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Research Article

Assessment of VDR Gene Polymorphism (FokI) in Epithelial Ovarian Cancer

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ABSTRACT

Background: Epithelial ovarian cancer (EOC) has been associated with genetic variations in the vitamin D receptor (VDR) gene among women in different geographical locations. Due to inadequate detection methods, many cases are diagnosed at advanced stages. Vitamin D deficiency and the FokI gene polymorphism in the VDR gene are known to increase cancer risk. The current study aimed to evaluate the correlation between the VDR gene polymorphism (FokI) and epithelial ovarian cancer risk

Subjects and Methods: A prospective case-control study with 160 participants comprised 80 patients with epithelial ovarian cancer and 80 controls without the disease. FokI genotyping was observed using the PCR-RFLP technique, which allows for the precise identification of genetic variants in the VDR gene. Additionally, vitamin D levels were assessed through chemiluminescence immunoassay, providing quantitative data on vitamin D status.

Results: Serum vitamin D levels showed no clear association with ovarian cancer risk across tertiles ($p > 0.05$). Genetic analysis identified significant genotype distributions in cases versus controls, with the CC genotype associated with reduced risk (OR = 0.5238, 95% CI: 0.042 - 0.5238) and the CT genotype with increased risk (OR = 1.9091, 95% CI: 0.047 - 1.9091) of ovarian cancer.

Conclusions: Findings underscore the multifaceted nature of ovarian cancer etiology, suggesting that CT genotype in FOK1 gene increases the risk of ovarian cancer

Introduction

Ovarian cancer (OC) often remains undetected until it reaches advanced stages, primarily affecting the pelvis and abdomen, contributing to its high fatality rate. Epidemiological studies position OC as the sixth most prevalent cancer in women globally (1). Epithelial ovarian tumors dominate OC cases, with incidence rising significantly above age 30 (2). Ovarian cancer remains a significant public health concern both in India and globally. In India, ovarian cancer ranks as the third most common malignancy among women, following breast and cervical cancers. According to the Indian study, the age-standardized incidence rate (ASIR) of ovarian cancer in India is 4.61 per 100,000 women, with a crude incidence rate of 5.08 per 100,000. The age-standardized mortality rate (ASMR) is 2.02 per 100,000, contributing to 76.5% of ovarian cancer cases and 77.5% of deaths among South-Central Asian countries (3-4). Globally, approximately 313,959 new cases of ovarian cancer were recorded in 2020, with an estimated rise to 445,721 cases by 2040, reflecting a

42% increase (5). Additionally, ovarian cancer remains one of the leading causes of gynecologic cancer-related mortality worldwide, emphasizing the need for early detection and improved treatment strategies (6).

The role of Vitamin D and its receptor (VDR) gene polymorphisms in cancer susceptibility has garnered significant attention, particularly concerning epithelial ovarian cancer (EOC). Recent studies suggest that VDR gene polymorphisms may influence cancer risk and progression through their effects on cellular growth and immune responses. The FokI polymorphism in the VDR gene, known to impact receptor function and vitamin D signaling, has been associated with various malignancies, including ovarian cancer. Moreover, VDR variants are risk factors for ovarian cancer, underscoring the relevance of genetic variations in VDR in modulating cancer susceptibility (7).

Additionally, the role of vitamin D in ovarian cancer has been explored as a comprehensive review of its molecular mechanisms and epidemiological evidence (8). In the context of gynecological cancers, recent findings suggest that the FokI polymorphism could be a significant factor in the development of EOC (9-10). The FokI polymorphism, in particular, has been linked to variations in receptor activity and vitamin D metabolism, potentially affecting cancer development (11).

Epithelial OC is the most common histological type (12) and is linked closely with breast cancer in global morbidity and mortality (13). Geographical studies indicate lower OC rates closer to the equator, suggesting a correlation between sunlight exposure and vitamin D levels in disease prevention (14). The current case-control study aimed to investigate the association of VDR gene polymorphism (Fok1) with epithelial ovarian cancer risk using PCR-RFLP and to evaluate the serum vitamin D levels among the study participants in both the groups.

Subjects and Methods

The study involved 160 participants in a case-control format, comprising 80 patients with epithelial ovarian cancer (cases) and 80 healthy controls matched for age, menopausal status, and blood draw month. Cases were aged 20-80 years with epithelial ovarian cancer, excluding non-epithelial types, chromosomal anomalies, and vitamin D disorders. Controls were healthy women aged 20-80 without malignancies, excluding unwilling participants. The current study was a prospective case-control study. The study included 160 participants: 80 patients with EOC (cases) and 80 without EOC (controls). The study was conducted from Jan 2021 to May 2022 in the Department of Obstetrics and Gynecology, SUM Ultimate, and Molecular Diagnostic and Research Center, IMS and SUM Hospital, Bhubaneswar, India. The study proposal and protocol were approved by the Institutional Ethics Committee, IMS and SUM Hospital Bhubaneswar.

Serum Vitamin-D Estimation

Serum vitamin D levels were assessed via Electrochemiluminescence immunoassay (ECLIA) Catalog number 07464215190, measuring changes in electrochemiluminescence signals post antigen-antibody immunoreaction.

DNA Isolation

Genomic DNA was extracted from 2 ml of peripheral blood collected after diagnosis. The DNA extraction process was carried out using the salting-out method (15). Red blood cell lysis, protein precipitation, and DNA precipitation with isopropanol were performed. DNA was washed with ethanol, air-dried, and rehydrated in TE buffer overnight for quantification.

DNA Quantification

DNA concentration was determined using a Bio-Spectrophotometer from Thermo Fisher Scientific, measuring absorbance at A260nm and A280nm to calculate DNA concentration (µg/µl) and assess purity (A260/280 ratio).

PCR Protocol for Fok I Gene Polymorphism

PCR reactions were set up using Ampli Taq Gold 360 Master Mix with Sequence-specific primers and template DNA. The standard three-step PCR profile, i.e., denaturation, annealing, and extension, was followed.

Agarose Gel Electrophoresis

Prepare agarose gel. For a 2% agarose gel containing 2g agarose in an Erlenmeyer flask add 100 ml 1X TAE buffer based on the current primer size (265bp). Therefore, before RFLP digestion, electrophoresis is performed on a 2% agarose gel to confirm successful PCR amplification of the target 265 bp fragment. The PCR product is loaded alongside a 100 bp DNA ladder and runs at 80-100V for ~30-45 minutes in 1X TBE/TAE buffer. A single, clear 265 bp band under UV transillumination confirms successful amplification, ensuring the sample is ready for Fok I enzyme digestion. After digestion, a 3.5% agarose gel containing is used to separate the restriction fragments for genotype identification.

Handling and Safety Protocols

Precautions were taken in handling hazardous materials such as ethidium bromide during gel electrophoresis. Safety measures included the use of gloves and proper disposal of contaminated materials.

PCR-RFLP Procedure

The RFLP method is used to detect the Fok I gene mutation by amplifying a 265 bp fragment of the VDR gene through PCR, followed by digestion with the Fok I restriction enzyme at 37ºC for 4 hours. For Fok I RFLP digestion, a master mix is prepared using Fok I restriction buffer (10X) (9 µL), Fok I restriction enzyme (20 U) (6 µL), and molecular-grade water (15 µL) for six reactions. Each reaction contains 10 µL of PCR product, and 5 µL of the prepared master mix is added to each tube. The samples are incubated at 37°C for 2-4 hours, followed by electrophoresis on a 3.5% agarose gel to analyze digestion patterns.

Genotype Analysis

Genotyping for the FokI SNP in the VDR gene was conducted blindly to the case/control status. PCR products were digested with FokI enzyme, and fragments were visualized in Bio-Rad Gel Doc™ EZ Imaging System via agarose gel electrophoresis to determine genotype. The RFLP is used to detect the Fok I gene mutation by amplifying a 265 bp fragment of the VDR gene through PCR, followed by digestion with the Fok I restriction enzyme. The digested DNA fragments are then separated on a 3.5% agarose gel using electrophoresis to distinguish different genotypes based on band

patterns: CC (265 bp), CT (265 bp, 196 bp, 69 bp), and TT (196 bp, 69 bp). This technique provides a reliable way to analyze genetic polymorphisms associated with Vitamin D receptor variations.

Statistical analysis

The statistical analysis was performed using the Chi-square test to evaluate differences in categorical variables between the two groups. The odds ratio (OR) was calculated to measure the strength of the association between exposure and epithelial ovarian cancer, indicating how the odds of exposure differ between cases and controls. The *p*-value was used to determine the statistical significance of the Chi-square test results and the odds ratio, with a value less than 0.05 typically signifying that the observed associations are unlikely to be due to chance

Results

The current study findings reveal the distribution of age ranges among cases and controls in the investigation of ovarian cancer. Among the 80 cases studied, the age distribution was as follows: 5% were under 30 years old, 20% were aged 31-40 years, 50% were aged 41-50 years, 10% were aged 51-60 years, 10% were aged 61-70 years, and 5% were over 70 years old. In comparison, among the 80 controls, the age distribution showed 10% under 30 years old, 35% aged 31-40 years, 45% aged 41-50 years, 10% aged 51-60 years. These findings underscore the differences in age distribution between ovarian cancer cases and controls, highlighting a notable concentration of cases in the 41-50 age range compared to controls. However, a notable difference was observed in the 61-70 age range, where 10% of cases and none of the controls fell, yielding a *p*-value of 0.004, indicating a statistically significant difference. Finally, for individuals under 90, the proportion was 10% in the case group and none in the control group, with a *p*-value of 0.046, suggesting a significant difference at the 0.05 level.

Table 1: Demographic characteristics of both case and control group

Age range	Case, N=80 (%)	Control N=80(%)	p-value
<30	4(5%)	8(10%)	0.25
31-40	16(20%)	28(35%)	0.07
41-50	40(50)	36(45%)	0.65
51-60	8(10%)	8(10%)	1.0
61-70	8(10%)	0	0.004
<90	4(10%)	0	0.046
Pre-menopausal	29(36%)	30(37%)	<0.001
Post-menopausal	51(64%)	50(63%)	<0.001
Family history of ovarian cancer	6(7%)	2(2%)	< 0.001
Parity			
Nulliparous	7(9%)	5(6%)	< 0.001
1	6(7%)	4(5%)	< 0.001
2-3	45(56%)	48(60%)	≈ 0.012
≥	22(28%)	23(29%)	<0.001
History of oral contraceptive	6(7%)	8(10%)	<0.001
Tubal ligation	22(28%)	10(8%)	< 0.001

The characteristics of epithelial ovarian cancer cases compared to controls were analyzed (Table 1). Among the 80 ovarian cancer cases, 36% were pre-menopausal and 64% were post-menopausal, significantly differing from controls (37% pre-menopausal, 63% post-menopausal; $p < 0.001$). A family history of ovarian cancer was more prevalent in cases (7%) than controls (2%; $p < 0.001$). Parity analysis showed that nulliparous women constituted 9% of cases versus 6% of controls ($p < 0.001$), while those with 2-3 children were 56% of cases compared to 60% of controls ($p \approx 0.012$). Additionally, history of oral contraceptive use was lower in cases (7%) compared to controls (10%; $p < 0.001$), and tubal ligation was more frequent among cases (28%) than controls (8%; $p < 0.001$) (Table 1). These findings highlight significant associations between these factors and the incidence of epithelial ovarian cancer. It was observed significant differences between the top and bottom tertiles of vitamin D concentrations. Among ovarian cancer patients, those in the top tertile (median 38 ng/ml, range 28-52 ng/ml) had a prevalence of 40%, compared to 51% in controls (OR = 0.5204, 95% CI: 0.5204 - 1.9215). Conversely, in the bottom tertile (median 13.5 ng/ml, range 6-17.3 ng/ml), 37% of patients had ovarian cancer compared to 25% of controls (OR = 0.5200, 95% CI: 0.5200 - 1.9224) (Table 2). These findings suggest a potential inverse association between higher vitamin D levels and ovarian cancer risk, although the confidence intervals indicate a need for further investigation to confirm these trends.

Table 2: Odds ratio (OR) and 95% CI for ovarian cancer according to Vit D levels

Median range of serum vitamin D levels in ng/ml	Ovarian cancer patients	control	OR (95% CI)
Top tertile 38 (28-52)	32(40%)	41(51%)	0.5204 (0.5204 - 1.9215)
Botton tertile 13.5 (6-17.3)	30(37%)	20(25%)	CI: 0.5200 - 1.9224)

The results from Table 3 depict the risk ratios associated with gene polymorphism in the study of ovarian cancer. Among the 80 cases analyzed, 55% exhibited the CC genotype, while among the 80 controls, 70% had this genotype. The difference in genotype distribution was statistically significant ($p = 0.042$), with an odds ratio (OR) of 0.5238 (95% CI: 0.042 - 0.5238), indicating a lower likelihood of ovarian cancer associated with the CC genotype compared to controls. For the CT genotype, 45% of cases and 30% of controls were observed, with a significant association ($p = 0.047$) and an OR of 1.9091 (95% CI: 0.047 - 1.9091), suggesting an increased risk of ovarian cancer associated with this genotype. Notably, no individuals with the TT genotype were found among either cases or controls. These findings underscore the potential role of genetic polymorphism, specifically the CC and CT genotypes, in influencing susceptibility to ovarian cancer in the studied population.

Table3: Risk ratio of gene polymorphism

Gene Poly	Groups Cases, N=80	Control, N=80	Total	P value	Odds Ratio at 95% confidential interval	Finding
CC	44(55%)	56(70%)	100 (62%)	0.042	0.5238(0.042 −0.5238)	Protective factor i.e., lowers the risk
CT	36(45.0%)	24(30%)	60 (37.5)	0.047	1.9091(0.047 −1.9091)	Risk factor i.e., increases the risk
TT	0	0				No detection

N: No valid cases; CC: homologous mutation; CT: Heterologous mutation

Discussion

Vitamin D plays a crucial role in calcium homeostasis and bone metabolism, but emerging research has expanded its significance to various diseases, including cancer. This interest is particularly relevant in the context of ovarian cancer, which involves a complex interplay of genetic and environmental factors, including hormonal imbalances and incessant ovulation. Recent studies have underscored the potential role of Vitamin D and its receptor (VDR) gene polymorphisms in cancer risk. For instance, the study conducted in a meta-analysis indicating that VDR variants, such as FokI, are significant risk factors for ovarian cancer, emphasizing the need for further exploration of these genetic influences (3). Moreover, another study reviewed the epidemiological and molecular mechanisms linking Vitamin D to ovarian cancer, suggesting that vitamin D's regulatory effects on cellular processes could impact cancer susceptibility (16). Similarly, the Vitamin D affects ovarian cancer at a molecular level revealed by another comprehensive review (8). The association between VDR polymorphisms, such as FokI, and cancer risk is further supported by evidence who highlighted the role of this polymorphism in various cancers, including ovarian cancer (11). This case-control study aims to assess the VDR FokI gene polymorphism in epithelial ovarian cancer to better understand its potential role in cancer susceptibility and to contribute to personalized medical strategies in oncology.

The study findings regarding the characteristics of epithelial ovarian cancer cases compared to controls reveal several significant associations, shedding light on potential risk factors for this malignancy. Firstly, the distribution of menopausal status differed significantly between cases and controls, with 36% of ovarian cancer cases being pre-menopausal compared to 37% in controls, and 64% post-menopausal cases versus 63% in controls ($p < 0.001$). This highlights a potential role of hormonal changes in ovarian cancer pathogenesis, aligning with existing literature suggesting that prolonged exposure to endogenous estrogen due to incessant ovulation may increase cancer risk (9). Moreover, a familial history of ovarian cancer was more prevalent among cases (7%) compared to controls (2%) ($p < 0.001$), emphasizing the importance of genetic predisposition in certain cases of ovarian cancer (3-4). Parity analysis revealed that nulliparous women constituted a higher percentage of cases (9%) compared to controls (6%) ($p < 0.001$), which is consistent with the protective effect of parity against ovarian cancer observed in previous studies (17-18). Conversely, women with 2-3 children were more represented among controls (60%) than cases (56%) ($p \approx 0.012$), suggesting a potential protective effect of higher parity. Regarding contraceptive use, a lower proportion of cases reported a history of oral contraceptive use (7%) compared to controls (10%) ($p < 0.001$). Oral contraceptives have been shown to reduce the risk of ovarian cancer by suppressing ovulation, supporting the findings of this study (19). Tubal ligation, a procedure associated with reduced ovarian cancer risk due to interrupted fallopian tube transport of potentially carcinogenic material, was significantly more frequent among cases (28%) than controls (8%) ($p < 0.001$) (9,20).

These results underscore the multifaceted nature of ovarian cancer etiology, influenced by hormonal, genetic, and reproductive factors. The significant associations observed between these factors and ovarian cancer incidence in this study is consistent with previous research, highlighting the complex interplay of genetics, lifestyle, and reproductive health in ovarian cancer development.

As it is known that, sunlight exposure, a key determinant of vitamin D synthesis in the skin, has been linked to lower cancer rates in populations with higher sun exposure (21). However, studies specifically exploring the relationship between vitamin D receptor (VDR) gene polymorphisms, such as FokI, and ovarian cancer risk are relatively scarce (22). These investigations underscore the complex interplay between genetic predisposition and environmental factors in cancer development. In regions like India, where vitamin D deficiency is prevalent due to lifestyle factors such as limited sunlight exposure, cultural practices influencing dairy product intake, and dietary habits, understanding these dynamics becomes crucial. The findings of the current study reveal a statistically significant difference in mean serum vitamin D levels between ovarian cancer cases (15.019 ng/ml) and controls (22.78 ng/ml), highlighting a potential protective role of adequate vitamin D levels against ovarian cancer. The association between gene polymorphism and ovarian cancer risk, particularly focusing on the distribution of VDR (Vitamin D receptor) genotypes (CC and CT) among cases and controls. Firstly, among the 80 ovarian cancer cases analyzed, 55% exhibited the CC genotype of the VDR gene, while among the 80 controls, 70% had this genotype. This observed difference in genotype distribution was found to be statistically significant with a p-value of 0.042. The odds ratio (OR) of 0.5238 (95% CI: 0.042 - 0.5238) suggests a protective effect associated with the CC genotype, indicating a lower likelihood of developing ovarian cancer compared to controls. This finding aligns with previous studies that have suggested a potential protective role of certain VDR genotypes, such as CC, against various cancers, including ovarian cancer (21-22). Conversely, for the CT genotype, 45% of cases and 30% of controls were observed, with a statistically significant association ($p = 0.047$). The OR of 1.9091 (95% CI: 0.047 - 1.9091) indicates an increased risk of ovarian cancer associated with the CT genotype. This finding suggests that individuals carrying the CT genotype may have an elevated susceptibility to ovarian cancer compared to those with the CC genotype. Such associations between specific VDR genotypes and cancer risk have been explored in various populations, highlighting the potential biological implications of these genetic variations (23-24).

Importantly, the absence of individuals with the TT genotype among both cases and controls in this study is noteworthy. The lack of TT genotype carriers may reflect population-specific genetic characteristics or the relatively small sample size, warranting further investigation in larger cohorts or diverse populations to fully elucidate the role of this genotype in ovarian cancer susceptibility.

Limitations of the study

Despite providing valuable insights into the association between VDR (Vitamin D receptor) gene polymorphism and ovarian cancer risk, this study is not without limitations, which need to be acknowledged to contextualize its findings appropriately on Sample Size and Generalizability, Selection Bias and Confounding Factors could have included in the current study.

Conclusion

In conclusion, these findings provide valuable insights into the genetic underpinnings of ovarian cancer risk associated with VDR gene polymorphism. The protective effect associated with the CC genotype and the increased risk linked to the CT genotype highlight the potential relevance of genetic screening in clinical settings for risk assessment and personalized interventions. Future research should explore the functional implications of these genotypes, their interaction with environmental factors, and their impact on cancer biology to advance our understanding of ovarian cancer etiology and improve strategies for prevention, early detection, and treatment. This study contributes to the growing body of evidence supporting the role of VDR gene polymorphism in ovarian cancer susceptibility, emphasizing the need for further exploration and validation in larger, more diverse cohorts to elucidate these genetic associations comprehensively.

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Conflict of Interest

No conflict of interest to be declared

Data availability

Data research data are accessible on reasonable inquiry

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