] on samples from the same department reported lower proportions of cases being triple negative. The results of the current study are, however, in agreement with other studies in Accra, Ghana [34,50], and sub-Saharan Africa [56–58].

5. Conclusion

In conclusion, findings from this study show an increase in the incidence of breast cancer compared to previous studies in our center. Similar trends have been observed in recent studies in Accra, Ghana. This supports a rise in breast cancer among Africans but also suggests an increased awareness and improvement in diagnosis. Triple-negative phenotype was predominant, in agreement with other studies in sub-Saharan Africa.

Disclosure statement

No potential conflict of interest was reported by the authors.

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