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Association between CYP17A1, CYP19A1, and HSD17B1 Gene Polymorphisms in Hormone Synthesis pathway with Ovarian Cancer Risk

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Abstract

Objective: To investigate the polymorphisms of genes in the steroidogenesis pathway to understand the etiological mechanisms to OC risk in the South Indian population Design: Case-Control Study Setting and Sample: Ovarian cancer cases (200) and healthy individuals (200) from the South Indian population. Methods: All the cases and controls were genotyped for SNPs by using allelic discrimination assay. Main outcome measures: Genetic distribution of SNPs of Steroidogenesis pathway genes in the South Indian population. Results: The observed results for rs743752, the homozygous CC genotype revealed significant association (OR; 1.68; 95%CI, 1.25-2.26; p =<0.05) and the dominant model, recessive model and additive model showed a significant association with an OR of 1.62; 95%CI, 1.09 – 2.42; p = 0.015, OR of 0.29, 95%CI, 0.14 – 0.60; p = <0.001 and OR of 1.68, 95%CI, 1.25 – 2.26); p = <0.001 respectively in cases and controls for OC risk. In rs10046, the heterozygous CT genotype (OR; 1.61; 95%CI 1.06 – 2.43; p = 0.023), the dominant (OR; 1.65; 95%CI, 1.11 – 2.45; p = 0.012) and the additive (OR; 1.46; 95%CI, 1.07 - 1.98; p = 0.015) models were found to be statistically significant. There was no significant association between rs605059 genotypes with ovarian cancer risk. Conclusions: To conclude, results indicated that the polymorphisms of CYP17A1 (rs743572) and CYP19A1 (rs10046) genes are associated with increased risk of ovarian cancer risk in South Indian population.

Introduction

Ovarian cancer (OC) is the most lethal gynecological cancer accounts for 2.5% of all cancers and the fourth most common cancer and the seventh leading cause of deaths among women worldwide[(1)]. In India, OC is the third leading site of cancer in women trailing behind cervical and breast cancers[(2,3)]. A number of studies gave an account of several diagnostic markers in OC[(4,5)]. In general, OC is characterized based on the molecular-based markers, histopathological parameters and clinical factors include age, age at menarche, menopause status, and stage of the disease at diagnosis (FIGO).

The OC is an endocrine-related tumor that arises from the ovaries in which the hormones such as estrogen, progesterone and testosterone are synthesized[(6)]. These steroid hormones are synthesized by a group of enzymes called cytochrome P450 which regulates a variety of physiological and development progressions in humans[(7)]. This process starts with cholesterol, which synthesizes pregnenolone with the help of an enzyme *CYP11A1* . Furthermore, the pregnenolone and progesterone are converted into androstenedione by the enzyme *CYP17A1* . The final products estrogen, progesterone and testosterone were produced by the enzymes*CYP19A1* and *HSD17B1* [(8)]. Ovarian steroidogenesis is a most complex process in which the granulosa and theca cells separate the enzymatic steps, which surround the oocyte and form a follicle[(9)]. In spite of the fact that the exact role of steroid hormones in OC risk is unclear[(10,11)].

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The production of estrogens, progesterone and testosterone occurs through the steroidogenesis process where cholesterol is firstly synthesized into pregnenolone by the enzyme, CYP11A1. Thereafter, progesterone is produced from pregnenolone by HSD3B1 and HSD3B2. CYP17A1 converts pregnenolone and progesterone into androstenedione, a precursor for estrogen and testosterone production. The enzymes, CYP19A1, HSD17B1 and HSD17B2, are involved in the production of estrogens (estrone, estradiol, estriol) and testosterone.

Studies that evaluating both steroid hormone synthesis and its associated genes with OC risk are required to understand the etiological mechanism of hormones in ovarian carcinogenesis. An epidemiological study suggested that the genes in hormone biosynthesis pathway are the candidates because OC is an endocrine-related tumor. The candidate genes*CYP17A1* , *CYP19A1* , and *HSD17B1* with common allelic variants in the hormone biosynthesis pathway that may increase the estrogen concentration are likely to be considered as risk factors for breast cancer[6,12,13]. The genes *CYP17A1* ,*CYP19A1,* and *HSD17B1* are found to have an important role in the metabolism, synthesis, and maintaining androgen and estrogen hormone levels[14]. The polymorphisms in these genes may alter the level of estrogen and other hormones, which may increase the risk of OC. Due to the scarcity of studies that investigated the association of steroidogenesis gene polymorphisms with the OC risk. Hence, the current case-control study and was focused on the association between three major polymorphisms rs743572, rs10046, rs605059 of the steroid synthesis genes *CYP17A1* , *CYP19A1* , and*HSD17B1* respectively, in the South Indian population with Ovarian cancer risk.

Material and Methods

Sample Selection: In the present study, a total number of 400 individuals comprising 200 OC patients and 200 controls were recruited based on the specific inclusion and exclusion criteria after obtaining the informed consent. Blood samples of cases were collected from the patients with histological confirmation of OC, visited the department of oncology and gynecology at Sri Ramachandra Medical Centre, Chennai, India between 2015 and 2018. Meanwhile, age-matched controls were obtained from the 200 individuals who visited the outpatient department for the treatment of common ailments such as common cold, fever, etc., with no prior diagnosis of benign ovarian diseases; no history of hysterectomy, mastectomy or oophorectomy; no relatives with breast, ovarian, endometrial cancer; no physical or mental disability which would preclude their participation in the study. The study was approved by the Institutional Ethics Committee (IEC) of Sri Ramachandra University, Chennai, to collect blood samples from the study participants.

DNA Extraction: 3-5ml of peripheral blood samples from all the study participants were collected using EDTA containers (BD, NJ, USA). Genomic DNA was isolated from 200µl of whole blood using a QIAamp DNA extraction kit by the manufacturer's protocol (Qiagen, Hilden, Germany. The isolated DNA samples were checked for quality and quantity using 0.8% agarose gel electrophoresis (AGE) and NanoDrop spectrophotometer (Thermo Fisher Scientific/NanoDrop Products, Wilmington, Delaware, USA) respectively which is then stored at -20°C until analysis.

Genotyping: Taqman allelic discrimination assay was performed using predesigned probes and primers for genotyping*CYP17A1* rs743572 (C_2852784_30), *CYP19A1* rs10046 (C_8234731_30), and *HSD17B1* rs605059 (C_2350902_10) polymorphisms. All the reactions were carried out using 384-well arrays at 60°C annealing temperature on the 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). Each well-contained 5ul of total reaction mix with universal Taqman genotyping master mix (Applied Biosystems, Foster City, CA, USA), probes (Applied Biosystems, Foster City, CA, USA) and 10ng/ul of DNA sample. Genotypes were called using the SDS v2.4 Allelic Discrimination sequence detection software (Applied Biosystems, Foster City, CA, USA). Genotyping success rates were [?] 99% for each genotype for all subgroups.

Statistical Analysis:

All the statistical analysis was performed using statistical software SPSS v25 (IBM Corporation) and Epi info v7.2.2.6 (Center for Disease Control and Prevention, Atlanta, Georgia). Genotype and allele frequencies for all three polymorphisms in cases and controls were calculated and tested for Hardy-Weinberg equilibrium. Association analysis of all the polymorphisms with OC risk was performed using odds ratio (OR) with a

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95% confidence interval (CI). The association between the genotypes of all three polymorphisms with clinical characteristics was evaluated using the chi-square test. Two-tailed P-value <0.05 was considered statistically significant. Bonferroni type adjustment was carried out for the statistically significant genotypes to test for multiple corrections. SNPstats, an online tool was used to estimate haplotype frequencies that use the Markov Chain Monte Carlo method (Sole' et al., 2006).

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Results:

Characteristics of the cases and controls:

The present case-control study comprises 200 OC cases and 200 healthy volunteers to match the cases were called up to investigate the association of *CYP17A1* (rs743572), *CYP19A1* (rs10046) and*HSD17B1* (rs605056) gene polymorphisms and its association with OC risk in South Indian population. Both cases and controls were selected based on the eligibility standards. The cases and controls were matched by age (P = 0.996). Student's t-test revealed a significant association in the BMI (p=0.0002) and the significant difference was observed in menopausal status by using the chi-square test (p = 0.008). There was no significant association found in menarche age. The demographic details of the cases and healthy individuals are presented in table 1.

Genotype frequency distribution among cases and controls:

The genotypic distribution of *CYP17A1* (rs743572), *CYP19A1*(rs10046) and *HSD17B1* (rs605056) gene polymorphisms in the control samples did not show any deviation from the Hardy-Weinberg equilibrium.

The genotype frequency distribution between OC patients and controls of all the studied polymorphism given in the table 2 and the distribution of alleles in genetic models were represented in table 3. For the polymorphism rs743572 of *CYP17A1* gene, our results revealed that the homozygous variant CC allele had 3.93 fold risk increased OC risk (OR = 3.93; 95% CI = 1.86 – 8.28; P – <0.001). Similarly the genetic models dominant, recessive and additive allele were found to be associated with a 1.62 (OR = 1.62; 95% CI = 1.09 – 2.42; P – 0.0158), 0.29 (OR = 0.29; 95% CI = 0.14 – 0.60; P – <0.001) and 1.68 (OR = 1.68; 95% CI = 1.25 – 2.26; P - <0.001) fold increased risk of OC respectively in South Indian population.

For the SNP rs10046 of the *CYP19A1* gene, the heterozygous allele (CT) was at 1.61 folds (OR = 1.61; 95% CI = 1.06 – 2.43) increased OC risk in patients when compared to controls. Additionally, results on the genetic models showed that the dominant allele had 1.65 (OR=1.65; 95% CI = 1.11 – 2.45); P – 0.023) folds and additive allele had 1.46 folds (OR = 1.46; 95% CI = 1.07 – 1.98) increased in OC patients compared to controls. Furthermore, in cases of rs605056 polymorphism of*HSD17B1,* no significant differences were seen in any of the genetic models between cases and controls with OC risk.

Haplotype analysis:

Haplotype analysis of the three polymorphisms revealed eight different haplotype combinations were observed in both cases and controls (Table 4). The results showed CCA and CTA were found to be higher in cases (0.2 and 0.07) compared to controls (0.13 and 0.04) with an OR of 0.46 (0.27 – 0.79) and 0.40 (0.18 – 0.91), respectively indicating that the possible contribution of the haplotypes to the risk of OC.

Discussion:

Main Findings:

To the best of our knowledge, this is the first study to provide solid evidence that the *CYP17A1* (rs743572) and *CYP19A1* (rs10046) polymorphisms showed significant association with ovarian cancer in South Indian population. However, the polymorphism rs605056 of*HSD17B1* did not show any significant association with ovarian cancer in the same population. The haplotype analysis results showed that the combination alleles are contributed to the risk of OC.

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Strength and limitations :

In the present study, 400 subjects that include 200 clinical proven OC cases and 200 healthy volunteers as a control group were analyzed for the genotype of three polymorphisms rs743572 of *CYP17A1* , rs10046 of *CYP19A1* and rs605056 of *HSD17B1* genes. However, some limitations need to be considered in interpreting our findings. Firstly, the main considered limitation was the sample size due to the low incidence of OC in the Indian population especially South Indian. Further studies are needed to confirm the association of gene polymorphisms with OC risk. Although, our study revealed that polymorphisms rs743572 and rs10046 are significantly associated with OC in the Indian population. These selected genes are highly involved in the synthesis of steroid hormones (estrogen, androgen and progesterone) which is having importance in the progression of breast and OC[15]. The function of these hormone synthesis genes, which may affect the estrogen levels and its harmful metabolites, which prompts OC[16]. Due to the lack of studies on steroid hormone synthesis with OC risk, we had to compare our results for all the polymorphisms with those of similar studies on OC risk.

Interpretation:

The *CYP17A1* is considered a key enzyme in the estrogen-signaling pathway. This gene was found to catalyze two different steps in the pathway, the 17, 20 lyases and 17 alpha hydroxylases reactions and it has an important function in synthesis, metabolism and maintaining the levels of estrogen and androgen hormones[17]. The polymorphism in the 5' promoter region has T/C substitution that creates an additional *SpI* type (CCACC) promoter site. This could alter the recognition site for the *MspAI* recognition site[18]. This rs743572 polymorphism is considered an increased risk of various cancers[19–23]. A study showed that the rs743572 T/C polymorphism in the *CYP17A1* gene may alter the binding characteristics of the promoter region and modifies the gene's function[18]. This could lead to a change in estrogen levels and the risk of OC. In the same way, our results were in agreement with many of the studies that reported the increased number of CC genotype than TT leads to increased circulating levels of estradiol[24,25]. A study, which was conducted in the North Indian population on breast cancer showed a significant association with *CYP17A1* rs743572 polymorphism[26]. Furthermore, a study engaged by Konstantinos et al, confirms our results by suggesting that the C allele of rs743572 polymorphism might influence promoter activity with an increased amount of *CYP17A1* mRNA transcription[27]. The rs743572 polymorphism increases the levels of androgen due to the induction of *CYP1A1* gene expression that ultimately resulted in the development and progression of prostate disorders[28].

CYP19A1 gene codes for the enzyme aromatase which plays a key role in the aromatization in which the androgens get converted into estrogens[29]. This 30kb coding region and 93kb regulatory gene is located on the chromosome 15q21.2[30]. In the meantime, variations in this gene have the ability to fluctuate the levels of circulating hormones which allude to speculate that the polymorphisms such as rs10046, a T/C substitution at the 3' untranslated region of *CYP19A1* gene, are having an impact on breast cancer risk[31]. The exact function of this polymorphism is properly unknown, yet it has been claimed that this may lead to influence levels of mRNA and its stability[32], therefore it can be associated with altered levels of the aromatase enzyme and affected estrogen metabolism. This rs10046 polymorphism was examined extensively in different populations. A study conducted on Chinese and a meta-analysis conducted in 20,098 subjects from Spain revealed an association between rs10046 and breast cancer risk[33,34]. However, no significant association was found in the studies conducted on Saudi and USA populations[35][36]. There are no studies available with respect to the association with OC. Since the *CYP19A1* was found to be significantly associated with breast cancer risk by several studies. These inconsistent results in different populations in different studies may attribute to several risk factors and it is necessary to examine the association of those individual populations. In the present study, the heterozygous, dominant and T allele was found to be higher in OC cases compared to controls and it is significantly associated with OC risk. These results suggest that the rs10046 polymorphism may have an impact on the progression of ovarian cancer. However, the rs605059 polymorphism of the *HSD17B1* gene did not show a significant association with OC in any of the genetic models on the South Indian population.

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In the haplotype analysis, the haplotype distribution of the polymorphisms rs743572, rs10046 and rs605056 on OC had shown 8 different combinations of haplotypes in which 2 combinations (CCA and CTA) were found to be significantly higher in cases compared to controls, thus it reveals an association with OC risk. Furthermore, this is the first study to report the association of *CYP17A1* , *CYP19A1,* and*HSD17B1* haplotypes with OC.

Conclusion:

In conclusion, our data provided the evidence for an association between the rs743572, rs10046 polymorphisms of genes *CYP17A1* and*CYP19A1* and OC risk, while no association was found with rs605059 polymorphism of the *HSD17B1* gene.

Disclosure of Interests: The authors did not have any conflict of interest to declare. There are no financial, personal, political, intellectual or religious interests to disclose.

Contribution to Authorship: All authors (GGK, AMF, SFDP, CM, MM, UR, RR, NG) contributed to the design, participant recruitment, data collection, and conception in the present study. GGK, AMF was involved in the manuscript drafting and data analysis. GGK and CM were collected the data. All the other authors were involved in interpreting data and critically reviewing the manuscript. All the author has given the approval of the final version of the manuscript.

Details of Ethics Approval: The study was approved on 06.10.2017 by the ethics committee of Sri Ramachandra Institute of Higher Education and Research (Reference Number - IEC-NI/17/JUN/60/80).

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Data sharing and Data Accessibility: All the data that supports the findings of this study are included.

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