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Histopathological and Molecular Aspects of Women's Breast Cancer in Bouaké: Preliminary Study on 43 Cases

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Abstract

The objective of the current study was to determine the expression profiles of the Breast Cancer genes 1 and 2, two tumor suppressing genes, in patients with breast cancer in the Gbêkê region of Côte d'Ivoire. This cross-sectional study was carried from September 2023 to January 2025. The patients came from five screening and management sites for breast diseases in the Gbêkê region. Breast micro-biopsies were stored in an RNA Protect solution at −80˚C before processing. RNA extraction was performed with RNAEsy/Triazol kit from Qiagen. And RT-qPCR was carried out using specific primers and probes for BRCA1 and 2 mRNAs. Fifty-eight participants were recruited. Among which them, 43 had breast carcinoma and 15 had various non-malignant breast tumors. The average age of the participants was 42.9 ± 10.1 with ages ranging from 24 to 71 years. These women were mostly unemployed and/or not civil servants in 93% of the cases. Out of them, 9.3% used hormonal contraceptives, and 72.1% were premenopausal. The BRCA1 gene was expressed in 25.6% of carcinoma patients and 20.0% of the non-malignant participants. And its expression levels were low in both groups. The BRCA2 gene was expressed in 62.8% of carcinoma cases and 66.7% of the non-malignant cases. And its expression levels were high in both groups. Breast cancer is frequent in the Gbêkê region. It would therefore be wise to integrate the expression profile of BRCA1 and BRCA2

in all women from adolescence for rigorous monitoring of the disease.

Keywords

Breast, Cancer, Pathology, BRCA, Bouaké

1. Introduction

Breast cancer is a malignant tumor that left untreated, leads to death. In 2022, 660,103 deaths were related to it worldwide [1]. In Côte d'Ivoire in 2020, 3306 new cases of breast cancer were recorded, including 1785 deaths [2]. Its management remains a challenge due to the generally late diagnosis [2], but also due to the absence of an in-depth molecular investigation. This investigation takes into account the assessment of the expression levels of the Breast Cancer 1 (BRCA1) and 2 (BRCA2) tumor suppressing genes [3]. Indeed, BRCA1 and BRCA2 are inherited from parents and as such, present in the genome of all human beings [4]. In approximately 5 to 10 % of the cases, breast cancers appear in a family context [5]. The hereditary changes in BRCA1 are responsible for around 40 to 45 % of hereditary cancers in the breast [6]. Indeed, a decrease or lack of expression of BRCA1 has been reported in hereditary breast cancers [6] [7]. On the other hand, the high gene expression of BRCA2 has been associated with cancer that intensely proliferates and are very aggressive [8]. The management of breast cancer in Côte d'Ivoire is mainly based on the results of imaging and immunohistochemistry [9]. The situation is similar in many countries in the African sub-region [10] [11]. Several groups, including the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) and the St. Gallen Group, have published directives and recommendations supporting the implementation of molecular analysis as useful for risk stratification and treatment planning in breast cancer [10] [11]. The objective of this study was to determine the expression profiles of BRCA1 and BRCA2 in patients affected by breast cancer in Bouaké, the capital city of the Gbêkê region in Côte d'Ivoire.

2. Materials and Methods

2.1. Type, Duration and Scope of Study

This was a cross-sectional study carried out in the Gbêkê region of Côte d'Ivoire, whose capital city is Bouaké. It is the country 2nd largest city, located around 350 km from Abidjan and 100 km from Yamoussoukro, the political capital city [12]. This city has a Teaching Hospital standing as the only one outside Abidjan. The study period was 16 months, starting from September 2023 to January 2025.

2.2. Methods

2.2.1. Patient Flow

The patients came from five primary healthcare facilities, which were located in

the neighborhoods of Sokoura, Diezoukouamekro, Koko, Dar Es Salam and Belleville in Bouaké. These clinical facilities were part of the regional integrated management program for breast cancer screening and treatment. They were supported by the Teaching Hospital, which was the central facility for the management of cases referred from the peripheral sites. The referred cases were managed by the gynecology, medical oncology, radiology and pathology services. The therapeutic itinerary of each participant started at the screening sites before heading to the gynecology, then radiology, pathology, and finally medical oncology services. Patients showing up with symptoms of breast disease such as breast nodule and/or breast discharge in these 5 peripheral centers were referred to the Teaching Hospital for a visit at the gynecology ward. At the end of the medical visit, a mammography was carried out, and the Breast Imaging Reporting And Data System (BIRADS) was performed. Participants grouped as BIRADS 4 or 5 underwent microbiopsy of the affected breast for pathology examination. Two sets of biopsies were collected. One set for the pathology examination and the second was kept into an RNA Protect solution (Qiagen, Hilden, Germany) at −80˚C before further processing for gene expression levels assessment.

2.2.2. Histology

The biopsies for pathology examination were dehydrated, kerosene embedded, microtome sectioned, hematoxylin-eosin stained and mounted within 36 to 72 hours to avoid the consequences of cold ischemia. After the pathology examination, the participants diagnosed with breast carcinoma made up the case group whereas those with non-malignant tumors formed the witness group for the purpose of gene expression assessment. The data collection was carried out using a survey sheet. The laboratory equipment and reagents included a Histo-Line dehydration machine (Milan, Italy), a Histo-Line Laboratories (Milan, Italy).

2.2.3. RT-qPCR

The tissue RNA was extracted from the second biopsy set with the RNEasy Plus Universal Tissue extraction kit (QIAGEN, HILDEN, Germany) and a one-step RT-qPCR kit (Qiagen, Hilden, Germany). Then RT-qPCR was carried out on a qPCR machine, the QuantStudio (Invitrogen, Manheim, Germany), after the reconstruction of the primers and probes sets and the preparation of the reaction mixture. These primers and probes were provided by Integrated DNA Technologies (IDT, Coralville, Netherlands). The Beta Actin (BACT), Beta 2-Microglobulin (B2M) and the calmodulin 2 (CALM2) housekeeping genes were used to normalize the BRCA genes expression. Relative quantitation was performed using the ΔΔCt method [13] [14]. The sequences are as follows [15] [16]:

BRCA1 Forward primer: 5'-ATCCCCCGTCCAAAAAATCT-3'
BRCA1 Reverse primer: 5'-TGGTAACGGAAAAGCGCG-3'
BRCA1 Probe (FAM): 5'-CACGCCGCGCAATCGCAA-3'
BRCA2 Forward primer: 5'-GAAAATCAAGAAAAATCCTTA AAGGCT-3'
BRCA2 Reverse primer: 5'-GTAATCGGCTCTAAAGAAACATGATG-3'

BRCA2 Probe (FAM): 5'-AGCACTCCAGATGGCACAATAAAAGATCGAAG-3'
BACT Forward primer: 5'-TGA GCG CGG CTA CAG CTT-3'
BACT Reverse primer: 5'-TCC TTA ATG TCA CGC ACG ATT T-3'
BACT Probe (CY5): 5'-ACC ACC ACG/TAO/GCC GAG CGG-3'
B2M Forward primer: 5'-CTGTGCTCGCGCTACTCT-3'
B2M Reverse primer: 5'-CTTTCCATTCTCTGCTGGAT-3'
B2M Probe (CY5): 5'-CTATCCAGCGTACTCCAA-3'
CALM2 Forward primer: 5'-GCAGAATCCCACAGAAGCA-3'
CALM2 Reverse primer: 5'-TTCTTGCCATCATTGTCAG-3'
CALM2 Probe (CY5): 5'-GATGCTGATGGTAATGGC-3'

The reaction mixture of 20 µl was made of 5 µL of the 4X PCR Master Mix, 0.5 µl of each specific forward and reverse primer (10 µm) and probe, 7.5 µL RNase-free water and 6 µl of RNA extract. The RNA was amplified in the QuantStudio real-time qPCR machine according to a program including a reverse transcription for 10 minutes at 50˚C, followed by an RT deactivation and Taq activation for 2 minutes at 95˚C, and 50 cycles of PCR. Each PCR cycle consisted of a denaturation at 95˚C for 5 seconds followed with a hybridization combined to an elongation for 1 minute at 60˚C. Amplification curves with Ct values between 14 and 29 were considered. The absence of an amplification curve meant that the target gene was not expressed. A level of expression ≤ 50% was considered low [13]; [14]. Beyond 50 %, the expression level was deemed high [13]; [14]. The expression status of each molecular target was settled with the agreement of at least two normalizing genes (BACT, B2M and CALM2) [13] [14].

2.3. Parameters Studied

The parameters analyzed were the epidemiological data (age, sex, number of previous pregnancies, work, and sector of activity), clinical and pathology data (hormonal contraceptive use, menopausal status, tumor type, and Nottingham grading if carcinoma), the molecular data (profiles of gene expression BRCA 1 and 2) and the correlations between BRCA gene expression and the tumor type.

2.4. Statistical analysis

Data collection and statistical analysis were carried out using the Microsoft Excel 2016 and SPSS25 softwares. The chi square test was used to analyze the correlation between the variables studied. A p-value < 0.05 was considered to be statistically significant.

3. Results

3.1. Participant Epidemiological Data

The average age of study participants (patients and controls) was 42.9 ± 10.1 years, with extremes at 24 and 71 years One participant was a male. Multiparous women were the main participants in both patients (62.8%) and controls (71.4%) groups. Unemployed participants accounted for more than a third of cases (46.5%) and a

third of controls (33.3%) (Table 1).

Table 1. Epidemiological data.

Parameters	Patients (43, 100)		Controls (15, 100)	
	n	%	n	%
Age group				
24 - 39	17	39.5	6	40.0
40 - 55	20	46.5	8	53.3
56 - 71	6	14.0	1	6.7
Sex				
Male	-	-	1	6.7
Female	43	100	14	93.3
Number of pregnancies carried				
Nulliparous = 0	7	16.3	2	14.3
Primiparous = 1	5	11.6	2	14.3
Multiparous = 2 to 6	27	62.8	10	71.4
Large multiparous ≥ 7	4	9.3	-	-
Work				
Civil servants	3	39.5	2	13.3
Non Civil servants	20	46.5	8	53.3
Unemployed	20	46.5	5	33.3
Sector of activity				
Informal	16	37.2	8	53.4
Private	4	9.3	-	-
Public	3	7	2	13.3
Unemployed	20	46.5	5	33.3

3.2. Clinical and Histological Data

The frequency of use of hormonal contraceptives was 9.3% in the patients and 7.1% in the controls The premenopausal status was frequent in both the patients (72.1%) and the controls (92.9%). Among the patients, non-specific infiltrating carcinoma was commonly diagnosed (95.3%) in the patients. The Nottingham grade II was generally observed (74.4%) (Table 2).

3.3. BRCA1 and BRCA2 Gene Expression

The BRCA1 gene was not expressed in 74.4% of the patients and 80% of the controls with breast tumors. The BRCA2 gene was expressed in 62.8% of the patients and 66.7% of the controls. BRCA1 gene expression was low in 81.8% of patients that expressed this gene. And the BRCA2 gene was expressed at a high level in 29.6% of cases that expressed it (Table 3).

Table 2. Clinical and histological data.

Parameters	Patients (43, 100)		Controls (15, 100)	
	n	%	n	%
Contraceptive use				
Yes	4	9.3	1	7.1
No	39	90.7	13	92.9
Menepausal status				
Premenopause	31	72.1	13	92.9
Postmenopause	12	27.9	1	7.1
Histopathology				
Non-specific infiltrating carcinoma	41	95.3	-	-
Lobular infiltrating carcinoma	2	4.7	-	-
Benign tumor	-	-	15	100
Nottingham grade				
I	2	4.7	-	-
II	32	74.4	-	-
III	9	20.9	-	-

Table 3. BRCA1 and BRCA2 gene expression profiles.

Parameters		BRCA1		BRCA2	
		n	%	n	%
Expression patients	Expressed	11	25.6	27	62.8
	Not expressed	32	74.4	16	37.2
	Total	43	100	43	100
Expression Controls	Expressed	3	20.0	10	66.7
	Not expressed	12	80.0	5	33.3
	Total	15	100	15	100
Level of Expression Patients	Low	9	20.9	19	44.2
	High	2	4.7	8	18.6
	No	32	74.4	16	37.2
	Total	43	100	43	100
Level of Expression Controls	Low	2	13.3	4	26.7
	High	1	6.7	6	40.0
	No	12	80	5	33.3
	Total	15	100	15	100

3.4. Correlation between BRCA1 and BRCA2 Gene Expression Profiles and the Presence or Absence of Carcinoma

The BRCA1 and BRCA2 gene expression profiles were not statically related to the

presence or the absence of breast carcinoma (Table 4).

Table 4. Correlation between BRCA1and BRCA2 gene expression profiles and presence or absence of breast carcinoma.

	Patients	Controls	Total	P-value
BRCA1 expression				
Expressed	11	3	14	
Not expressed	32	12	44	0.664
Total	43	15	58	
BRCA1 expression level				
Null and low	41	14	55	
High	2	1	3	0.790
Total	43	15	58	
BRCA2 expression				
Expressed	27	10	37	
Not expressed	16	5	21	0.788
Total	43	15	58	
BRCA2 expression level				
Null and low	35	9	44	
High	8	6	14	0.221
Total	43	15	58	

4. Discussion

The average age of 42.9 years of participants is in line with those reported in Cameroon, Senegal and Benin [17]-[19]. The participants were almost exclusively female. Of note, one participant was a male. Mammary gland diseases including cancer can also affect men [20]. There are many similarities with female cancer as well as particularities in terms of management, patient age, and the small size of the men's breast [20]. The rate of contraceptive use was lower compared with European countries, where contraception is widely available to all. In Côte d'Ivoire, it has been shown that a limited number of women used some contraceptive methods [21] [22]; The contraceptive use rate was 14% in 2012, 21% in 2017 and 22.5% in 2020 [21] [22]. The non-specific infiltrating carcinoma was the most common diagnosis. This histological type is the most common worldwide, with a frequency ranging from 77% to 88% on the African continent [23] as well as Asia with frequencies ranging from 80 to 94.5% [24]. The Nottingham grade II prevailed in this study, as reported by several authors [25] [10] [26] [27] and corresponds to an intermediate prognosis for survival [28]. Gene expression profiling is not routinely performed in sub-Saharan Africa, although it is recommended by the ASCO [29]. And our study represents a preliminary step in this direction. Nearly 3/4 of the patients (74.4%) did not express the BRCA1 gene. The trend seems to be re-

versed for BRCA2, for which nearly 2/3 of the patients expressed it (62.8%). Non-expression of BRCA1 or BRCA2 in these patients could suggest a mutation in these genes. Cheng et al [30] identified three pathogenic BRCA1 variants by sequencing. As revealed by Szender *et al* [4], some people acquire a mutated or altered copy of BRCA1 or BRCA2, which exposes them to several types of cancer. The BRCA1 expression was low in 81.8% of biopsies expressing it. Mueller *et al* [28] also noted low BRCA1 expression in their work, and linked the degree of BRCA1 downregulation to the extent of breast cancer. Thompson *et al* [31] also reported the same observations. Breast cancer is not the only pathology generally marked by an absence or a low expression of the BRCA1. Indeed, Taron et al [16] have highlighted low BRCA1 expression in lung cancer. Several other studies have linked the absence of BRCA1 expression to the hypermethylation of the BRCA1 promoter [7] [32]-[34]. This hypermethylation was observed in 82.6% of cancer tumors lacking BRCA1 expression, in contrast to cancer-free tissue in which there was no hypermethylation [33]. The mutations or alterations in the BRCA1 or BRCA2 genes have a highly significant impact on the cell cycle, as they inhibit genomic DNA damage repair in these cells [34]. Correlation studies have shown that the BRCA1 and 2 gene expression profile was not statistically linked to the presence or absence of breast carcinoma. These data are in contradiction with previous reports highlighting the higher risk of developing breast cancer in the absence or presence of low expression of these tumour suppressor genes [3] [35] [36]. This difference could be explained by the fact that the controls in the study, although free of breast carcinoma, still had non malignant tumors. Another reason could be the small sample size in the current study. Previous studies have highlighted the possibility of transformation from non malignant to carcinoma for certain benign breast tumors. Henceforth, it is important to regularly monitor that category of patients [37] [38]. The results of the current study add value to the management, in that they point practitioners in the direction of other, more targeted therapeutic approaches. Indeed, BRCA1 and BRCA2 mutations have been targeted by the polyADP-Ribose Polymerase (PARP) inhibitors [30]. These new molecules have shown convincing results in the treatment of breast cancer in patients with BRCA1 or BRCA2 mutations [30]. Other studies have also noted the positive effects of these inhibitors in the treatment of BRCA1 and/or BRCA2-mutated breast cancer [39] [40]. One limit of this study is that the BRCA1 and BRCA2 mutations were not investigated.

5. Conclusion

This preliminary study made it possible to look into the gene expression profile of the BRCA1 and 2 genes in women's breast cancers in Côte d'Ivoire, precisely in Bouaké for the first time. These genes were expressed respectively in 25.6% and 62.8% of the carcinoma patients. Among those with BRCA1 expression, the level of expression was low in 20.9%. Whereas, the BRCA2 gene was expressed at a low level in 44.2% of the carcinoma cases. These results demonstrate the interest in

assessing the gene expression profiles of BRCA1 and BRCA2 in patients affected by breast cancer. That assessment could help with the steering clinicians towards targeted therapies such as PARP inhibitors. It is therefore useful to integrate them into the examination packages set up for women and teenagers in order to rigorously monitor of the disease.

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Statements

The ethical approval of the protocol and written consent of the participants were secured. All procedures were approved by the National Ethics Committee of Côte d'Ivoire under the authorization number 142-23/MSHPCMU/CNESVS-km. The anonymity and data confidentiality were ensured.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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