CCL11 rs16969415 and CCR3 rs4987053 gene variants and endometrial cancer risk

CCL11 rs16969415 ve CCR3 rs4987053 gen varyantları ve endometrium kanseri riski

Abstract

Aim: Endometrial cancer is the sixth most frequent malignancy in women worldwide. Chemokines are tiny cytokines that are produced to enable different cell types to migrate in different directions. They are crucial for a number of physiological functions, including immunological responses, wound healing, and the development of cancer. Our study aimed to determine the association between CCL11 rs16969415 and CCR3 gene rs4987053 variants and the risk of endometrial cancer.

Methods: Ninety healthy controls and ninety endometrial cancer patients participated in this case-control research. Blood samples were used to obtain genomic DNA, and the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) method was used to determine genotypes.

Results: The CCL11 gene rs16969415 and the CCR3 gene rs4987053 genotype distributions and allele frequencies were found to differ substantially between the patient and control groups (respectively $p<0.001$, $p<0.05$).

Conclusions: As a conclusion, the CCL11 rs16969415 and CCR3 rs4987053 variations were determined to be closely associated with endometrial cancer risk.

Keywords: Chemokine; cytokines; endometrial cancer

Öz

Amaç: Endometrium kanseri dünya çapında kadınlarda en sık görülen altıncı malignitedir. Kemokinler, hücrelerin farklı yönlere göç etmesine neden olmak için üretilen küçük sitokinlerdir. İmmünolojik tepkiler, yara iyileşmesi ve kanser gelişimi gibi fizyolojik işlevler için çok önemlidirler. Çalışmamızın amacı CCL11 rs16969415 ve CCR3 geni rs4987053 varyantları ile endometrial kanser riski arasındaki ilişkiyi belirlemektir.

Yöntemler: Bu vaka-kontrol araştırmasına doksan sağlıklı kontrol ve doksan endometrial kanser hastası katılmıştır. Genomik DNA elde etmek için kan örnekleri kullanılmış ve genotipleri belirlemek için Polimeraz Zincir Reaksiyonu-Restriksiyon Fragment Uzunluk Polimorfizmi (PCR-RFLP) yöntemi kullanılmıştır.

Bulgular: CCL11 geni rs16969415 ve CCR3 geni rs4987053 genotip dağılımları ve alel frekanslarının hasta ve kontrol grupları arasında önemli ölçüde farklılık gösterdiği bulunmuştur (sırasıyla $p<0,001$, $p<0,05$).

Sonuç: Sonuç olarak CCL11 rs16969415 ve CCR3 rs4987053 varyasyonlarının endometrium kanseri riski ile yakın ilişkili olduğu belirlendi.

Anahtar Sözcükler: Endometrium kanseri; kemokin; sitokinler

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INTRODUCTION

The sixth most prevalent malignancy in women is endometrial cancer (1, 2). Its incidence and mortality are increasing and are expected to continue with the increasing prevalence of endometrial cancer risk factors (3). The usual age of diagnosis for endometrial cancer in women is 61 years old, and the risk is roughly 3% (4). More than 90% of uterine cancers are adenocarcinomas. The main risk factors for endometrial adenocarcinoma are excess exogenous and endogenous estrogen (5).

Having a first-degree relative with endometrial cancer doubles a woman's risk of developing the disease, even in the absence of a specific genetic variant, and a significant portion of this familial risk can be explained by common single nucleotide polymorphisms (6, 7).

Chemokines are chemotactic cytokines that control immune cell movement and act as indicators to draw immune cells into tissues. Their interactions with the extracellular matrix (ECM) are particularly important in controlling the directed migration(chemotaxis) of cells (8). They are crucial to many physiological processes, including the development of cancer, immunological responses, and wound healing (9). Chemokines are key players in controlling immune cell migration, which is necessary for the development of an efficient antitumor immune response. However, they also have an impact on the development and attraction of immune cells that support the emergence of a pro-tumorigenic environment (10).

Immune cells, tissue-resident cells, and cancer cells that express a diverse range of chemokine ligands and receptors all influence the process of carcinogenesis. In tumor cells, chemokines control stem cell-like characteristics, proliferation, and invasiveness; on stromal cells, they control neurogenesis, neoangiogenesis, and fibrogenesis (10).

In chemokines, ligands with C-C motifs are called CCL. The CCL chemokine family includes *CCL5, CCL24, CCL26*, and *CCL11*. The human Eotaxin (*CCL11*) gene contains three exons, spanning approximately 8 kb and is located on chromosome 17q21. The rs16969415 Single Nucleotide Polymorphism (SNP) is located in the promoter region of the *CCL11* gene at position -426, where a C/T exchange occurs between the pyrimidic bases (11, 12). *CCL11* rs16969415 variant is upstream transcript variant/regulatory region variant.

CCR3 is a receptor for several chemokines, including *MCP-2, RANTES*, and eotaxin (*CCL11*), and is expressed predominantly on basophils, eosinophils, and T helper 2 (Th2) lymphocytes.

The gene encoding the chemokine receptor *CCR3* is located on chromosome 3p21.3. The rs4987053 polymorphism is a synonymous SNP located in exon 3 and amino acid position 17 (Y17Y) of the *CCR3* gene (13).

In line with the information given, the purpose of our investigation was to determine the association between endometrial risk and the genetic variations *CCL11* rs16969415 and *CCR3* rs4987053.

MATERIAL AND METHODS

Study population

Ninety-nine healthy controls and ninety patients with endometrial cancer who applied to the Department of Gynecology at the Eskişehir Osmangazi University, Faculty of Medicine in Eskişehir, Turkey, were included in this case-control research. All patients and control people provided informed consent in accordance with our protocol, which has been validated This study was approved by the Non-Interventional Clinical Research Ethics Committee of Eskişehir Osmangazi University (date: 20.06.2023, decision no: 2023/13). We implemented the study in accordance with the Helsinki Declaration's ethical guidelines. The patient and control groups were homogeneous Turkish population as ethnicity.

Inclusion criteria

Inclusion criteria for selecting individuals with endometrial cancer: 30-75 years old women, diagnosed with endometrial cancer, individuals who accept to volunteer in the study with their own consent will be included.

Inclusion criteria for control individuals; 30-75 years old women, individuals who do not have another chronic disease and who accept to volunteer in the study with their own consent will be included.

Since endometrial cancer is a pathology seen only in women, the control group consists of only female individuals in the controls in order to match in terms of gender.

Exclusion criteria

Individuals without endometrial cancer for the patient group and individuals with another chronic disease for the control group will not be included in the study. Individuals with previous treatment and surgery for patient group were not included in the study. In addition, pediatric populations and individuals who do not consent to participate in the study will not be included in the study.

DNA isolation and quantification

Following the kit's instructions, genomic DNA isolation kit (New England Biolabs) was carried out from drawn blood samples using the Monarch® Genomic DNA Purification Kit (New England Biolabs). Briefly, 10 µl of Proteinase K, 3 µl of RNase A, and 100 µl of Blood Lysis Buffer were added to 100 µl of whole blood. Incubation was carried out at 56°C for 5 min. 400 µl of gDNA Binding Buffer was added to the sample. The lysate/binding buffer mixture was transferred to the gDNA Purification Column and centrifuged (1,000 x g for 3 min followed by 12,000 x g for 1 min). The flow-through was discarded. The column was transferred to a new collection tube, and 500 µl of gDNA Wash Buffer was added. It was immediately centrifuged at maximum speed (>12,000 x g) for 1 min, and the flow-through was decanted. The column was placed back into the collection tube. Add 500 µl of gDNA Wash Buffer, capped and centrifuged for 1 min at maximum speed (>12,000 x g), then discard the collection tube. Place the gDNA Purification Column in a DNase-free 1.5 ml microcentrifuge tube. Add 50 µl of pre-warmed gDNA Elution Buffer, capped and incubated for 1 min at room temperature. Centrifuge for 1 min at maximum speed (>12,000 x g) to elute the gDNA.

Using a NanoDrop (Allsheng, Nano300, Micro-spectrophotometer) spectrophotometer, the quantity and purity of DNA samples were assessed. In order to perform genotype analyses, a large amount of PCR amplicon is needed. For this, the template genomic DNA must be of high purity. Therefore, the ratio of absorbance values measured by the NanoDrop at 260 and 280 nm wavelengths (A260/A280) was required to be between 1.7 and 2.0. Ratio values in this range indicate the lowest protein contamination. After the measurement, the samples were diluted with elution solution so that the DNA stock concentration would be 50 ng/µL.

Genotyping

The *CCL11* rs16969415 and *CCR3* rs4987053 variants were analyzed by PCR-RFLP. The sequence of primers utilized in the amplification of all of the variants is shown in table (Table 1).

The PCR reactions were performed following the protocol, and all amplification reactions were performed on a thermal Cycler (Thermo Scientific, VeritiPro Thermal Cycler). The PCR mix was equipped in a total reaction volume of 20 µl, consisting of 4 µl master mix (Solis Biodyne, FIREPol Master Mix Ready to Load, 12.5 mM $MgCl_2$), 0,5 µl Reverse and 0,5 µl Forward primer, 14 µl distilled water, and 1 µl genomic DNA. The amplification protocol included initial denaturation at 95°C for the 3 minute, followed by 30 cycles of denaturation at 95°C for 30 seconds, annealing at the 54-66°C for 30 seconds and an extension at 72°C for a further 60 seconds with a final extension 72°C for 5 minutes, cooling to 4 °C for all variants. Annealing temperatures were 55.5°C for *CCL11* rs16969415 and 54.8°C for *CCR3* rs4987053.

Amplification products were digested with appropriate restriction endonucleases (*Taq*$^{\alpha}$*I for CCL11* rs16969415 variants*, NlaIII* for *CCR3* rs4987053 variant*)* and analyzed using 3% agarose gel electrophoresis (Invitrogen, UltraPure™ Agarose, Carlsbad CA, 10X TBE Buffer, ABT). The yields were viewed using a (Bio-Rad, ChemiDoc MP Imaging System) and electrophoresis on a 3 percent agarose gel stained with RedSafeTM nucleic acid staining solution (Intron Biotechnology Inc., Seoul, Korea) (Figure 1).

Statistical analysis

The percentage of categorical data was calculated (percent). The examination of the constructed cross tables included Pearson Chi-Square analyses. The analysis was conducted using Statistical Package for the Social Sciences software for Windows, version 27.0 (SPSS

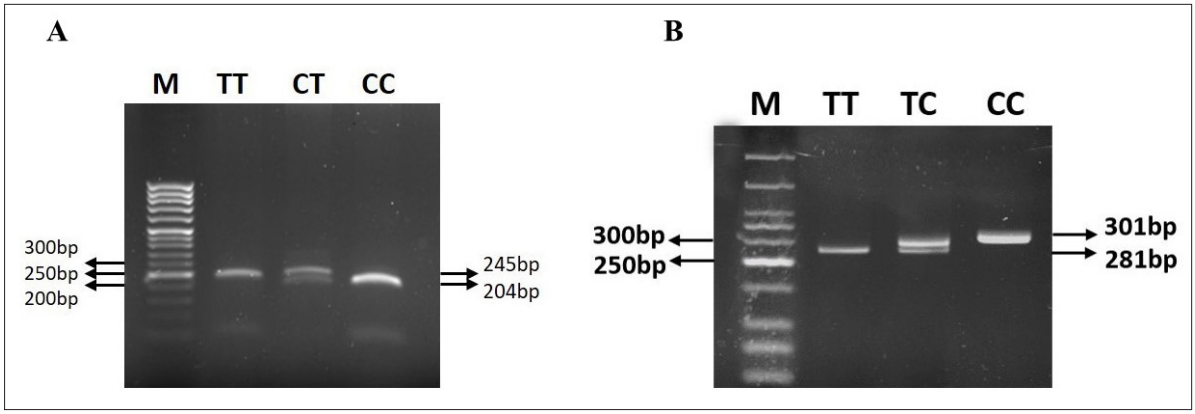

Figure 1. A. RFLP-PCR product gel electrophoresis on 3% agarose gel to identify the genotypes of *CCL11* rs16969415 (*Taq*$^{\alpha}$*I*). CC: 204 + 41 bp, CT: 245 + 204 + 41 bp, TT: 245 bp, M: marker. **B.** RFLP-PCR product gel electrophoresis on 3% agarose gel to identify the *CCR3* rs4987053 genotypes (*NlaIII*). CC: 301 bp, TT: 281 + 20 bp, TC: 301 + 281 + 20 bp, M: marker. (The 20 bp fragment is not visible on the 3% agarose gel).

Inc., Chicago, IL, USA) p values of less than 0.05 were considered substantial in all of the analyzes. To determine whether the observed genotype frequencies were consistent with the Hardy-Weinberg equilibrium, the formulation created by Michael H. Court (2005-2008) was used in the Excel program. Odds ratios (OR) and their 95% confidence intervals (95%CI) were calculated with the online medcalc program (https://www.medcalc.org/calc/odds_ratio.php).

Power analysis was performed to determine the sample to be included in the study. Confidence intervals for the examined gene were selected as 0.15, 0.16, 0.17, 0.18, 0.19 and 0.20, and the number of patients was found to be between 86-94 individuals. When calculated based on these measurements, 80% power was obtained for 90 individuals in the group and 180 individuals in total. Statistical power was calculated using the PASS11 package.

RESULTS

The primary outputs of our study are the determination of genotypes of the variants examined for each individual based on imaging results. Alleles are determined based on genotype data, and with these data, allele and genotype distributions are obtained in patient and control individuals. As a result of statistical analyses, the relationship between these alleles and genotypes and disease risk is determined. These data are also secondary outputs of our study.

Genotype findings

rs16969415 variant of CCL11 gene

An analysis of the *CCL11* rs16969415 variant genotype frequencies revealed a statistically significant distinction between the endometrial cancer and control groups ($p<0.001$). Furthermore, a significant variation in allele frequencies was found between the endometrial cancer and control groups ($p<0.001$) (Table 2).

A statistically significant difference was determined between the endometrial cancer and control groups in the genotype distributions in the homozygous and recessive models ($p<0.001$) (Table 2).

rs4987053 variant of CCR3 gene

Following an investigation of the genotype frequencies and allele frequencies of the *CCR3* rs4987053 variant, a difference of statistical significance was found between the endometrial cancer and control groups ($p<0.05$) (Table 2).

It was found that a statistically significant difference between the endometrial cancer and control groups in the genotype distributions in the homozygous, heterozygous, and dominant models ($p<0.05$) (Table 2).

DISCUSSION

The development of multiple chronic inflammatory illnesses, such as asthma, rhinitis, sinusitis, nasal pol-

Table 1. Forward and reverse primer pairs designed for PCR.

Gene	SNP	Forward (5'-3') primer sequence	Reverse (5'-3') primer sequence
CCL11	rs16969415	GACCACCATGTGAACACAGG	GCTAGTAGGAGGGACTTGGT
CCR3	rs4987053	CTTTGGTACCACATCCTACCA	TGAGAGGAGCTTACACATGC

SNP: Single Nucleotide Polymorphism

Table 2. Genotype and allele frequencies of *CCL11* rs16969415, *CCR3* rs4987053 polymorphisms in the endometrial Cancer and Control group.

SNP rs16969415	**Allele**		Statistic P	OR (95 % CI)	**Genotype**			Statistic P	HWE
	C n(%)	**T** n(%)			**CC**	**CT**	**TT**		
Control	143 (79.4)	37 (20.6)	**<0.001**	0.231 (0.145-0.368)	53	37	0	**<0.001**	**0.014**
Endometrial Cancer	85 (47.2)	95 (52.8)			0	85	5		**0.000**

OR (95 % CI) (Risk allele T)			
Heterozygous TT vs CT	Homozygous TT vs CC	Dominant TT vs CC+CT	Recessive CT +TT vs CC
0.207 (0.011-3.844) p=0.290	0.000 (0.000-0.047) **p<0.001**	0.085 (0.004-1.576) p=0.098	0.003 (0.000-0.064) **p<0.001**

SNP rs4987053	**Allele**		Statistic P	OR (95 % CI)	**Genotype**			Statistic P	HWE
	T n(%)	**C** n(%)			**TT**	**TC**	**CC**		
Control	154 (85.6)	26 (14.4)	0.016	0.521 (0.305-0.892)	65	24	1	**0.003**	0.454
Endometrial Cancer	136 (75.6)	44 (24.4)			59	18	13		0.000

OR (95 % CI) (Risk allele C)			
Heterozygous CC vs TC	Homozygous CC vs TT	Dominant CC vs TC+TT	Recessive CC+TC vs TT
0.057 (0.006-0.482) p=**0.008**	0.069 (0.008-0.550) p=**0.011**	0.066 (0.008-0.520) p =**0.009**	0.732 (0.388-1.379) p=0.334

SNP: Single Nucleotide Polymorphism

CI: Confidence interval, OR: Odds ratio, HWE: Hardy-Weinberg equilibrium

p<0.05 values were considered statistically significant.

yposis, ulcerative colitis, and various gastrointestinal disorders, has been linked to *CCL11*. Also, overexpression of *CCL11* has been associated with coronary artery disease and inflammatory bowel syndrome. Furthermore, numerous facets (including cell migration, cell proliferation, angiogenesis, and survival) of the development of ovarian tumors have been linked to *CCL11* (14).

As a result of the literature review, no study was found associating endometrial cancer with *CCL11* gene rs16969415 polymorphism. Variants of the *CCL11* gene has been found to be frequently associated with pulmonary diseases such as asthma and respiratory complications in the literature (12, 15). It is believed that immunological alterations and deregulation of the inflammatory response are crucial to the pathophysiology of schizophrenia. Since it has been suggested that chemokines are involved in brain development, chemokines and schizophrenia have been studied extensively. Research has revealed a connection between *CCL11* and neurogenesis as well as synaptic plasticity. Furthermore, it has been noted that individuals with schizophrenia have changed *CCL11* levels (11).

In the study where 4 promoter SNPs of *CCL11* (rs17809012, rs16969415, rs4795896 and rs17735961) were linked with schizophrenia, the genotype frequency of *CCL11* rs4795896 showed a significant association with schizophrenia in the recessive model and the log-additive model. The allele frequency of rs4795896

also found a substantial association with schizophrenia. In both the dominant model and the log-additive model, the genotype distributions of rs16969415 demonstrated a substantial difference between individuals with schizophrenia and those without persecutory delusions. Furthermore, an examination of allele frequency found a noteworthy correlation between auditory hallucinations and rs16969415. In both the dominant model and the log-additive model, the genotype distribution of rs16969415 was linked to symptoms of auditory hallucinations and concentration impairment. When combined, these findings imply that in schizophrenia patients, *CCL11* rs16969415 is linked to auditory hallucinations, attention problems, and persecutory delusions (11).

Chemokines have been linked to the pathophysiology of glucose intolerance, type 2 diabetes, and obesity, as well as the development of chronic inflammation in adipose tissue, according to recent studies. Furthermore, across several ethnic groups, it has been discovered that some SNPs in chemokine genes are linked to obesity, insulin resistance, type 2 diabetes, and complications from diabetes. The rs16969415 SNP in *CCL11* was linked to type 2 diabetes's age of onset, duration, and HbA1c levels in a case-control study that examined the relationship between SNPs in chemokine genes and the disease. These findings imply that type 2 diabetes and obesity are linked to variations in the chemokine gene (16).

Another study conducted in 2025 evaluated the relationship between inflammatory gene variants and prostate cancer. As a result of the study, it was determined that the genotype distributions and allele frequencies of the CCR3 gene rs4987053 and COX-2 gene rs689466 variants differed significantly between the groups. In addition, a significant difference was found in the genotype distributions of the NOD1 gene rs5743336 variant between the non-cancerous and prostate cancer groups. However, no significant relationship was determined between the rs16969415, rs1801157, rs2228014, rs2066847, rs4986791 variants and prostate cancer risk (17).

In our study, a substantial association was determined between the *CCL11* gene rs16969415 variant and the risk of endometrial cancer. There is a statistically substantial difference between the endometrial cancer and control groups in terms of both genotype and allele frequencies. The T allele for the *CCL11* rs16969415 polymorphism appears to be a risk factor for endometrial cancer.

There are several studies examining the relationship between the *CCR3* rs4987053 variant and inflammatory diseases. There is a study investigating the relationship between *CCR3* gene polymorphisms and diseases such as asthma and Kawasaki disease (13, 17). Additionally, the *CCR3* rs4987053 polymorphism has been identified to be associated with poorer survival among women with serous ovarian cancer (18). As stated in these studies, there are studies that associate the *CCR3* rs4987053 polymorphism with various diseases and ovarian cancer. However, our study is the first to examine the relationship between endometrial cancer and the *CCR3* rs4987053 polymorphism.

There have been reports of elevated proinflammatory cytokine and chemokine levels in Kawasaki disease (KD). The control of cytokines and chemokines may be impacted by genetic variation in these genes and their receptors. In the *CCR5-CCR2-CCR3* gene cluster, four of the eight SNPs under investigation revealed a strong correlation with KD vulnerability. Within the *CCR5-CCR2-CCR3* gene cluster, two haplotypes seem to be linked with an increased risk of KD, while one haplotype appears to be protective (18).

The study conducted at the Mayo Clinic between 1999 and 2006 analyzed germline DNA SNPs in invasive epithelial ovarian cancer patients. The results showed borderline significance in the inflammatory pathway, and SNPs in *CCR3, IL1B, IL18, CCL2*, and *ALOX5*, which were associated with survival, were identified as contributing to disease risk. The comprehensive review provided evidence that hereditary differences may play a role in ovarian cancer patients, particularly genes involved in angiogenesis and inflammation pathways (19).

In our study, a substantial relationship was revealed between the *CCR3* rs4987053 polymorphism and the risk of endometrial cancer. A statistically significant difference was found between the patient and control groups in terms of both genotype and allele frequencies. The C allele for the *CCR3* rs4987053 polymorphism appears to be a risk factor for endometrial cancer.

Limitations of the Study

Our study is a hospital-based case-control study. Although power analysis was used to determine the sample, the relationships between SNPs and pathologies can be determined more clearly with a larger sample size. In this sense, the relationship between the gene variants we examined and endometrial cancer can be understood more clearly with studies that include larger cohorts.

CONCLUSION

With metastases occurring in the great majority of cases, cancer is more of a systemic illness. Since the majority of existing treatments aim to eradicate or inhibit tumor cells, the efficacy of current therapies is insufficient, as nonmalignant cells in the tumor microenvironment (TME) play a major role in the successful formation of metastases. In addition to encouraging leukocyte migration to specific areas and regulating host immunological responses and other physiological processes, chemokines and their receptors are also hypothesized to be involved in the formation, progression, and metastasis of tumors. Tumor-associated macrophages in the TME are regulated by chemokines, which in turn stimulate tumor invasion and metastasis through chemokine-associated signaling pathways (20).

Findings from biomarker-based studies may reveal molecular elements that may form the basis of targeted treatment of endometrial cancer, thus enabling both early diagnosis and subsequent targeted treatment of endometrial cancer. Chemokines, whose relationship with cancer and metastatic processes has been identified, can be potential markers and targets for this purpose.

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Conflict of interest and financial disclosure

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