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Molecular Biology of Breast Cancer in the Africa with the study of Ductal Breast Carcinoma in Situ

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Abstract

Casting-type calcifications and a histological image showing cancer-filled duct-like structures have been described as breast cancer with neoductgenesis. In a group of women with DCIS who had received a lot of follow-up, we associated histological neoductgenesis and mammographic characteristics with prognosis. According to Tabár, the characteristics of mammography were divided into seven classes. Lymphocyte infiltration, periductal fibrosis, and duct concentration were used to characterise histopathological neoductgenesis. IBE in situ and invasive occurrences were the endpoints. High nuclear grade, ER and PR negative, and HER2 overexpression were all associated with casting-type calcifications, but not with neoductgenesis or each other. Neoductgenesis and casting-type calcifications were both associated with a nonsignificantly decreased risk of invasive IBE, with corresponding HRs of 0.38 (0.13-1.08) and 0.82 (0.29-2.27); the respective HRs for an in situ IBE were 0.90 (0.41-1.95) and 1.60 (0.75-3.39). There is no evidence that DCIS patients with casting-type calcifications have a worse prognosis. We are unable to explain why a more severe DCIS phenotype did not indicate a worse prognosis. It is necessary to conduct more research on the factors that induce the transition from in situ to invasive cancer.

A recent classification of breast cancer into four unique molecular subtypes, each with a distinctive prognosis, targeted treatment options, and/or clinical outcomes, was made using gene expression profiling and its substitute immunohistochemistry (IHC) markers. In order to better understand the clinical pathological characteristics and taxonomy of the many molecular subtypes of breast cancer in Eritrea, in the Horn of Africa, preliminary research will be conducted. Twenty patients were female, and at the time of presentation, 68% of them were under 50 years old. Ninety percent were histological grade 3 invasive carcinomas of no particular type. The molecular subtypes were basal-like (10%), unclassified (5%), HER2 (5%), luminal A (55%) and luminal B (5%). (25%). 35 percent of women under 50 with grade 3 tumours had triple negative carcinoma (basal-like and unclassified combined), that was most common in these women (71 percent). Eritrean women experience breast cancer at a younger age and with a higher histologic grade. The triple negative and luminal a molecular subtypes are the two most common forms. For Eritrean women with breast cancer, knowing the molecular subtype via surrogate IHC markers has significant therapeutic and prognosis consequences.

Keywords: Calcification; Mammography; Neoductgenesis; Immunohistochemistry; Breast Cancer

Introduction

A subtype of early breast cancers exhibiting distinctive "casting type" calcifications on mammograms, either with or without an associated tumour mass, has been described. These casting-type calcifications can occasionally be found in great abundance and are abnormally densely packed; they frequently fill a whole lobe. As duct-like structures loaded with malignancy that are linked to periductal lymphocyte infiltration and a periductal desmoplastic reaction. Breast cancer with neoductgenesis was used to describe this duct-forming process because it does not meet the traditional definition of invasive or in situ breast cancer [1]. This mammographic and histological image was likewise connected to tenascin-C (Tn-C) overexpression. Recently, we published a report in which we attempted to define and quantify the histopathological criteria for the suggested diagnosis of breast cancer with neoductgenesis.

We demonstrated that in cases with ductal breast carcinoma in situ (DCIS), with or without an invasive component, the combination of duct concentration, lymphocyte infiltration, and fibrosis was associated to mammographic calcifications (crushed stone-like and casting type calcifications combined). Together, these three histopathological characteristics—particularly HER2 overexpression—were also linked to a more aggressive tumour phenotype [2]. Mammography is frequently used to diagnose DCIS, and instances with malignant micro calcifications on the mammogram frequently show DCIS on a preoperative core biopsy. Overall, the prognosis for women with DCIS is very good, but occasionally, the condition might return as an invasive cancer or even a generalised disease.

A group with DCIS with a markedly increased chance of recurrence or even risk of breast cancer death may be identified, which may have an impact on treatment choices. If we were able to identify those with a low risk of developing invasive cancer, we might be able to avoid radiation vigour mastectomy in many cases. The purpose of this study was to compare the prognosis of a large cohort of women with primary DCIS who had a lengthy follow-up with mammographic characteristics, particularly casting type calcifications [3]. Additionally, we examined the relationship between the mammographic criteria and previously established histological standards for breast cancer with neoductgenesis.

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The biggest cause of cancer-related death worldwide among women is breast cancer. Africa has the lowest incidence; however it has recently been rising along with a rise in mortality. When compared to Caucasian American and western European women, breast cancer in African and African-American women is characterised by late presentation, younger age, advanced stage, higher grade, more negative hormone receptor status, and poorer prognosis [4]. Although socioeconomic background, availability to screening, and variations in treatment choices may be the root causes of these discrepancies, the disease's inherent biology may also contribute to the various outcomes.

Breast cancer is now thought to be a heterogeneous disease made up of various molecular subgroups that independently correlate with disease outcomes. Different breast cancer molecular subtypes have been found using gene expression microarrays, including two types of ER-negative tumours (basal-like and HER2-enriched) and two types of ER-positive cancers (luminal A and luminal B) [5]. Using antibodies to the ER, PR, HER2, and Myoepithelial markers cytokeratin (CK) 5/6, immunohistochemistry (IHC) is a more straightforward technique for identifying these molecular subtypes. Despite being more precise, gene microarray analysis is not frequently employed in clinical practise due to its higher cost.

Breast cancer is divided as luminal A (ER+ and/or PR+, HER2+), luminal B (ER+ and/or PR+, HER2+), HER2 type (ER, PR, and HER2+), basal-like (ER, PR, HER2 and CK 5/6 positive), and unclassified using these surrogate IHC markers (negative for all markers). According to the Carolina breast cancer study, the distributions for luminal A, luminal B, HER2 type, basal-like, and unclassified were 51%, 16%, 7%, 20%, and 6%, respectively. The proportions of luminal A, luminal B, HER2 type, basal-like, and unclassified cancers were found to be 27 percent, 2 percent, 15 percent, 27 percent, and 28 percent, respectively, in a study of native West African women. In a different study from Nigeria, it was discovered that 77.6 percent of the tumours were luminal type A, 2.6 percent were luminal type B, 15.8 percent were basal-like, and the remaining 4.0 percent were HER2 type. Studies from Sudan and North Africa (Egypt) found higher percentages of ER- and PR-positive tumours and lower percentages of basal-like (10%) phenotypes, while studies from North Africa (Egypt) reported luminal A, luminal B, 11.8 percent HER2 type, 11.3 percent basal-like, and 7.9 percent unclassified. The HER2 subtype of breast cancer was not evaluated in the most recent study [6]. Therefore, no consistent pattern of breast cancer biology within the continent of Africa has been shown by the available literature.

Patients with luminal A subtype typically have the best prognosis, while those with luminal B subtype typically have a somewhat worse prognosis. The prognosis is the worst for the HER2 and basal-like subtypes. HER2 and HER2-positive luminal cancer outcomes, however, have significantly improved more recently because to HER2 targeting drugs. Compared to postmenopausal African-American and non-African women, premenopausal African-American women tend to have a higher prevalence of the most aggressive type of triple negative breast cancer, known as basal-like (39 percent, 14 percent , and 16 percent resp) [7]. Black women are less likely to develop luminal A cancers with a favourable prognosis. African women's breast cancer is more likely to be triple negative, express hormone receptors less frequently, and develop at a younger age, according to studies.

According to the studies described above, there are variations among molecular subtypes in terms of their geographic distribution, racial makeup, age, prognosis, and expressed therapeutic targets. It's possible that the biological characteristics of breast tumours in various parts of Africa vary. More in-depth research, such gene microarray expression profiling and proteomics, are required to further our understanding of the potentially unique biologies of breast cancer in various African locations, and these current IHC findings are only proxies for those biologies [8].

The prevalence of the molecular subtypes and their relationship to clinical-pathological characteristics has not been documented in the Horn of Africa, including Eritrea. The purpose of this study was to identify these parameters utilising surrogate IHC analysis and to give evidence-based data for management guidelines for breast cancer in the future. This is the first case series pilot research of its kind in this part of Africa.

Materials and Methods

Patients

All the Uppland and Västmanland counties in Sweden's women who received a primary DCIS diagnosis between 1986 and 2004 were included. In a previous presentation, the population-based cohort's initial clinical and histological characteristics were discussed.

Histopathology and Immunohistochemistry

Prior to the creation of tissue microarrays (tma), a second histological examination of each case was performed, and the histopathological grade of DCIS was categorised in accordance with the European Organization for Research and Treatment of Cancer (EORTC) standard. Immunohistochemistry (IHC) was used to analyse Tma data for ER, PR, and Ki67, while SISH or IHC was used to analyse Tma data for HER2. When SISH was unsuccessful, the HER2 status was primarily relied on the IHC data, and cases were deemed HER2 positive if the IHC score was 3+ using the HercepTest.

Classification of Mammographic

Seven groups of mammographic findings were reclassified: (1) a stellate lesion without associated calcifications, (2) a circular or oval mass without associated calcifications, (3) powdery calcifications with or without an associated tumour mass, (4) crushed stone-like (pleomorphic) calcifications with or without an associated tumour mass, (5) casting type calcifications with or without an associated tumour mass, (6) others, that is, galactographic findings, and (7) Those who had a normal mammography made up the last group, which was included in the analyses [9].

Immunohistochemistry

Using the standard (H + E) morphological assessment, the invasive breast cancer histologic subtype and Nottingham histologic grade were determined. Using a Ventana Benchmark immunostainer (Tucson, Arizona), the manufacturer's antibodies (clones 6F11 for anti-ER, 1A6 for anti-PR, 4B5 for HER2/neu, and D5/16B4 for CK5/6) were used to perform the immunostaining for the human epidermal growth factor 2 (HER2/neu), the oestrogen receptor (ER), the progesterone receptor (PR), and the CK5/CK6. If 1% or more of the invasive carcinoma cells' nuclei were stained, ER and PR were declared positive. HER2/neu stains were graded according to the College of American Pathologists' criteria as 0, 1, 2, and 3+. More specifically, a score of 3+ indicated that there was an overexpression of the HER2/neu gene in more than 30% of the tumour cells. A smaller amount of discoloration was viewed negatively. For the HER2/neu gene amplification, fluorescence in situ hybridization was not done. Any (weak or strong) cytoplasmic and membranous invasive carcinoma cell staining was considered positive for cytokeratin 5/6.

The 3, 3-diaminobenzadine chromagen and the haematoxylin counter stain, respectively, were used to observe colour development and background staining. By skipping the primary antibody process, suitable negative controls for immunostaining were created.

In this study, the molecular subtypes of breast cancer were classified as luminal A (ER positive and/or PR positive, Her2 negative), luminal B (ER positive and/or PR positive, Her2 positive), Her2 type (ER negative, PR negative, Her2 positive), basal-like (ER negative, PR negative, Her2 negative, and CK5/6 positive), and unclassified (ER, PR, Her2, and CK5/6 negative). By this classification, both the basal-like and the unclassified categories are included in the term "triple negative" (ER, PR, and Her2 negative) cancers.

Data Analysis

The SPSS version 17 programme was used for data analysis. The Chi-square test for categorical variables was used to examine tumour behaviours between breast cancer subtypes. The age of diagnosis varied between breast cancer subtypes, hence a one-way analysis of variance was used to compare this. The size of the tumour and the histologic grade of the various subtypes were compared using Kruskal-Wallis tests. The connection between subtypes with fewer than five categorical cells and categorical pathologic features was investigated using Fisher's exact tests. When is deemed statistically significant, all values were based on 2-tailed tests of significance.

Results

Mammograms were reviewable in 432 of the 458 instances. 89 (20.6%) of the 432 mammograms were deemed to have casting-type calcifications. In classifying the mammograms as having casting type calcifications or not, the kappa-value between the two reviewers was 0.66 (95 percent CI 0.57-0.76). In comparison to other mammographic features, screening mammography was more frequently able to identify the casting type calcifications as well as other forms of calcifications. Casting-type calcifications on the mammography were not associated with more mastectomies being performed or more adjuvant RT being administered following breast-conserving surgery, as far as we could tell (BCS). The presence of HER2 overexpression, ER negative, PR negativity, and greater nuclear grade were all associated with casting type calcifications.

Only four of the seven women who met all three criteria—casting type calcifications, DCIS with neoductgenesis, and high expression of Tn-C—had both casting type calcifications and a DCIS displaying histological neoductgenesis.(fig.1) These seven women were the only ones. Survival analyses were performed despite the limited sample sizes, and no statistically significant differences were found. In situ IBEs were established in two of the seven instances with casting-type calcifications and DCIS with neoductgenesis. The remaining five instances didn't happen again. Only two of those four cases—the same two with an in situ IBE—had occurrences that met all three criteria (mammographic casting type calcifications, neoductgenesis histopathologically, and Tn-C overexpression).

Tumor size, lymph node metastasis, and invasive tumour necrosis had little effect on the distribution of molecular subgroups. Molecular subtype significantly correlated with grade and lymphatic invasion (P = 0.04, respectively).The majority of molecular intrinsic subtypes other than luminal A tumours were grade 3 (8/9, 89%) while luminal A tumours were generally Nottingham grades 1 or 2 (64 percent, 7/11).

Discussion

Based on a cohort of women with pure DCIS and more than 15 years of follow-up, casting type calcifications could not be linked to a worse prognosis in this study. In cases with casting-type calcifications, we discovered a lower probability of invasive events and a non-significantly higher incidence of brand-new in situ IBEs.

Our goal was to incorporate DCIS cases with calcifications resembling mammographic casting, neoducta symptoms on histopathology, and high Tn-C expression in a model designed to find lesions with a poor prognosis. Only 4 out of 458 instances in this cohort met these requirements, a small number. Casting type calcifications and histological evidence of neoductgenesis were linked to a more aggressive tumour phenotype, which included high grade, ER-, PR-, and HER2 overexpression. Unexpectedly, there was no correlation between casting type calcifications and neoductgenesis, and neither condition was associated with a worse prognosis.

Earlier research has suggested a link between casting type calcifications and a worse prognosis in invasive breast cancer, but the findings are ambiguous. There are few studies on the prognosis for DCIS with calcifications of the casting type. Casting-type calcifications have been linked in several studies to high grade and more severe illness. There has also been information on a correlation with HER2 overexpression. Because of how closely our consequences resemble theirs, it appears that casting type calcifications are connected to a more aggressive tumour phenotype. Casting type calcifications were shown to have a no statistically substantially higher relative risk of local recurrence (in an examination of a subset of women in a randomised trial (SweDCIS) examining irradiation after BCS. But only in situ IBE was at a higher risk; invasive IBE was not. As there is little evidence and we were unable to confirm it in our investigation, Tot's prior suggestion that DCIS with neoductgenesis symptoms may have a worse prognosis is not supported by this data.

Although the cohort's risk of breast cancer death was very low, we anticipated that the number of recurrences would be sufficient to identify a connection between tumour biology and micro calcifications. Our findings raise concerns about the mechanisms behind the transition from in situ to invasive carcinoma, and we need to identify more elements contributing to the development of DCIS naturally. When choosing a course of treatment for this group, the presence of HER2 and ER was unknown, but mammographic characteristics may have played a role.

The majority of Eritrean women who come with breast cancer are under 50 years old, according to this case series study. The most frequent histologic type is invasive carcinoma (NST), and the majority are Nottingham grade 3 tumours. African-American and native African women have revealed similar effects. Despite the small sample size of our investigation, the investigations are comparable with those of numerous previous studies in that there is a correlation between high tumour grade and the aggressive intrinsic molecular subtypes.

The percentage of female-specific ER-positive tumours in this study was 60%. Despite the small size of our sample, our outputs are fairly similar to those from Uganda and in African-American women, but slightly lower than those from Egypt and central Sudan, even if they are far higher than those from West Africa (Nigeria and Senegal) A excellent prognosis, a superior response to hormone therapy, and a higher survival rate are all characteristics of luminal A, which made up nearly half of the cases in our case series. This outcome is considerably different from the study in Nigeria and Senegal, but it is consistent with the population-based Carolina Breast Cancer Study, North Africa, and Egypt. The regional distribution of the prevalence of the molecular subtypes of breast cancer appears to vary. Technical

factors, such as the calibre of tissue fixation and processing, different staining methods, and various grading and reporting criteria, could be to blame for these variations. The biological diversity of the molecular phenotypes of African breast cancer may possibly be the outcome of genetic variations among regional populations and environmental variables. For instance, despite the fact that both the basal-like and the "triple negative" subtypes are more common, the prevalence of BRCA1/2 mutations in African-American women is not significantly higher than in Caucasian-American women, indicating that there are likely additional genetic pathways for this molecular subtype.

The study does have certain restrictions. It has a tiny number of cases, to start. The correctness of preserved pathology records is the second factor. Third, only 22 of the 33 cases of histologically proven breast cancer found in pathology records during the period under consideration were used in this investigation, mostly because to the inability to find FFPE blocks with invasive carcinoma. This gap might have had a substantial impact on our findings. The outcomes of the immunostaining could have been impacted since the tissue processing was not consistent (prolonged formalin fixation is thought to affect antigen preservation). Because the study was conducted using a small case series, the outcomes might not be applicable to all Eritrean women.

Conclusion

It is impossible to link casting type calcifications to a worse prognosis in pure DCIS. Invasive events were shown to be at a reduced risk, but the risk of new in situ IBEs was non-significantly higher. However, ER-negativity, PR-negativity, and HER2 overexpression were not associated to each other in DCIS tumours with casting-type calcifications on mammograms or tumours with a histological appearance of neoductgenesis. Why a more aggressive phenotype of DCIS did not indicate a worse prognosis is a mystery to us. We need more research on the factors that cause the transition from in situ to invasive cancer [10].

According to this pilot case series, the majority of breast cancer cases in Eritrea are "triple negative" (35 percent of patients, basal-like, and unclassified combined), which is not hormonally sensitive and has a poor prognosis, and luminal A (55 percent of patients), sensitive to hormonal therapy and with a good prognosis. For these cases, new treatments are required. According to these outcomes, biomarker tests performed in the pathology laboratory are essential for the efficient treatment of breast cancer in Eritrean women.

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Conflict of Interest

The author has no known conflicts of interested associated with this paper.

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