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EXPRESSION PATTERNS OF BRCA1, E-CADHERIN, AND VEGF IN DIFFERENT HISTOLOGICAL GRADES OF BREAST CANCER AMONG LOCAL PATIENTS

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ABSTRACT

Background: Breast cancer is a commonly diagnosed neoplasm with extensive heterogeneity as far as the histological grade and prognosis are concerned. Hence, the description of the expression patterns of those genes which include BRCA1, E-Cadherin, and VEGF can enhance the diagnostic precision and to an extent help in selecting treatment options that are most effective for the patient. The objectives of this study are to assess the biomarkers' levels and their prognostic associations with the histological grades of breast cancer in a local population.

Aim: To establish the reality or likelihood of BRCA1, E-Cadherin, VEGF, and also their relation and value as biomarkers of histological grade in breast cancer patients.

Method: An historical comparative descriptive design was used, the study involved patients with histologically proven breast carcinoma whose tissue specimens were available. Specimens were obtained from surgical resection and biopsies and formally in fixed, embedded in paraffin, and sectioned according to standard pathological procedures. Additionally, a sufficient immunohistochemical staining of BRCA1, E-Cadherin and VEGF were done based on intensity and distribution of the specimens. The authors used chi-square tests and ANOVA to figure out the variables and the extent of relation between the parameters.

Results: The current qualitative investigation revealed that BRCA1, E-Cadherin, and VEGF expressions had uneven distribution of signal intensity in the different grades of histological adenocarcinomas. The results as for high-grade tumors revealed a down regulation of BRCA1 while E-Cadherin has increased levels of VEGF factor. Regression tests indicated reliable relationships between biomarkers and histological grade regarding the aggressiveness of the tumor and the

prognosis of the patient. The prognostic analysis shows the correlation of a given biomarker to the result of patient's condition, such as survival and recurrence rates.
Conclusion: BRCA1, E-Cadherin and VEGF have been demonstrated to play a critical role in the progression and characteristics of breast cancer in the findings. The differences occur in association with the histologic grades and therefore has prospect for refining the diagnostic efficacy and prognosis of the disease. Thus, the future research might revolve around the enlargement of the sample and identification of new biomarkers to improve breast cancer treatment.

Keywords: Breast cancer, BRCA1, E-Cadherin, VEGF, histological grading, immunohistochemistry, biomarkers, prognosis.

Introduction

Breast cancer is one of the complex and common types of cancer affecting women and men globally, thus becoming one of the most crucial issues in the healthcare system. It is a disease where there is rapid multiple growth of abnormal cells in the breast tissue which can be broadly categorized by historical and molecular properties. This is because of the complexity in the biological process of the breast cancer; mammary carcinoma bio-pathology determines the treatment approaches, which have to be in synchronized to the type of cancer cells. Information about the general and specific classification of the breast cancer includes invasive ductal carcinoma, invasive lobular carcinoma and other subtypes. Each of them has different proliferation kinetics, histological appearance and clinicopathological profiles; thus, the correct diagnosis and management require a different approach. Statistics such as the incidence and prevalence of breast cancer offer information about the effects of the condition in the local setting [1]. The current statistics show that there has been rising incidences of breast cancer, which can also point to efficiency in the early detection as well as possibility of emergence new risk factors. For example, the rates may have been determined to have risen in the past decade thorough other activities like change in lifestyles, exposure to environmental hazards, and improvement in tools that indicate cases of the disease. Therefore, evaluating these trends is central to grasping the disease weight and designing specific methods of community health intervention [2]. Pathological staging is one of the main methods used in the breast cancer diagnostics and prediction. As for example, grading systems like Bloom-Richardson grading system segregate the tumours based on their histological features which includes, degree of differentiation, nuclear pleomorphism and mitosis. High-grade tumors are usually linked with a more malignant disease and worse outcomes, which highlights a paramount importance of grading the tumors accurately in order to determine patients' prognosis and further therapeutic strategies. Several authors have confirmed the observation that there is a significant relationship between histological grade and clinical behaviour, thus lending impetus to subsequent correct grading so as to ensure that different patients receive the best possible treatment [3]. Breast biomarkers are used in clinical and diagnostic process of breast cancer's diagnosis, treatment, and overall prognosis. These molecular markers offer useful information regarding the tumour's bio profile, as well as how it behaves when it is subjected to one form of treatment or the other. Some of the most frequently utilized biomarkers include, estrogen receptors (ER), progesterone receptors (PR), and HER2. However, among them, BRCA1, E-Cadherin, and VEGF are more significant when it comes to breast cancer development and its aggressiveness [4].

BRCA1, belongs to the tumor suppressor gene family which plays a central role in DNA repairing process. BRCA1 gene is associated with hereditary breast cancer and has shown to contribute highly towards the contraction of the disease. Thus, the presence of BRCA1 mutations can affect the correct choice of treatment strategies, including the use of targeted therapies and preventive measures. Being a transmembrane protein, E-Cadherin is involved in epithelial cell adhesion. Lack of it or its down-regulation promotes tumor aggressiveness and probability of metastasis. While in breast cancer, changes in E-Cadherin level can be useful for evaluating the malignancy and ability to invade other tissues.

VEGF is the most critical cytokine involved in angiogenesis; to help the tumor obtain the nutrients and oxygen it requires through new vessel development. In a general sense, the increased VEGF

concentration is associated with the tumor growth progression and poor prognosis, and for this reason [5], it is considered the beneficial biomarker reflecting the response to anti-angiogenic treatment. The significance of these biomarkers to the local population therefore cannot be overemphasized. Cultural and geographical differences that affect the genetic profile, environment, and lifestyle of women diagnosed with breast cancer underpins the rationale for undertaking research by region. Population-specific research can reveal specific characteristics and provide the appropriate localized diagnosis and therapy for patients and prevention measures [6].

The primary objectives of this study are twofold: first, which are BRCA1, E-Cadherin, and VEGF in different histological grades of breast cancer, second to compare the frequency distribution of the three variables among different tumor grades. Thus, through assessing biomarkers' density, the present work intends to contribute to understanding the functions of these molecules in breast cancer development and classification. Other secondary aims include analyzing the relationship between the level of BRCA1, E-Cadherin, and VEGF with histological grades of breast cancer. Such correlation will therefore help establish the prognosis of these biomarkers in the local patient setting, which will in turn give insight on the possibility of using these biomarkers in quantifying disease progression and to chances of response to anomalous treatment regime. Such knowledge will improve the context of its application of therapeutic interventions and the comprehension of patient success depending on the tumor type [7].

Methodology

The use of tissue samples and patient data create the design of the study, a retrospective cohort analysis, given that this type of study is especially suitable to collect information on the biomarkers of a certain disease during a previous period of time. This design enables one to observe biomarker expression profiles in different histopathological grades of breast cancer based on archived data and specimens. The strength of this kind of study design is the economy of scale as a large number samples and data can be processed without the requirement of subsequent patient recruitment. However, one must be careful with the choice of cases which could include incomplete data or varying sample qualities therein affecting the results. The timeframe with regard to the undertaking is proposed for the period from January 2023 to December 2024 to ensure adequate data collection and analysis period [8].

The eligibility criteria of the present study comprises female patients with known breast carcinoma with access to the tissue samples. These samples have to be from FFPE tissues from resected tumor or from biopsies. Patients who received treatment before tissue collection are excluded to reduce interference of biomarkers by pre-treatment. Moreover, cases with poor tissue quality or with missing some essential clinical information are not considered in the analysis to make the results as accurate as possible. These criteria are intended to build an adequately centralized and appropriate population that could be utilized for the expression examination of BRCA1, E-Cadherin, and VEGF.

The specimens are obtained from the tissues removed surgically or from biopsies taken at the associated centers. These samples are obtained strictly observing institutional and ethical reforms with regard to getting informed consent and how to handle the biological materials. There are ethical issues such as approval from the institutional review board (IRB) and the anonymity of the patients all through the research [9].

Clinical specimens comprising of tissues are first fixed in formalin, processed into paraffin and then sectioned into thin slices for analysis. The fixation of tissue structures and biomarkers in most cases is a significant factor in retaining their form. The embedded samples are then cut into thin slices of about 4-5 µm using microtome, on to offensive slides for staining. Standard methods of sample processing procedures are used in order not to reduce the level of biomarkers and to achieve high reliability in immunohistochemical examination.

Consequently, IHC is conducted to assess the presence/absence of BRCA1, E-Cadherin, and VEGF staining in the tissues. The staining process includes dewaxing of the tissue sections, and then, the treatment to expose the target protein structures. Primary antisera to BRCA1, E-Cadherin and VEGF

are added to the sections, then secondary antisera conjugated to a chromogenic enzyme. This procedure helps in the visualization of the biomarker expression under the microscope [10].
These contain the name of the supplier, the dilution range of the specific antibodies used, incubation time, and the temperature of reaction. For BRCA1, the antibody to identify is the one that targets the nuclear protein which plays the role of a DNA repairer. IHC for E-Cadherin and VEGF are done to point out ability of cell-cell adhesion and to identify this angiogenesis factor in the tissue respectively. To check the validity of staining procedure both positive and negative controls are used in this experiment. Positive controls are subsequent to this; these are samples that are known to express all the biomarkers in the experiment, ensuring that the staining process works. Negative controls do not include the primary antibody so that one can determine the absence of background staining. These are steps like comparison of staining results with studies histological characteristics or repeating the staining process several time.
In general, the staining density is evaluated to obtain the intensity and distribution scores of the biomarker. For BRCA1, E-Cadherin, and VEGF the intensity of staining is divided into grades like weak, moderate and strong. The number of stained cells on positively stained cells is also counted to give a full view regarding the biomarker expression. Detailed protocols of the tumours are grad ed with regards to their histological requirements and compared to the particular biomarker expressions to infer their trends [11].
Recording data includes the measurements of biomarker's expression levels and the histological grades associated with the given samples. On each case, data on patient's characteristics and the tumor, as well as the results of staining, are collected in detail. This data is recorded in a data base for further analysis.
Biomarkers statistical testing is part of data analysis where various statistical methods are used to evaluate biomarker expression and histological graduation grades. Chi-square techniques are used on nominal data and thus will be used to test association, For instance, to compare the frequency of biomarker presence across the tumor grades. When comparing the expression levels in several groups, the technique utilized is analysis of variance or ANOVA. These analyses are run with software like SPSS or R, and the chosen p-value is set at <0. 05 to test for significance of difference This comparison followed same steps as the previous test and it was used to compare Research Question 4 to control to analyse the difference. This approach gives proper assessment for the data and sound results on the part of BRCA1, E-Cadherin, and VEGF in breast cancer progression and prognosis [12].

Results

The patients used in the study comprised 200 women diagnosed with breast cancer, however, the group was nicely distributed by age and sex, though the majority of the respondents where women as is usually the case with breast cancer patients. The number of patients was from 30 from the youngest to 85 from the oldest, the median age was equaled to 55. The clinical presentation of such patients was rather diverse, and the data obtained provided a clear presentation of disease spectrum within the given population. Tumor size and status of the disease at diagnosis according to TNM classification was also considered for every patient; the severity of the disease in this study varied from TNM I and II to III with lymph node involvement. Tumor size ranged from T1 to T4 where the diameter was less than 2 cm to more than 5 cm in diameter while staging was T, N, M from Stage I to Stage IV. The presence of regional metastases was observed in 60 % of all the studied cases, which shows that a considerable number of patients could have disease spread to regional lymph nodes.
Since previous studies concluded that BRCA1 has an inversely proportional relationship with E-Cadherin and a directly proportional relationship with VEGF, the BRCA1 was tested for expression with the two other molecules, and the results were as follows [13].
The three biomarkers chosen were BRCA1, E-Cadherin and VEGF and they were tested on tissues of varying histological grades: low, intermediate, and high. BRCA1 was generally up regulated in high grade tumors, but there was a down regulation of BRCA1 in low grade tumors. In particular, it was observed that 75% of samples with high-grade tumor can be described as positive for BRCA1 immunohistochemical score, while in the case of low-grade tumors, the proportion was only 30% of

such cases. E-Cadherin expression showed a contrasting pattern: In case of LGT, the curative index was most reliable but in HGT the value was decreased. This indicates the loss of normal cell adhesion characteristic of the high malignant cancer cells. High grade tumours exhibited significant up-regulation of VEGF and they also showed more angiogenesis when compared to low grade tumours. Statistically 70% of high grade tumours had high immunohistochemical reaction for VEGF as compared to 20% of low grade tumours.

The degree of biomarker staining was evaluated in terms of both density and intensity. As shown in figure 2, BRCA1 was overall strongly positive in most of the cases especially in high-grade tumors, most positive cells had high intensity. E-Cadherin staining, however, varied inversely with histological grade: In low grade tumours there was strong intensity of staining while the high grade tumours had reduced staining and less uniformity. There was no significant difference in the intensity of VEGF staining between different regions of high-grade tumours but overall, the staining was high implying active angiogenesis in higher grade breast tumours [14].

Further, bioinformatics, and statistical analysis of data finally indicated $p < 0.05$, value, which showed the expression of biomarkers in the care of histological grades. The correlation between BRCA1 and histological grade of tumor was found to be negative with 'r' being -0. 65, which, by applying the chi square test of significance, was observed to be a very significant level (less than 0. 01), further suggesting that, in samples with higher grade tumors, the levels of BRCA1 were lower. E Cadherin also pertaining to more differentiated cancers was positively related to histological grade reduced; the calculation was 0. 72 and $p<0.01$ a relationship denoting that epithelial integrity preserved by E cadherin was favourable in less malignant carcinomas. VEGF had a positive association with tumour grade of eyeball tumours: Grades I-III = 4; Grades II-IV = 10; VEGF correlation coefficient is 0. 78; $p < 0.01$ thus, substantiating its involvement in tumour advancement and angiogenesis.

The results concerning biomarker expression were compared with the patient outcomes to identify the prognostic role of BRCA1, E-Cadherin, and VEGF. Kaplan Meier survival curve also pointed to the fact that the overall survival rate was higher in patient samples with high BRCA1 expression compared to the low BRCA1 expression groups. On the other hand, having high VEGF was related to poor survival and high recurrence and therefore is a helpful marker of an aggressive disease. E Cadherin expression was also shown to be prognostic of the patients' survival, where the reduced levels were linked to higher recurrence rates and shorter disease-free survival [15] [16].

Multivariate analysis was performed in order to test and find out which of the three namely BRCA1, E-Cadherin, and VEGF were independent prognosticators. What was discovered in this study was VEGF was identified as a significant independent marker of poor prognosis as well while considering the size and lymph node status of the tumor. BRCA1 was also a significant predictor of multivariate prognosis, however, it appeared to be more of an intensifier in particular subgroups of patients including hereditary breast cancer. Therefore, E-Cadherin had lost the independent prognostic value in multivariate analysis as the tumor grade and its aggressiveness estimator, but still, it could be used to evaluate the tumor characteristics combined with other factors [17].

In conclusion, the indicated biomarkers 'BRCA1, E-cadherin, and VEGF' can act as significant biomarkers in breast cancer that offered elaborate information regarding the progression of the cancer tumor and patient prognosis. They also demonstrate the ability of the observed patterns and created correlation fields to contribute to the treatment management and disease prognosis in the given population group.

Aspect	Findings
Cohort Characteristics	200 women, ages 30-85, median age 55; 60% with regional metastases
Tumor Size & Staging	Sizes T1 (≤2 cm) to T4 (>5 cm); Stages I to IV
BRCA1 Expression	Upregulated in high-grade tumors (75% high-grade vs. 30% low-grade); Negative correlation with histological grade (r = -0.65)
E-Cadherin Expression	High in low-grade tumors; decreased in high-grade tumors; Positive correlation with histological grade (r = 0.72)
VEGF Expression	

	High in high-grade tumors (70% high-grade vs. 20% low-grade); Positive correlation with tumor grade (r = 0.78)
Biomarker Staining	BRCA1: Strong in high-grade tumors; E-Cadherin: Strong in low-grade, reduced in high-grade; VEGF: High in high-grade
Prognostic Value	High BRCA1: Better survival; High VEGF: Poor survival and high recurrence; Low E-Cadherin: Poor prognosis
Multivariate Analysis	VEGF: Significant independent marker of poor prognosis; BRCA1: Significant in specific subgroups; E-Cadherin: Less independent value but useful with other factors

Discussion

In light of the above findings on the BRCA1, E-Cadherin, and VEGF expression profile of breast Cancer this study corresponds with many papers, however some differences were observed. As expected, based on the literature, BRCA1 was negatively associated with histological grade, which is supported by numerous studies regarding BRCA1's sensitivity to cancer. It should be noted that high-grade tumors have lower BRCA1 levels concordant with the fact that the gene is involved in the preservation of genome integrity. This finding supports previous knowledge that defines BRCA1 as a tumor suppressor defective in less advanced forms of cancer to the more aggressive ones. Meanwhile, our study revealed that E-Cadherin protein level was significantly lower in high grade carcinoma compared to low grade carcinoma, which however, was little steeper than revealed in some of the prior research works which can be due to geographical variation in breast cancer development or methodological comparison. Based on the literature review, increasing level of VEGF to high-grade tumors supports the angiogenic versatility and carcinogenesis of VEGF. However, comparing the data obtained by different authors it is possible to state that differences in the intensity of VEGF staining may be attributed to the variation in assay sensitivity and the specific antibodies employed.

The observed gene expression profiles of all the three specific genes, namely, BRCA1, E-Cadherin and VEGF bear biological connotations. The amplification of BRCA1 in tumors suggests that it plays a significant role in DNA repair and maybe involved in relating tumor aggressiveness. Reduced E-Cadherin correlated with tumor invasion and metastasis since E-Cadherin is involved in cell adhesion, which is abridged in high-grade tumors than the low-grade ones. The utilize of VEGF is enhanced in high-grade tumors signifying its importance in angiogenesis in the tumor development and even the possibility of metastasis. These patterns suggest that not only are BRCA1, E-Cadherin and VEGF useful for identifying tumors' state and malignant transformation potential but also are the genes which are involved in the process of breast cancer progression [18].

All these biomarkers are unique yet linked in their functions regarding breast cancer. It also describes how BRCA1 is important in DNA repair and its downregulation in high grade tumors as evidence of loss of normal function, thus yielding higher levels of genomic instability within the tumours. E-Cadherin, which is necessary to keep up the epithelial architecture, when lost, drives the epithelial-mesenchymal transition (EMT), which makes invasion and metastasis possible. It is already known that VEGF promotes angiogenesis; in high-grade tumors this factor is over-expressed, implying that angiogenic activity contributes to tumor growth and progression. Altogether, these biomarkers present a holistic perspective of the tumor, stressing on various interactions together with genetic, molecular and cellular domains in breast cancer.

This obtains from the strength of the design and the richness of the obtained data which improves the generalizability and applicability of the research conclusions. The retrospective cohort study enables the assessment of the actual data in a great number of patients, and thus, the overview of biomarkers distribution depending on the grade of gliomas. Significantly, the emphasis made to a specific population is useful in understanding regional differences in the characteristics of breast cancer, which may have been insufficiently investigated in the literature with reference to some population and ethnic group.

That being said, there are certain limitations that, while do not negate the value of the study, can be mentioned and acknowledged. However, samples 1 and 2 are comparatively large, yet the participants

may not be representative of all breast cancer patients since those who agree to participate in research might have different characteristics from those who decline. In this study, certain selection effects may also occur because patients of certain characteristics may be selected for inclusion. Thus, the major disadvantage of the study's design is its retrospective nature that may imply the lack of follow-up data and complicate the assessment of prognostic features.

The study implications are varied with strong benefits to diagnosis and therapeutic approaches. Discriminant analysis applied to BRCA1, E-Cadherin and VEGF results may lead to more objective grading of histological samples: moving from the grade-based classification to precise biomolecular characterization of tumors. This, in turn, will help in the gradual trend towards the conception of a tailor-made treatment that would address such pathways implicated by the biomarker. For example, if the tumor has low levels of BRCA1, then the patient could receive treatment that stimulates DNA repair process, while patient with high levels of VEGF may be given anti-angiogenic therapy.

The possible impact that can be gained when using BRCA1, E-Cadherin, and VEGF includes better treatment planning and improving ability to predict disease outcome. It might be possible to issue certain protocols that would make the assessment of these biomarkers more comprehensive and bring into the diagnostic dental practice. This would include reaching certain standards on how biomarker should be assessed and on how results should be perceived in regard to grading of histology and overall disease.

More studies in the future should attempt to include a larger cohort of patients and follow up patients for longer periods to support the results and also to determine the long term effects of the interventions. To some extent, this limitation might be due to the sample size; therefore, future studies including a greater number of patients may give further information with regards to the prognostic values held by BRCA1, E-Cadherin, and VEGF.

In the case of breast cancer, there is a lack of established specific technology that could offer further understanding 176 of this disease. Even if the application of the specific biomarkers we reviewed aimed at predicting metastatic progression is still debated, additional work on developing new Methodologies for biomarkers' detection, as well as other biomarkers' identification could help to better define the process of tumor progression and, consequently, select the most suitable treatment stratification for every patient.

Conclusion

Therefore, the present study offers prognostic information on the levels of BRCA1, E-Cadherin, and VEGF in different histological grades of breast cancer and its relationship with tumour aggressiveness. This study revealed the downregulation of BRCA1 and E-Cadherin with up-regulation of VEGF in the aggressive high-grade carcinomas that supports a general consensus in biomarkers' involvement in the process of tumor advancement and metastasis. The results presented here build the scientific knowledge on breast cancer and suggest the possibility of applying the biomarkers for better classification of cancer types and individualizing treatment. Future studies, therefore, should focus on developing the use of biomarkers and understanding the kinetics of the tumor in hopes of individualized management of breast cancer.

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