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CYP17 Genetic Polymorphism among Female Patients with Breast Cancer, A retrospective Study at Central of Sudan

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ABSTRACT

Background: Estradiol (E2) has a significant impact on the development and progression of breast cancer via oxidative metabolism. It regulates cell proliferation and death in breast tissue by interacting with the Estrogen Receptor (ER). The CYP17 gene, which is essential for estrogen metabolism, has been linked to an increased risk of breast cancer.
Objective: The aim of this study was to determine blood levels of estradiol and the association between three different CYP17 gene types and breast cancer risk in Sudanese women who went Wad-Madani Teaching Hospital in Gezira State.
Methods: Before participating in this experimental case study, 130 female breast cancer patients were completed consent forms. Blood samples were used to measure estradiol levels, and PCR and RFLP analysis were used to figure out the CYP17 genotype. Structured questionnaires helped us collect clinical and socioeconomic data. SPSS Version 19.0 was used for data analysis.
Results: The majority of patients had ductal carcinoma, with stages III and IV being most prevalent (P=0.004). Of postmenopausal women, 35.5% had elevated estradiol levels (P=0.009). The CYP17 M1 (A1A1) genotype was linked to a lower risk of breast cancer (P=0.004) in postmenopausal women, but the M2 (A1A2) genotype showed no significant link (P=0.101). The M3 (A2) genotype had a big effect on premenopausal Sudanese women (P=0.075) and seemed to raise the risk of breast cancer (OR=2.305, 95%). CI: 0.843-6.301.
Conclusion: Postmenopausal individuals may have an increased risk of breast cancer when exposed to estradiol (E2). The CYP17 M3 (A2A) polymorphism is also highly associated with higher breast cancer risk in premenopausal Sudanese women. These genetic variations might serve as indications for assessing the Sudanese population's breast cancer risk.

Keywords: Estradiol (E2), CYP17 M3(A2A2), breast cancer, postmenopausal

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INTRODUCTION

Breast cancer (BC) is the most frequent malignancy among women globally and the leading cause of cancer-related mortality (21). Estradiol, estrone, androstenedione, dehydroepiandrosterone, and testosterone levels in the blood of premenopausal women are strongly linked to their risk of getting breast cancer (9). The estrogenic environment of obesity is a major risk factor for estrogen receptor-positive cancers in women who have gone through menopause (13).

C0YP17, an essential enzyme in estrogen production, has been associated with cancer risk in epidemiological research (22). CYP17A1, a member of the cytochrome P450 superfamily, is involved in drug metabolism as well as cholesterol, steroid, and lipid production. Mutations in this gene have been linked to various illnesses and impairments, including adrenal hyperplasia (10, 14, 15).

In certain breast tumors, the CYP17 A2 allele has been established as an independent risk factor. Three genotypes are made up of a single T to C polymorphism in the 5' untranslated region: A1A1 (wild-type), A1A2 (heterozygote), and A2A2 (homozygote). There have been mixed findings about the link between the A2 allele and the risk of breast cancer. Some studies have found a strong positive link in advanced cases (3). The aim of this study was to determine blood levels of estradiol and the association between three different CYP17 gene types and breast cancer risk in Sudanese women who went Wad-Madani Teaching Hospital in Gezira State.

METHODS

One hundred and thirty recently diagnosed Sudanese female breast cancer patients who visited the surgical department of Wad-Madani Teaching Hospital in Gezira State, Sudan. Included patients were between the ages of 25 and 90; data were gathered using structured questionnaire face-to-face interviews under signed informed permission.

Five-millilitre blood samples were collected in EDTA tubes and centrifuged them for three hours. The plasma and buffy coat were kept at -80°C until analysis. We used an ELISA kit to ascertain estradiol levels, followed by PCR and RFLP analysis to genotype CYP17.

Analysis for Estradiol Level (E2)

To help figure out the amount of estradiol present, a polyclonal anti-estradiol antibody was used to coat 96 microtiter wells (12 x 8 break-apart strips). Standard 0–6 had seven pre-prepared standards with concentrations of 0, 25, 100, 250, 500, 1000, and 2000 pg/mL (conversion: 1 pg/mL = 3.67 pmol/L). Preservatives in these standards were 0.03% Proclin 300 and 0.005% gentamicin sulfate.

The enzyme conjugate solution (25 mL, ready-to-use) was kept safe with 0.03% Proclin 600, 0.015% BND, and 0.010% MIT. It was made up of horseradish peroxidase (HRP) attached to estradiol. The stop solution was 0.5 M sulfuric acid (H_2SO_4, 14 mL), and the substrate solution already had tetramethylbenzidine (TMB) in it. A 30 mL wash solution that was 40 times stronger was diluted with 1,170 mL of deionized water to make a final volume of 1,200 mL that stayed stable at room temperature for two weeks.

Assay Methodology

All reagents and samples were equilibrated at room temperature (18–25°C) and gently mixed to stop foaming before analysis. Pipettes were used to put small amounts of standards, controls, and patient samples into the right wells. Then, 200 µL of enzyme conjugate were added to each well. The dish was gently swirled for ten seconds and then left at room temperature for 120 minutes.

The wells were rinsed three times following incubation using 400 µL of diluted wash solution each cycle, with the remaining liquid immediately thrown away. To get extra droplets out, wells were blotted on absorbent paper. Each well received 100 µL of TMB substrate solution, and then the plate was left at room temperature for 15 minutes. The enzymatic process was stopped by adding 50 µL of stop solution. After 10 minutes, optical density (OD) was measured with a microtiter plate reader (18).

Standard Curve Development

The mean absorbance values for patient samples as well as for standards were computed. Plotting absorbance on the Y-axis versus estradiol concentration on the X-axis produced a standard curve. We used the 4-parameter logistic (4PL) curve-fitting model for data analysis, following the Instructions for Use (IFU). Although other data

processing techniques might produce different findings, the 4PL model is still the advised way for exact quantification.

Estradiol Reference Ranges

The ELISA kit states that reference estradiol levels as follow:

Men: 10–36 pg/mL

Women in premenopausal range: 13–191 pg/mL Postmenopausal women range in pg/mL from 11 to 65.

Genetic Analyses for Cytochrome P-450 Gene (CYP17)

The QIAamp DNA Mini Kit (Qiagen, Inc., Chatsworth, CA) helped extract DNA from blood. We used room temperature—15–25°C— for all chemicals, samples, and procedures. Twenty µL of QIAGEN Protease, sometimes known as proteinase K, was pipetted into the bottom of a 1.5 mL microcentrifuge tube. The tube then housed 200 µL of the material. One used 200 µL of PBS with up to 200 µL of buffy coat. The sample received 200 µL of Buffer AL next, and the combination was pulse-vortexed for 15 seconds and then incubated at 56°C for 10 minutes. We momentarily centrifuged the tube to extract drips from the inside of the lid. The liquid was pulse-vortexed once again for 15 seconds after adding 200 µL of cold ethanol (96–100%). After mixing, we quickly centrifuged the tube to extract drips from the interior of the lid.

We carefully placed the mixture in the QIAamp Mini column without wetting the rim and ran it through the vacuum pump. As suction was being applied, the cover of the QIAamp Mini column remained open. The vacuum pump was turned off once all lysates had passed the spin column. The QIAamp Mini column was then fed 500 µL of Buffer AW1 (1:1.6) without wetting the rim. We turned on the vacuum pump again and then turned it off once all of the Buffer AW1 had passed through the column. Then, without wetting the column's rim, 500 µL of Buffer AW2 (1:2.4) was added. After all of Buffer AW2 had gone through the column, the vacuum pump was shut off. To properly dry the membrane, the QIAamp Mini column was put in a clean 2 mL collecting tube and centrifuged at 20,000 x g (14,000 rpm) for one minute. Finally, add 200 µL of distilled water, or Buffer AE, equilibrated to room temperature. The mixture was left at ambient temperature for five minutes and then centrifuged for one minute at 6,000 x g (8,000 rpm). To do polymerase chain reaction (PCR) amplification and restriction endonuclease digestion on all three CYP17 variants (A1/A1, A1/A2, and A2/A2), an Analytik Jena Biometra TAdvanced Thermal Cycler was used. The pieces turned out either the A1 homozygote (459 bp), the A2 homozygote (335 bp and 124 bp), or the A1/A2 heterozygote (459 bp, 335 bp, and 124 bp). Macrogen Inc., South Korea amplified the CYP17 variation using the following primers: Reverse: 5′-AGG CTC TTG GGG TAC TTG-3′ (1); Forward: 5′-CAT TCG CAC TCT GGA GTC-3′.

A ready-made master mix of 5.0 µL of deoxynucleotide triphosphates, $MgCl_2$, and Taq polymerase was used for all three polymorphisms. A thermocycler was filled with 25 µL portions of a PCR reaction mixture that had 13 µL of distilled water, 5 µL of genomic DNA, and 1 µL of both forward and reverse primers. Following denaturation at 95°C for five minutes, the DNA was amplified for thirty-five cycles at 94°C for one minute, 57°C for one minute, and 72°C for one minute, then subjected to a final extension at 72°C for five minutes. Included in the PCR experiment was a positive control of genomic DNA. Then each PCR result was ran on a 1% agarose gel, ensuring the production of the intended fragment product. For restriction digestion, the manufacturer said to use 5.0 µL of the PCR product, 2.0 µL of 10x buffer, 0.2 µL of PSA, 7.3 µL of distilled water, and 0.5 µL of enzyme for each CYP17 MspA1I variation. Digestion took 16 hours at 37°C and found three pieces: a 459-bp piece, a 335-bp piece, and a 124-bp piece for the CYP17 (A1) allele. The CYP17 variation revealed two fragments of 335 bp and 124 bp, as well as a 459 bp fragment for the A1/A2 allele. The pieces were put on a 3% agarose gel and stained with 10 µL of ethidium bromide, 200 mL of TBE, and 3.0 g of agarose (1).

Statistical Analyses

SPSS (Statistical Package for the Social Sciences, Version 22.0) was used to conduct data analysis. For two-sided analyses, univariate logistic regression models that were adjusted for variables and ANOVA tests were used. A value of $P < 0.05$ was used to define statistical significance. Chi-square tests were employed for bilateral analyses, with statistical

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significance established at P < 0.05. We conducted tests on specific medical parameters based on the menopausal state of premenopausal and postmenopausal women.

Ethical Authorization

The study received approval from the Ethics and Research Committees of the Public Health Department at the University of Bahri and the University of Science and Technology, Yemen (Approval Number: MEC AD053).

RESULTS

Clinical Characteristics of Female Patients with Breast Cancer

Table 1 indicates that there were no significant disparities in selected clinical features between premenopausal and postmenopausal women. Nonetheless, 53.9% of premenopausal women and 44.4% of postmenopausal women were diagnosed with left-sided breast cancer. The predominant kind of breast cancer among patients was ductal carcinoma (P=0.002). Additionally, 57.9% of premenopausal women had a diagnosis of stage III breast cancer (P=0.004).

Table 1: Selected Clinical Characteristics Among Premenopausal and Postmenopausal Female Patients with Breast Cancer (n=130)

Clinical Characteristics	Premenopausal (n=76) n (%)	Postmenopausal (n=54) n (%)	P-Value
Age by years (Mean ± SD)	38.94 ± 5.86	57.72 ± 8.87	0.000
Site of Breast Cancer			0.565
- Right	27 (35.5%)	23 (42.6%)	
- Left	41 (53.9%)	24 (44.4%)	
- Both	8 (10.6%)	7 (13.0%)	
ER/PR Status			0.248
- ER/PR +ve	35 (46.1%)	29 (53.7%)	
- ER/PR -ve	41 (53.9%)	25 (46.3%)	
Type of Breast Cancer			0.002
- Ductal Carcinoma	65 (85.5%)	54 (100%)	
- Others	11 (14.5%)	-	
Stage of Breast Cancer			0.004
- Stage I	-	2 (3.70%)	
- Stage II	10 (13.2%)	10 (18.5%)	
- Stage III	44 (57.9%)	23 (42.6%)	
- Stage IV	13 (17.1%)	19 (35.2%)	
- Free Margarine	9 (11.8%)	-	
Grade of Breast Cancer			0.619
- Grade 1	2 (2.6%)	3 (5.6%)	
- Grade 2	30 (39.5%)	25 (46.3%)	
- Grade 3	26 (34.2%)	14 (25.9%)	
- Unknown Grade	18 (23.7%)	12 (22.2%)	

*ER (Estrogen Receptor), **PR (Progesterone Receptor)

Research including 130 Sudanese women diagnosed with breast cancer revealed that just under half of the postmenopausal women and over half of the premenopausal women had left-sided breast cancer, characterized by high grades (exceeding grade II). This outcome aligns with substantial research

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performed in the United States by the National Cancer Database (NCDB), which indicated that both the left and right breasts were equally susceptible, but with a little prevalence of left breast cancer. The predominant grade upon diagnosis was grade II (19). The majority of breast cancer patients in the research were diagnosed with ductal carcinoma, aligning with findings from prior studies done at Khartoum Hospital and in Gezira State. The investigations indicated that invasive ductal carcinoma was the predominant form of breast cancer in Sudanese women (4). Also, most of the breast cancer patients in this study were in stages III and IV, which is the same as what other studies in Sudan have found (4, 12, 19).

Levels of Estradiol (E2)

Table 2 shows that premenopausal female patients had clearly higher average estradiol levels; the two groups had a statistically significant difference (P=0.000). Of the postmenopausal female patients, 48.1% showed low levels of estradiol and 35.2% demonstrated high levels of estradiol (E2), which may increase the group's risk of breast cancer given P=0.009.

Table 2: Levels of Estradiol (E2) in Premenopausal and Postmenopausal Female Patients with Breast Cancer (n=130).

Levels of Estradiol	Premenopausal (n=76)	Postmenopausal (n=54)	P-Value
Estradiol (E2) (pg/mL)	162.5 ± 155.09	61.879 ± 79.51	0.000
Low Estradiol (E2) n (%)	19 (25.0%)	26 (48.1%)	0.009
Normal Estradiol (E2) n (%)	28 (36.8%)	9 (16.7%)	
High Estradiol (E2) n (%)	29 (38.2%)	19 (35.2%)	

*Premenopausal: Low level <13 pg/mL, normal level 13-191 pg/mL, high level >191 pg/mL
**Postmenopausal: Low level <11 pg/mL, normal level 11-65 pg/mL, high level >65 pg/mL

The study reported that premenopausal women with breast cancer had higher estradiol (E2) levels. Fascinatingly, over half of the postmenopausal women had low estradiol levels, and almost one-third of them had high levels, which would increase their risk of breast cancer. Breast cancer is well recognized to be caused in part by estrogen, and differences in estrogen metabolism across individuals can also raise a person's risk of the illness (7). Other research has shown that different ways of breaking down estrogen can make postmenopausal women more likely to get breast cancer (6, 11, 16, 17). These results add to that body of evidence. The study also suggests that E2 might raise the risk through processes in adipose tissue. In postmenopausal women, high levels of estradiol have been linked to a higher risk of breast cancer. To lower their risk of breast cancer, overweight postmenopausal women should thus give weight reduction first priority (2, 11).

Allele and Genotyping Frequencies for CYP17 Polymorphisms

Table 3 shows the allelic and genotypic frequencies for CYP17 M1, M2, and M3 in female breast cancer patients, broken down by whether they were premenopausal or postmenopausal. The prevalence of allele A1 for CYP17 was 58.5% in premenopausal women and 75.95% in postmenopausal individuals. Conversely, premenopausal individuals (41.5%) had a higher prevalence of allele A2. The two groups had significantly different frequencies of A1 versus A2 alleles (P=0.025). It's interesting that the homozygous CYP17 M1 (A1A) genotype was linked to a lower risk of breast cancer in Sudanese women who had gone through menopause (P=0.004). Nonetheless, in both cohorts, the heterozygous CYP17 M2 (A1A2) genotype exhibited no significant effect (P=0.101). Moreover, the homozygous CYP17 M3 (A2A2) genotype exhibited no significant difference in premenopausal and postmenopausal women, with P=0.075. CYP17 M3 (A2A2) may elevate the risk of breast cancer by 22.4% in premenopausal women from Sudan.

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Table 3: Allelic and Genotypic Frequencies of CYP17 Alleles and Genotypes for Premenopausal and Postmenopausal Female Patients with Breast Cancer (n=130)

Genetic Variables	Premenopausal Age (n=76) n (%)	Postmenopausal Age (n=54) n (%)	OR	95% CI	P-Value
Allele Frequency					
- Allele (A1)	44.5 (58.5%)	41 (75.95%)	0.436	(0.201-0.944)	0.025
- Allele (A2)	31.5 (41.5%)	13 (24.05%)			
Genotypic Frequency					
- M1 (A1A1)	30 (39.4%)	34 (63.0%)	0.354	(0.172-0.730)	0.004
- M2 (A1A2)	29 (38.2%)	14 (25.9%)	1.763	(0.821-3.787)	0.101
- M3 (A2A2)	17 (22.4%)	6 (11.1%)	2.305	(0.843-6.301)	0.075

DISCUSSION

Recent findings underscore a significant difference in the frequency of A1 and A2 alleles across premenopausal and postmenopausal women. Postmenopausal women display a higher frequency of the A1 allele (75.95%), while premenopausal women show a greater frequency of the A2 allele (41.5%), which is linked to an elevated risk of breast cancer. Previous research has linked the A2 allele to higher enzyme activity and higher levels of estradiol production. This is likely because the CYP17 gene is more active when it comes to transcription. Higher levels of dehydroepiandrosterone sulfate are linked to the A2 allele in premenopausal women, while higher levels of total estradiol are linked to it in postmenopausal women. Several studies back up this link, showing that people with at least one A2 allele are more likely to get breast cancer, especially women before menopause, compared to people with the A1/A1 genotype (3, 5).

This study revealed that the homozygous CYP17 M1 (A1A1) genotype has a protective effect against breast cancer in postmenopausal Sudanese women. In contrast, the heterozygous CYP17 M2 (A1A2) genotype did not have a significant effect on premenopausal or postmenopausal women. The homozygous CYP17 M3 (A2A2) genotype dramatically increased the risk of breast cancer in premenopausal Sudanese women (8). Some studies indicate that CYP17 polymorphisms may elevate breast cancer risk, while other data show a possible protective benefit. CYP17 may also affect the risk of breast cancer in women who have gone through menopause, but its impact on women who have not yet gone through menopause or on larger groups is still unclear (20). Based on these findings, genetic screening is advised for Sudanese women at elevated risk of breast cancer to facilitate early identification and risk evaluation.

CONCLUSION

The research highlights the complex relationship between CYP17 gene polymorphisms and breast cancer risk in Sudanese women. The homozygous CYP17 M1 genotype may reduce breast cancer risk in postmenopausal women, while the homozygous CYP17 M3 genotype may increase the risk in premenopausal women. The heterozygous genotype seems to exert a negligible impact. These results underscore the need for genetic testing, especially for Sudanese women at increased risk of breast cancer, to improve understanding of individual susceptibility and tailor.

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Conflict of Interest

The authors declare that no conflict of interest.

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