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Influence of the CYP19A1 rs10046 Variant on Hormonal Signatures in Breast Cancer: Evidence from an Iraqi Cohort

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ABSTRACT: Breast cancer is the leading cause of diagnosed cancer cases in Iraq, making it the leading cause of cancer-related death among Iraqi women. BCs are characterized by genetic heterogeneity and complexity because of the overlap of numerous genes. Therefore, it is important to study genetic variants that increase the risk of breast cancer. Polymorphisms in genes encoding regulatory hormones have been shown to increase the risk of breast cancer. In addition, the level of estrogen is associated with the expression of the aromatase enzyme-encoding gene CYP19A1, which is a risk factor for breast cancer development. This study included 40 women with breast cancer and 40 women as controls. BC patient samples were collected from Baghdad Medical City Hospital and Baghdad-Iraq, and control samples were collected after confirming that the patients were free of any disease. Estradiol E2, progesterone, and testosterone T levels were measured using electrochemical chemiluminescence (ECL) with an automated Cobas e411 analyzer. DNA was extracted, and the CYP19A1 rs10046 gene was subjected to a PCR-RFLP technique. The results of the current study revealed p values for comparisons between women with breast cancer and control women, with estrogen, progesterone, and testosterone levels being 0.291, 0.18, and 0.473, respectively. Additionally, the E2/T ratio in the two study groups was 0.866. A positive correlation was also found between E2 and progesterone ($p=0.46$ $P<0.001$) and between progesterone and T ($p=0.25$ $P<0.01$). The distribution of the CYP19A1 rs10046 polymorphism in the patient population was 52.5% TT, 25% TC, and 22.5% CC, whereas in the control population, 52.5% TT, 32.5% TC, and 15% CC were present, and the allelic frequency was T=0.65 and C=0.35. Estradiol was significantly associated with the TC genotype. Breast cancer is an age-related disease that is strongly associated with menopause ($p=0.80$, $P<0.001$). These findings suggest that malignant tumors require age-related changes in the tissue or cellular microenvironment of the tumor, leading to the selection of mutations that promote the proliferation and spread of transformed cells. Elevated E2 levels may be positively correlated with the prognosis of patients with breast cancer. The discrepancy in hormone levels between the two groups may be attributed to the exclusion of menstrual cycle data from the study sample. E2 levels were associated with genotypes TT, TC and CC, particularly TC. Therefore, the rs10046 polymorphism in the Iraqi population may have a predictive and diagnostic role. These findings contribute to understanding the genetic basis of breast cancer.

1. INTRODUCTION

Breast cancer is the most common cancer among women worldwide and is responsible for high incidence and mortality rates in both developed and developing countries. The interplay between genetic predisposition, epigenetic regulation, and the tumor microenvironment is pivotal in tumor development. Breast cancer is the leading cause of cancer cases in Iraq, making

it the leading cause of cancer-related death among Iraqi females. Among the ten most common malignancies reported in 2019, 22.58% were cancer cases, with an age-standardized incidence rate of 35.95/100000 women [1].Studies on the immunohistochemical and molecular expression profiles of key genes have classified breast cancer into four broad subtypes: estrogen receptor positive (ER+), progesterone receptor positive (PR+), human epidermal growth factor receptor 2 positive (HER2+), and triple negative [2,3]. The estrogen-sensitive nature of breast cancer was reported by Beatson more than 100 years ago [4], and estrogen are still considered among the main risk factors for this disease. Estrogen contributes to cancer development by promoting cell proliferation and altering cell differentiation and gene expression and is also involved in initiating carcinogenesis via reactive metabolites [5]. Estrogen acts through two receptors, αER and ßER. ER is present in approximately 50–80% of breast cancer; therefore, estrogen receptor alpha is considered the most important target for both chemopreventive and therapeutic agents in breast cancer [6]. Aromatase is among the key enzymes involved in estrogen synthesis. It is encoded by the CYP19A1 gene, the first member of the cytochrome P450 19 subfamily A. This gene is located on the short arm of chromosome 15 (15q21 2), whose total length is 123 kb (Figure 1) [7], of which 30 kb corresponds to the coding region (nine exons for expression) and 93 kb comprises an untranslated region (10 exons for regulation) [8,9,10].

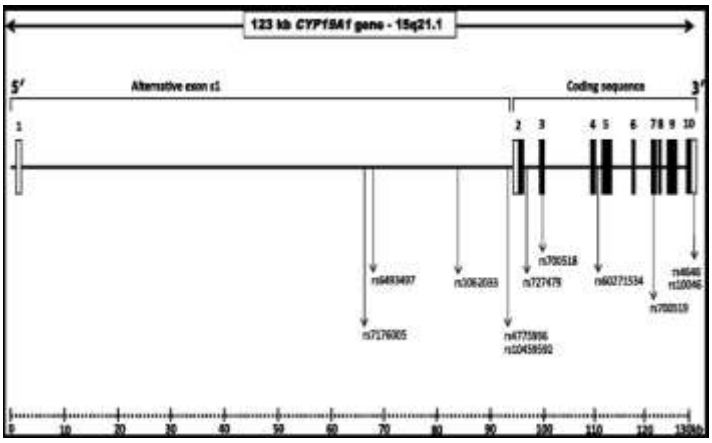

Figure 1: The structure of the CYP19A1 gene.

This enzyme is found in the endoplasmic reticulum of estrogen-producing cells in several vital organs, including the ovaries, testes, placenta, bones, skin, brain, and adipose tissue [11]. In premenopausal women, estrogens are primarily synthesized in the ovaries (ovarian granulosa cells and corpus luteum cells), which in postmenopausal women are synthesized in various extraovarian tissues, such as adipose tissue and bone tissue [4,12]. Aromatase is present in both normal and cancerous cells of mesenchymal connective tissue and human breast cancer epithelium. However, higher levels of enzyme activity and gene expression of this enzyme are observed in cancer cells [8,13]. Polymorphisms in CYP19A1 have been associated with altered aromatase levels in various conditions leading to estrogen-stimulating disorders, including breast cancer and endometriosis. Some researchers have described a close association between CYP19A1 gene expression levels and breast cancer, but further clarification is needed regarding the relationships between these levels and increased risk of breast cancer, survival rates, and disease progression [9,14,15].

2. MATERIALS AND METHODS

2.1 Sample Collection

This study included 40 females with breast cancer and 40 healthy women. Samples were collected from patients who visited Baghdad Medical City Hospital, Baghdad-Iraq, between June and November 2025. The pilot study was conducted at the Ministry of Science and Technology and the laboratories of the College of Science for Women, University of Baghdad. The confirmed diagnosis of breast cancer for the patients was based on imaging, clinical examination, and histological examination. All participants were 30 years and older. The criteria for selecting healthy women included good health, not currently taking any medications, good reproductive health, and no known hormonal or psychological disorders. Samples from both patients and healthy females were collected by drawing 5 ml of whole blood. The first part of the blood sample was placed in a gel tube for serum separation, and estradiol, progesterone, and testosterone levels were measured by using

electrochemiluminescence (ECL) with an automated Cobas e411 device according to the manufacturer's instructions. Another portion was placed in an anticoagulant tube (EDTA) for DNA extraction in subsequent stages.

2.2 DNA extraction

Whole-blood DNA was extracted from manual solutions prepared in the laboratory, after which the concentration and purity of all the samples were measured using a NanoDrop device (1 µl).

2.3 Amplification of rs10046 in the CYP19A1 gene.

Genotyping for restriction fragment length polymorphism–polymerase chain reaction (RFLP–PCR) of the CYP19A1 gene was performed using a freeze-dried primer provided by Macrogen and generated using NCBI-BLAST primer generation software, and the sequences of the primers used for genotyping were as follows: forward: 5'-TAGAGAAGGCTGGTCAGTGCC-3' and reverse: 5'-CTCTGGTGTGAACAGGAGCA-3'. Two primers produced a sequence of 196 bp and, after restriction enzymes, produced only 196 bp (TT), 196 bp and 169 bp (TC), or 169 bp (CC). PCR amplification of the rs10046 bp gene was performed in a 25 µl reaction mixture containing 12.5 µl of Taq2x master mix (ELK Biotechnology), 1 µl of each primer, and 3 µl (100 ng) of genomic DNA. The PCR conditions were as follows: initial denaturation at 95°C for 4 minutes, followed by 35 cycles of 95°C for 1 min, 58°C for 50 sec, 72°C for 1 min, and 72°C for 10 min as the final extension step. Electrophoresis was then performed on a 1% agarose gel to confirm the accuracy of the PCR amplification. The restriction enzymes were subsequently mixed with 10 µl of the PCR product with 1 µl of restriction enzyme in 2 µl of the buffer, after which the mixture was incubated for 6 hours and then electrophoresed on an agarose gel at a concentration of 2% for 45 minutes.

2.4 Statistical Analysis

Statistical analysis was performed using Spearman correlation to evaluate the relationships among age, menopausal status, the CYP19A1 rs10046 genotype score, progesterone levels, estradiol levels, testosterone levels, and the E2/T ratio in breast cancer patients. The genotype distributions were compared using Pearson's chi-square test (P = 0.6092). HWE in controls: P= 0.1425. Odds ratios are presented with 95% confidence intervals. C was treated as the reference allele, and T was treated as the variant allele according to the adopted PCR-RFLP nomenclature. Comparisons between breast cancer patients and healthy controls were performed using the Mann–Whitney U test, and P values were calculated using the Kruskal–Wallis test within each group. An advanced heatmap was generated using sample-level log-transformed and Z score-standardized hormonal variables. Rows represent individual samples, and columns represent hormonal variables. Row annotations indicate disease status, rs10046 genotype, and menopausal status.

3. RESULTS AND DISCUSSION

3-1 Distribution of age and hormonal value in women with breast cancer and controls

The age range of the breast cancer patients was 27–75 years, while it was 30–75 years for the control subjects, and the difference was not statistically significant ($P < 0.05$); the p values between the breast cancer patients and control women were 0.291, 0.18, and 0.473, respectively. Additionally, the E2/T ratio in the two study groups was 0.866 (Table 1).

Table 1. Baseline clinical and hormonal characteristics

Variable	Control	Patient	P value
Age (years)	50 (39-59.25)	51.5 (44.5-61)	0.5
Progesterone (ng/mL)	0.4 (0.09-2.2)	0.11 (0.06-0.71)	0.18
Estradiol, E2 (ng/mL)	25.94 (15.82-34.78)	29.5 (16.04-58.56)	0.291
Testosterone (ng/mL)	0.21 (0.11-0.3)	0.21 (0.12-0.35)	0.473
E2/Testosterone ratio	137.11 (72.31-228.69)	139.75 (82.92-205.14)	0.866

3-2 Distribution of the genotypes and allele frequency of CYP19A1 rs10046 polymorphisms in breast cancer patients and controls

The results of the current study revealed distributions of TT (52.5%), TC (25%), and CC (22.5%), as shown in Table 2, while the allelic frequency was T=0.65 and C=0.35 (Table 3).

Table 2. CYP19A1 rs10046 genotype distribution

Group	CC	TC	TT
Control	6 (15%)	13 (32.5%)	21 (52.5%)
Patient	9 (22.5%)	10 (25%)	21 (52.5%)

Table 3. CYP19A1 rs10046 allelic and genetic model association

Model	OR_95_CI	P value
Dominant model: CC vs TC+TT	0.612 (0.159-2.184)	0.5679
Recessive model: CC+TC vs TT	1 (0.38-2.632)	1.0000
Overdominant model: CC+TT vs TC	0.696 (0.231-2.042)	0.6219
Additive model: CC=0, TC=1, TT=2	0.882 (0.496-1.557)	0.6649

Figure1. Distribution of progesterone, estradiol (E2), and testosterone levels and the ratio of E2 to testosterone according to the CYP19A1 rs10046 genotype. Progesterone (Figure 1, panel A): The progesterone concentration did not differ according to the genotype of CYP19A1 rs10046 (P = 0.594). The individual variation in progesterone levels was large, and no specific trend according to genotype was observed.

As shown in Figure 1, panel B (estradiol, E2), a significant correlation was observed between the CYP19A1 rs10046 genotype and the estradiol concentration (P=0.023). The highest concentrations of estradiol were found in the heterozygous TC genotype, particularly in patients with breast cancer, while the median levels of E2 in homozygotes (CC and TT) were significantly lower.

Figure 1, Panel C (Testosterone): No significant difference in testosterone levels was observed between different CYP19A1 rs10046 genotypes (P = 0.116). However, compared with CC and TT subjects, heterozygous TC subjects had slightly higher testosterone levels. Figure 1, panel D (E2/Testosterone ratio): No differences were found in the E2/testosterone ratio by genotype (P = 0.909). Similar trends in estrogen and testosterone concentrations were observed among the different genotypes, with some extreme values.

CYP19A1 rs10046 was correlated with estradiol levels but not with progesterone levels, testosterone levels or the E2/testosterone ratio. Subjects with heterozygous TC had the highest estradiol concentration levels.

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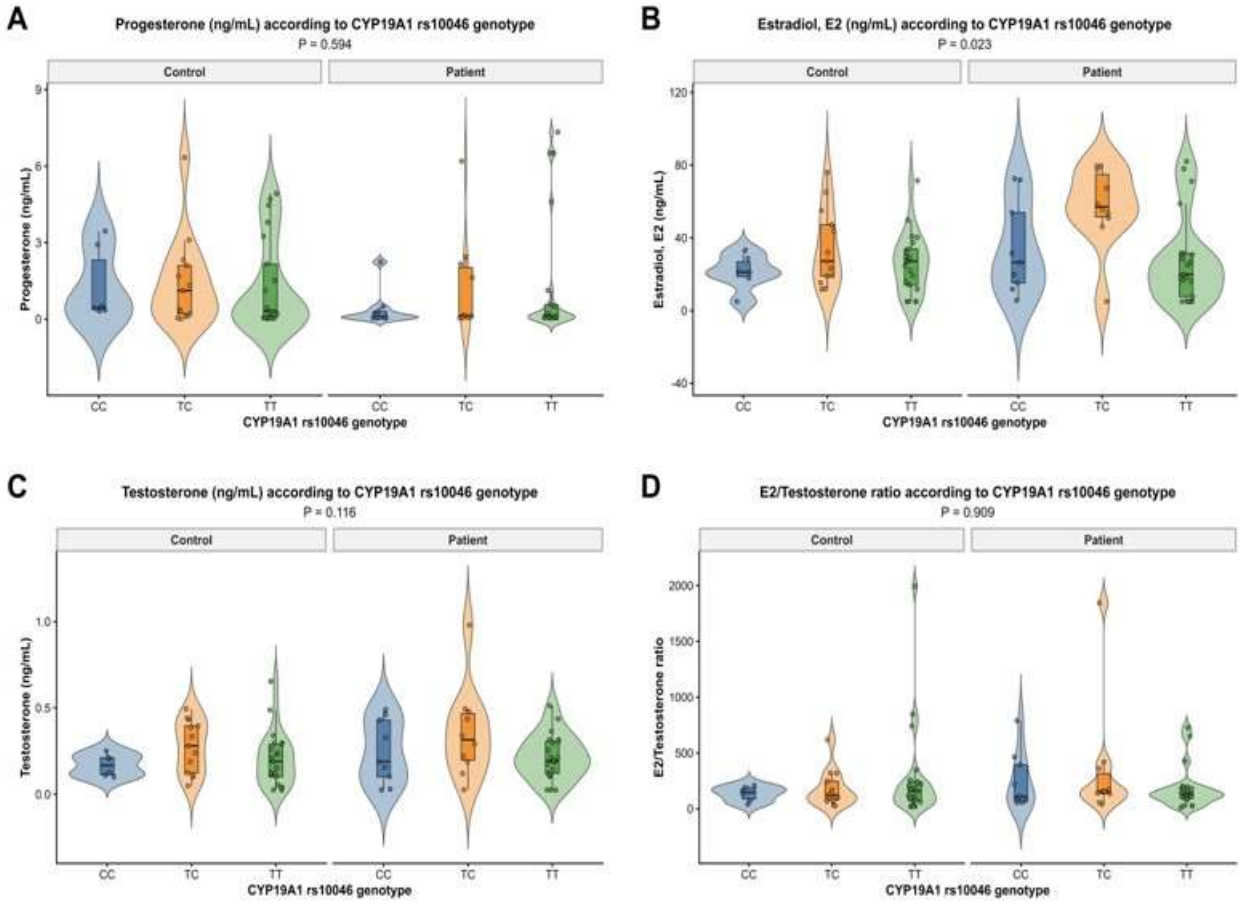

Figure 2: Association of CYP19A1 rs10046 genotypes with hormonal profiles in breast cancer patients and healthy controls

Panel A (Progesterone): Progesterone levels exhibited substantial within-group variation across all genotype groups. There was no consistent pattern of genotype-dependent associations among premenopausal or postmenopausal women, supporting the overall nonsignificant association (P=0.594).

Panel B (Estradiol, E2): Estradiol was the only hormone that was significantly associated with the rs10046 genotype (P=0.023). Compared with the CC and TT genotypes, the TC genotype generally resulted in higher E2 concentrations in both menopausal strata. This tendency was more pronounced in breast cancer patients whose TC carriers had the highest estradiol levels, which might indicate a potential role for rs10046 in estrogen biosynthesis.

Panel C (Testosterone): Testosterone levels did not differ among genotypes in the premenopausal or postmenopausal subgroup (P = 0.116). Although TC carriers tended to have slightly higher values, the differences were not statistically significant.

Panel D (E2/Testosterone ratio): The E2/testosterone ratio showed a large spread and some outliers, but no significant differences were observed between genotypes (P=0.909). Thus, the overall estrogen-to-androgen balance appeared to be independent of the rs10046 genotype.

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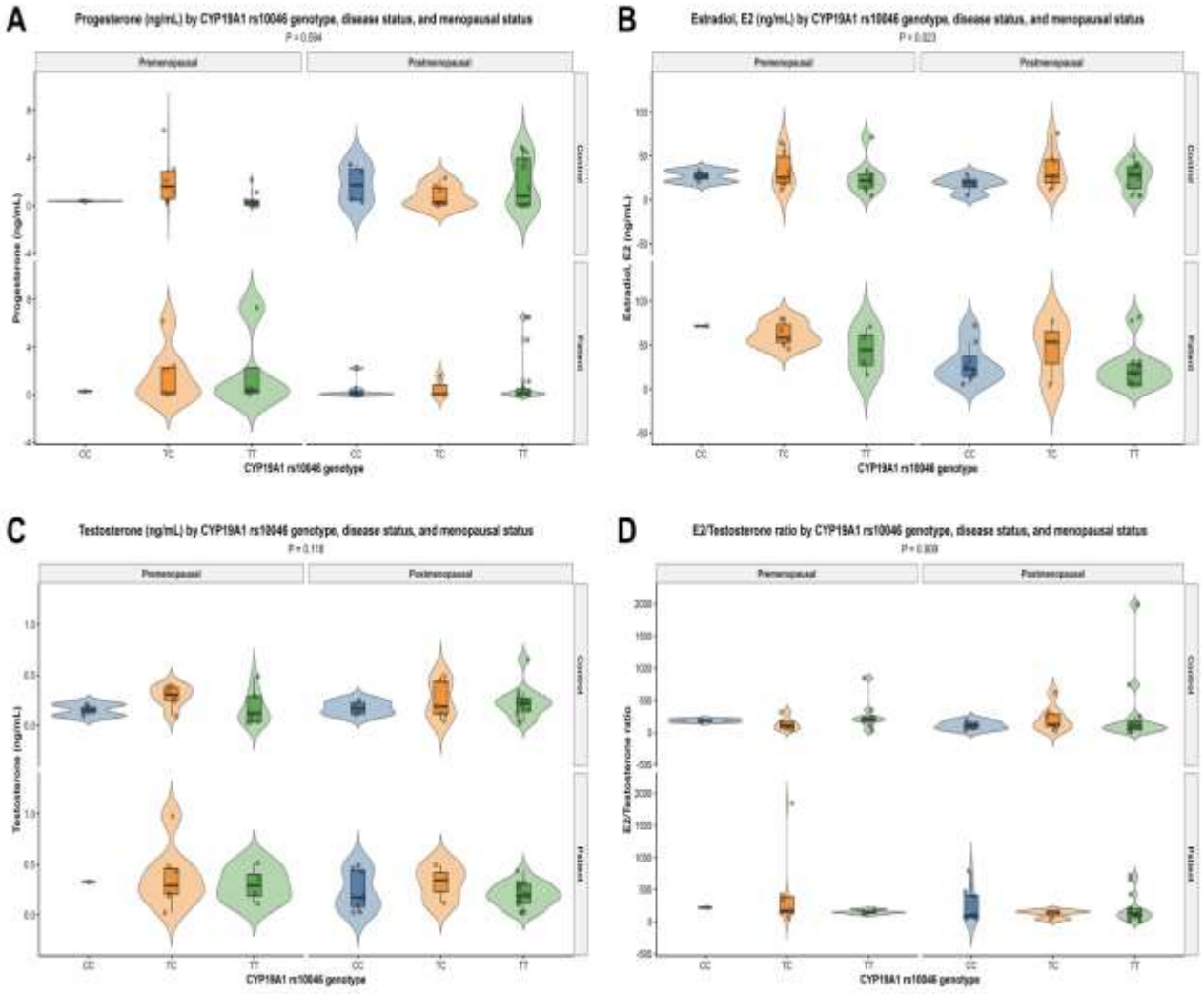

Figure 3: Stratified association of CYP19A1 rs10046 genotypes with hormonal profiles according to disease status and menopausal state

Hierarchical clustering of standardized hormonal variables revealed a high degree of interindividual heterogeneity across the study population. No specific clustering pattern was observed for disease status, menopausal status or the CYP19A1 rs10046 genotype, suggesting that the overall hormonal profile was affected by several biological factors rather than by genotype alone.

The heatmap showed a high degree of variation in estradiol (E2), with some samples showing high positive standardized values (red color), especially among the carriers of the TC genotype. In contrast, progesterone and testosterone were more heterogeneously distributed, and there was no clear clustering according to genotype. The E2/testosterone ratio had the largest dynamic range, suggesting a wide variation in hormonal balance between individuals.

Overall, the clustering pattern is consistent with the statistical findings that rs10046 is associated with estradiol-related hormonal variation rather than the formation of a unique global hormonal profile.

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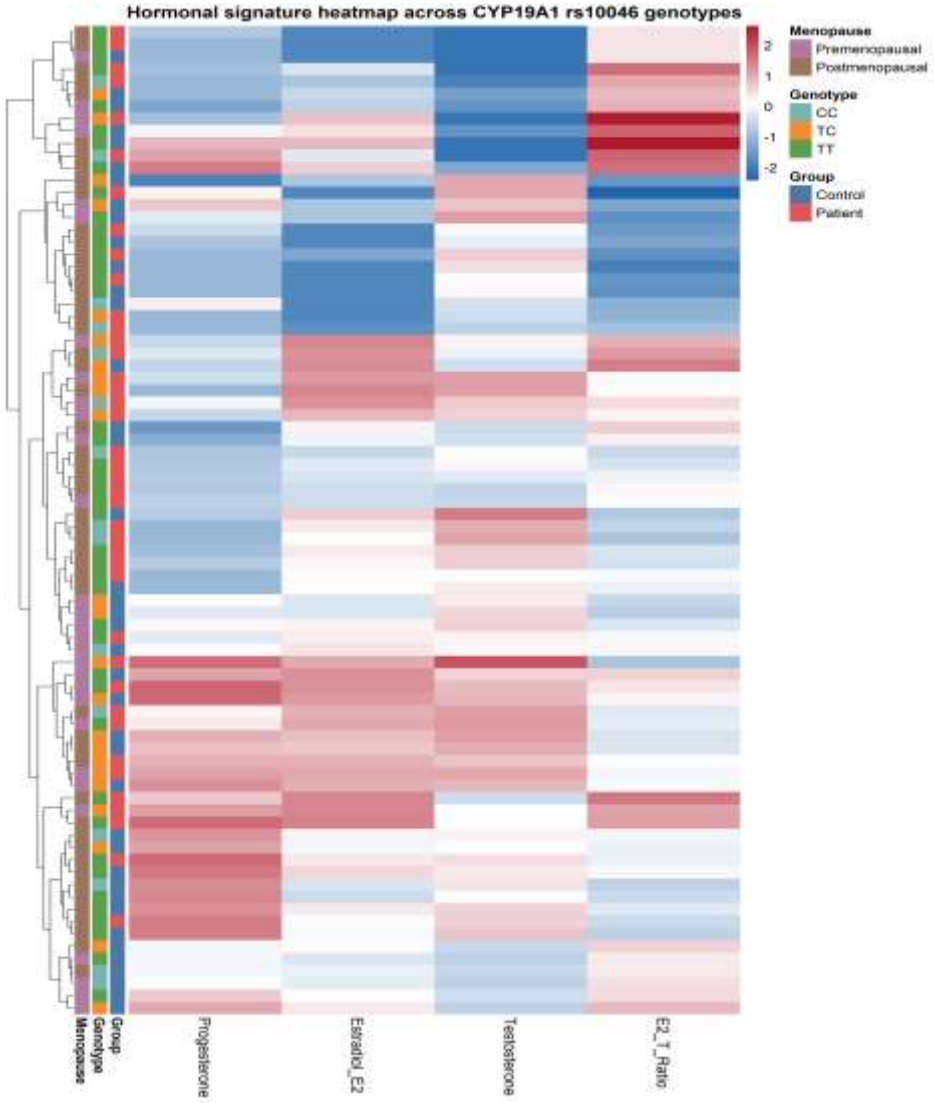

Figure 4: Hormonal signature heatmap across CYP19A1 rs10046 genotypes

Across all the participants, age was significantly negatively correlated with estradiol (ϱ = -0.33; P < 0.01) and the E2/testosterone ratio (ϱ = -0.27; P < 0.05), indicating that estrogen-related hormonal activity decreases with age. Progesterone was positively correlated with estradiol (ϱ = 0.46, P < 0.001) and testosterone (ϱ = 0.25, P < 0.05). Estradiol levels were positively correlated with testosterone levels (ϱ 0.35; P 0.01) and the E2/testosterone ratio (ϱ 0.49; P 0.001). Testosterone was negatively correlated with the E2/testosterone ratio, as expected (ϱ = −0.57, P < 0.001). No significant correlations were found between the rs10046 genotype score and any hormonal variables.

In healthy controls (Panel B), progesterone was positively correlated with estradiol (ϱ = 0.47, P < 0.01). Estradiol levels were strongly positively correlated with the E2/testosterone ratio (ϱ = 0.52, P < 0.001). Testosterone was strongly negatively correlated with the ratio (ϱ = −0.72, P < 0.001). The rs10046 genotype was not significantly associated with any hormone parameters.

In breast cancer patients (Panel C), patient age was strongly negatively correlated with the levels of estradiol (ϱ = -0.65; P < 0.001) and progesterone (ϱ = -0.46; P < 0.01) and the E2/testosterone ratio (ϱ = -0.41; P < 0.05). Estradiol levels were positively correlated with progesterone levels (ϱ = 0.53, P < 0.001). Estradiol levels were positively correlated with testosterone levels (ϱ=0.47; P<0.01) and the E2/testosterone ratio (ϱ=0.47; P<0.01). As in the overall analysis, no significant association was observed between the rs10046 genotype score and any hormonal marker.

In premenopausal women (Panel D), testosterone was positively correlated with age (ϱ = 0.42, P < 0.05), progesterone (ϱ = 0.50, P < 0.05), and estradiol (ϱ = 0.41, P < 0.05). Progesterone was also positively correlated with estradiol (r = 0.45, P < 0.05). Testosterone was strongly inversely correlated with the E2/testosterone ratio (ϱ = −0.68; P < 0.001). No significant association was found between the rs10046 genotype and hormone levels.

Postmenopausal (Panel E) age was inversely correlated with estradiol levels in postmenopausal women (ϱ = −0.33, P < 0.05). Estradiol remained positively correlated with progesterone (ϱ = 0.41, P < 0.01). Estradiol levels were positively correlated with testosterone levels (ϱ = 0.31; P < 0.05) and the E2/testosterone ratio (ϱ = 0.54; P < 0.001), and testosterone levels were strongly negatively correlated with the ratio (ϱ = -0.55; P < 0.001). However, there was no significant correlation between the rs10046 genotype score and hormone variables.

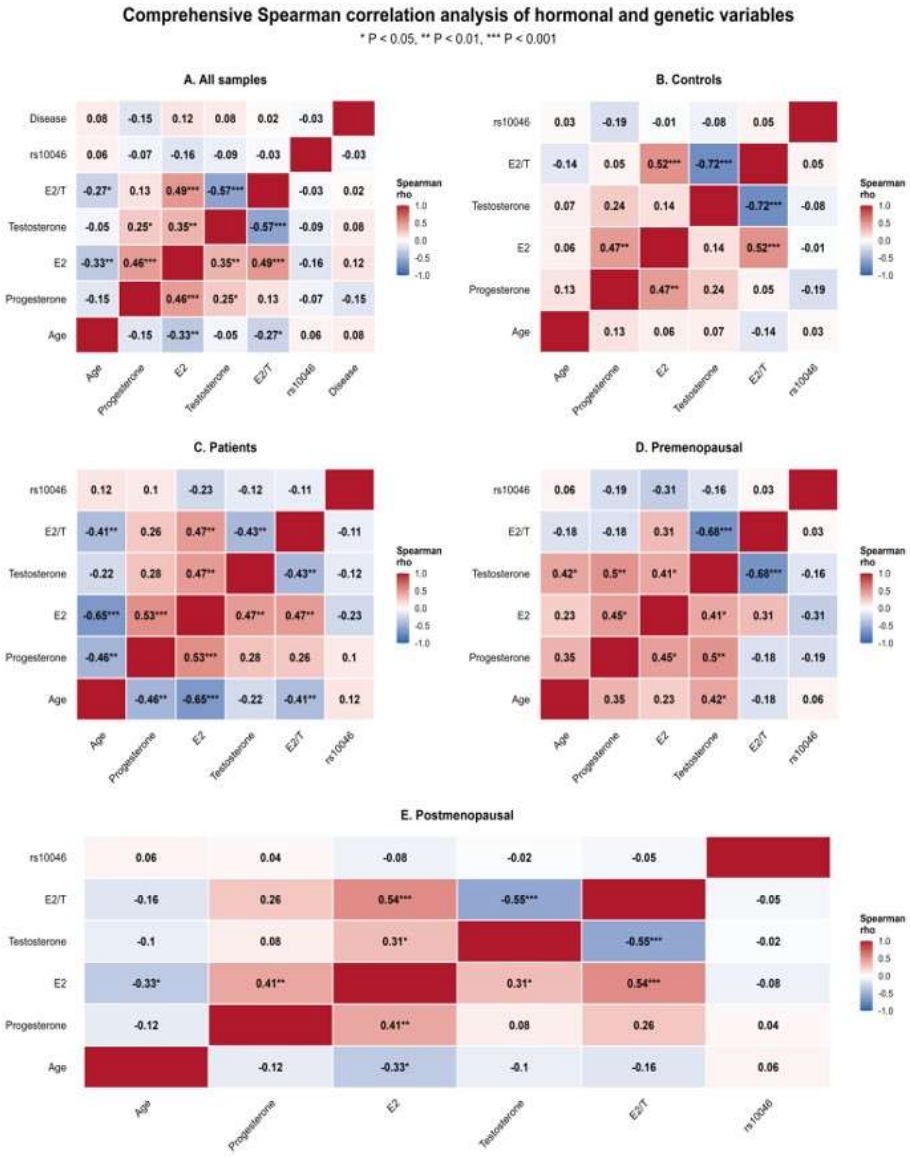

Figure 5: Comprehensive Spearman correlation analysis of hormonal and genetic variables

3-3 Association of CYP19A1 rs10046 genotypes with hormone levels and the E2/T ratio in breast cancer and control samples.

Table 4. Median hormonal values according to disease status and the CYP19A1 rs10046 genotype

Group	Genotype	N	Progesterone	Estradiol_E2	Testosterone	E2_T_Ratio
Control	CC	6	0.47 (0.37-2.32)	21.1 (18.67-26.82)	0.17 (0.11-0.21)	147.21 (87.32-184.32)
Control	TC	13	1.12 (0.21-2.1)	27.19 (19-47.26)	0.28 (0.12-0.4)	122.75 (79.17-247.18)
Control	TT	21	0.3 (0.05-2.16)	27.19 (14-33.91)	0.19 (0.1-0.29)	159.06 (72.65-240.64)
Patient	CC	9	0.07 (0.05-0.3)	26.51 (15.25-53.93)	0.19 (0.1-0.43)	110.06 (73.4-395)
Patient	TC	10	0.14 (0.07-2.03)	57.06 (51.56-74.88)	0.32 (0.2-0.47)	157.19 (136.03-313.66)
Patient	TT	21	0.09 (0.06-0.57)	19.99 (7.72-31.44)	0.19 (0.12-0.31)	128.88 (92.48-195.52)

3.4 Discussion

Breast cancer is an age-related disease, and the risk of developing it has been shown to increase with age. Research has indicated that the transformation of breast tissues into malignant tumors requires age-related changes in this tissue or cellular microenvironment, leading to the selection of mutations that promote the proliferation and spread of transformed cells [16,17]. In this study, the age of the breast cancer patients was strongly correlated with menopausal status ($\varrho = 0.80$, $P < 0.001$), which is consistent with the findings of a study in the United States that demonstrated a 4% decrease in incidence rates among women under the age of 40 years [18]. A study in Jordan indicated that the incidence of breast cancer among women over fifty years of age was approximately 53.7% [19], whereas in Saudi Arabia, women over the age of 40 were more susceptible to breast cancer [20]. In Iraq, the highest incidence rate was reported for women ≥ 40 years [21,22].

Several studies have shown that elevated levels of steroid sex hormones are associated with an increased risk of breast cancer [23,24]. The results of the current study revealed elevated estradiol levels with nonsignificant decreases in progesterone and testosterone levels compared with those in the control group. These findings are consistent with those of other studies demonstrating a positive correlation between estradiol levels and breast cancer risk. This correlation may be attributed to differences in menstrual cycle status. In the premenopausal stage, estradiol levels, progesterone levels, and the E2/T ratio were positively correlated. In the postmenopausal stage, estradiol levels, progesterone levels, and the E2/T ratio were negatively correlated. These findings suggest that local estradiol production occurs within mammary adipose tissue because of the presence of ER and PR after menopause, which serve as the primary source of estradiol production [4]. In the current study, no statistically significant correlation was observed for testosterone levels between the premenopausal and postmenopausal control groups. Androgens are produced by the adrenal glands. The fact that androgen levels do not decrease during menstruation may explain why they either directly stimulate breast cancer growth or are converted to estradiol by the aromatase enzyme [25] Aromatase is a crucial factor in breast cancer development because of its role in the production of estrogen from androgens, including estradiol from testosterone [26].

The CYP19A1 rs10046 gene encodes an aromatase enzyme that affects estrogen biosynthesis and thus promotes breast cancer. The results of the current study revealed an association between estradiol levels and all genotypes, with a statistically significant association with the TC genotype ($p=0.023$) in both menopausal states (Fig.). The number of alleles varies considerably among different ethnic groups. Consequently, the presence of CYP19A1 rs10046 alleles may contribute to some ethnic variations in the incidence of certain cancers. Epidemiological and experimental studies have indicated that women with breast cancer exhibit high levels of CYP19A1 gene expression in addition to elevated estrogen levels [14,27]. Increased gene expression of the CYP19A1 enzyme is a key regulatory event for intertumor estrogen production in these malignant tissues. The rs10046 polymorphism in the Iraqi population may have a predictive and diagnostic role, and the research findings contribute to understanding the genetic basis of breast cancer. However, further studies are needed on other SNP polymorphisms of the CYP19A1 gene and their relationship to breast cancer development, as well as their connection to tumor stage and hormone receptors.

4. CONCLUSION

Compared with control patients, patients with breast cancer presented elevated progesterone levels and elevated estradiol levels. This results in a higher E2/T ratio in breast cancer patients than in control women. The results also revealed a correlation between estradiol and the CYP19A1 TC polymorphism, suggesting a possible link to aromatase activity in the conversion of androgens to estrogens. The CYP19A1 gene, which is responsible for aromatase production, could be considered a potential therapeutic target for reducing estrogen levels in the body. Despite these findings, the study has several limitations, including a small sample size and the absence of aromatase measurements or comprehensive molecular characterization to elucidate the complete biological mechanism involved. Further investigation of other CYP19A1 gene polymorphisms and their gene expression in breast tissues is recommended to elucidate the underlying mechanisms leading to breast cancer development.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

None

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