Clinical and Experimental Health Sciences

NF-κB and COX-2 Relation Between Endometrial Cancer and the Clinicopathological Parameters

Ahmet Cem Iyibozkurt[1], Baris Ertugrul[2,3], Elif Sinem Iplik[4], Bedia Cakmakoglu[2]

[1] Florence Nightingale Hospital, Department of Obstetrics and Gynecology, Istanbul, Türkiye.
[2] Istanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Molecular Medicine, Istanbul, Türkiye.
[3] Istanbul University, Institute of Graduate Studies in Health Sciences, Istanbul, Türkiye.
[4] Acibadem University, Faculty of Pharmacy, Department of Biochemistry, Istanbul, Türkiye.

Correspondence Author: Bedia Cakmakoglu
E-mail: bedia@istanbul.edu.tr

Received: 03.01.2022 **Accepted:** 28.03.2022

ABSTRACT

Objective: Our study examines nuclear factor kappa B (NF-κB) and cyclooxygenase-2 (COX-2) polymorphisms in the most common gynecological cancer type, endometrial cancer, and the relationship between disease parameters and these polymorphisms.

Methods: In our patient group; while 109 endometrial cancer patients were examined and treated in the Department of Gynecology and Obstetrics, Istanbul Medical Faculty, and 106 healthy women without the disease were included in the control group. DNA of blood samples taken from all groups were isolated; COX-2 765C> G and COX-2 1195A> G polymorphisms were studied with NF-κB-94 ins / delATTG. Genotypes analyzed using the PCR-based restriction fragment length polymorphisms (RFLP) method were investigated in terms of the relationship between endometrial cancer susceptibility and endometrial cancer disease parameters. Results in SPSS 17 program; Student's t-tests were analyzed using Anova, Fisher's exact, and Chi-square tests.

Results: NF-κB D + and DD genotype, COX-2 765 G + and GG genotype, and COX-2 1195 AA genotype were found to be significantly more common in the endometrial cancer group compared to the control group ($p < 0.05$). However, no significant relationship was found between polymorphisms and disease parameters.

Conclusion: NF-κB and COX-2 polymorphisms are more common in women with endometrial cancer. However, the absence of a link between these polymorphisms and the prevalence or violence of the disease suggests that they often trigger cancer development.

Keywords: COX, endometrial cancer, genotype, NF-κB, polymorphism

1. INTRODUCTION

Endometrial cancer is one of the most common gynecological cancers in developed countries. In Turkey, it is also included in the first row in the incidence of gynecological cancer with cervical cancer (1). The development of the disease can be seen due to the deterioration of the balance between cell proliferation and apoptosis in the direction of loss in tumor suppression genes or increase in oncogene activation (2).

The average age of onset is 61 years, and prognostic variables include histological grade, depth of myometrial invasion, stage, cervical invasion, and metastases. The existence of these numerous criteria determines whether surgical therapy is adequate, and adjuvant treatment is used if necessary (3). To improve outcomes in the treatment of endometrial cancer, research are ongoing to split patients into subgroups based on clearer prognostic markers and to develop therapy groups tailored to them. At this point, cyclooxygenase (COX-2) and nuclear factor kappa B (NF-κB) also among the important parameters investigated. NF-κB is a primary transcription factor effective in the control of immune and inflammatory responses in the reproductive tract. One of the pathological conditions caused by loss of activity is endometrial cancers. Tumorigenesis, inhibition of apoptosis, and metastases are usually triggered by inflammatory factors (4,5). By regulating immune and inflammatory responses with cytokines and their receptors, it has been shown that cell differentiation, apoptosis and migration are involved in gene regulation mediated by cell adhesion molecules (6). Oh et al (7) showed in their studies that myometrial invasion in endometrial cancer can also develop through NF-κB. There are two isoforms of COX-2, and it has been shown in recent studies that it may be associated with malignant transformation and tumor progression in endometrial cancer (8). There are studies in the literature showing that COX-2 expression is increased in endometrial cancer and supporting that this may be a prognostic marker. Lambroupoulou et al (9,10),

DOI: 10.33808/clinexphealthsci.1049382

in their immunohistochemistry-based studies in 28 women with endometrial cancer, found that COX-2 expression was significantly correlated with the grade, myometrial invasion, histological type, and survival, and demonstrated the prognostic significance of COX-2 expression. It is thought that COX-2 shows its effects on cancer through NF-κB activation and apoptosis mechanism (11). NF-κB is thought to be important in this context and may be a marker for some types of endometrial cancer (12). It is known that loss of control in NF-κB activation leads to endometrial cancer by causing an increase in cell proliferation and inflammation, and suppression of apoptosis (13).

The aim of this study is to investigate the relationship between NF-κB-94 ins / delATTG, COX-2 765 C> G, and COX-2 1195 A> G gene variants in women with endometrial cancer, disease clinicopathological parameters in endometrial cancer and the frequency of these gene variants in Turkish population.

2. METHODS

2.1. Study Subjects

In this study, women who were treated by the Istanbul Faculty of Medicine, Department of Obstetrics or Gynecology or applied to the polyclinics were included in the study in two groups, after obtaining their informed consent. In the first group, 109 patients who were followed up and treated in the Gynecological Oncology Department of Istanbul Medical Faculty, Department of Obstetrics and Gynecology and were diagnosed with endometrial cancer after their operations were included. In the second group, 106 healthy individuals who were close to the average age of the patients in the age group and had no history of cancer were included. Ethical approval was obtained by the Medical Ethics Committee of Istanbul University Faculty of Medicine on 11.11.2010 (Number: 2009/2897-92). All demographic, clinical and pathological information of the individuals in the patient and control groups were transferred to a database and recorded in the study.

2.2. DNA Isolation

Blood samples from each individual were collected in EDTA tubes. Samples were isolated using the Invitrogen Purelink Genomic DNA Kit.

2.2.1. Lysate Preparation from Blood Samples

The temperature of the water bath or heatsink is set at 55°C. A sterile microcentrifuge tube is filled with 200 µl of fresh or frozen blood. Fill the sample with 20 µl of the Proteinase K included with the kit. Then, 20 µl of the RNase A supplied with the kit is added to the sample, vortexed vigorously, and incubated at room temperature for 2 minutes. To create a homogenous solution, add 200 µl of PureLink Genomic Lysis/ Link solution and thoroughly mix by vortexing. To enhance protein digestion, incubate for 10 minutes at 55°C. To the lysate, add 200 µl of 96-100 percent ethanol. Vortex the mixture for 5 seconds.

2.2.2. Binding to DNA

Add the Genomic Lysis/Link solution and ethanol-supplemented lysate (640 µl) to the PureLink spin column. Colon 1 min. Centrifuge at 10,000xg at room temperature. The collection tube is discarded and placed in a new PureLink Collection tube supplied with the kit. The DNA wash phase begins.

2.2.3. Washing Step

500 µl of Washing Solution I prepared with Ethanol is added to the column. The columns are centrifuged at 10,000xg for 1 minute at room temperature. The collection tube is discarded and placed in a new PureLink Collection tube supplied with the kit. 500 µl of Washing Solution II prepared with Ethanol is added to the column. Column at room temperature at maximum speed for 3 min. centrifugation is done. The collection tube is discarded.

2.2.4. DNA Elution Step

In a sterile 1.5 ml microcentrifuge tube, put the column. Fill the column with 25-200 µl of PureLink Genomic Elution Solution. At room temperature for 1 minute. After incubation, centrifuge at highest speed for 1 minute. Purified genomic DNA is included in the tube. To retrieve additional DNA, a second elution step is done into a fresh sterile 1.5 ml microcentrifuge tube with the same amount of elution solution. At room temperature, the column is centrifuged at maximum speed for 1.5 minutes. Purified genomic DNA is included in the tube. The column will be removed.

2.3. Polymorphism Analysis

In genomic DNA samples, alleles of COX-2 765C> G, COX-2 1195A> G and NF-κB – 94ins / del regions were amplified by polymerase chain reaction (PCR). A total of 25 µl PCR mix was prepared for the amplification of each of the DNA samples. This PCR mixture was prepared to have 100-200 ng of DNA, 1µl of each primer, 1mM dNTP, 1.5mM $MgCl_2$ and 1.0U Taq DNA Polymerase. Amplification reactions performed in Thermal Cycler. Amplification of PCR condition for both COX-2 regions was 94°C for 3 min for the initial denaturation step, followed by 33 cycles of denaturation at 94°C (15 sec), annealing at 58°C (30 sec), and extension at 72°C (60 sec). The final extension step was at 72°C for 7 min. Primer sequences for 765C>G polymorphism of COX-2 gene were forward – 5'-AGGCAGGAAACTTTATATTATTGG-3' and reverse – 5'-ATGTTTTAGTGACGACGCTTA-3'. The primers for 1195G>A polymorphisms of COX-2 gene were forward – 5'-CCCTGAGCACTACCCATGAT-3', reverse – 5'-GCCTTCATAGGAGATACTGG-3'. The primer sequences used for NF-B-94 ins/del were selected as forward-5' – TTTAATCTGTGAAGAGATGTGAATG-3', reverse – 5'-GCCTTCATAGGAGATACTGG-3'. Enzymatic digestions were performed with AciI, PvuII and Van91I enzmes for COX-2

765C>G, COX-2 1195A>G and NF-κB – 94ins / del polymorphisms respectively.

2.4. Statistical Analysis

In the statistical analysis of this study, SPSS 11.0 package program was used. Statistical significance was taken as $p < 0.05$. Chi-square (χ^2) and Fisher tests were used to evaluate the differences in the frequency of genotypes and alleles between groups. Student's t-test and Annova were used to compare demographic data between groups. Allele frequencies were made according to the gene counting method. Fisher's exact and χ^2 tests were used to investigate the relationship between endometrial cancer disease parameters and polymorphisms.

3. RESULTS

3.1. Demographical Data

The demographic information of the study groups is shown (Table 1). For the control group, the mean and standard deviation of age distribution was found 52.81± 8.4, and it was found 55.25 ± 8.37 for the patient group. There was no statistically significant difference between the control and patient groups in terms of age distribution (p= 0.07).

Table 1. *Demographic data of the study group*

	Patient (N=109)
Age of menarche, age ±SD	13.39 ± 1.64
Last menstrual time	51.40 ± 4.83
Oral contraceptive use (%)	
Yes	76.9
No	23.1
Family planning (%)	
Yes	41.3
No	58.7
Diabetes (%)	
Yes	25.7
No	74.3
Hypertension (%)	
Yes	44.6
No	55.4
Hystology (%)	
Endometrioid	87.5
Adenocarcinoma	2.5
Serous	5.0
Clear cell	2.5
Indifferentiated	2.5
Grade (%)	
I	61.5
II	23.1
III	15.4

SD: standart deviation

3.2. COX-2 765 C → G genotype distributions

COX-2 765 C → G genotype distributions in control and patient groups are shown in Table 2. COX-2 765 CC genotype distribution was significantly different in the control group compared to the patient group (χ^2= 4.55; p= 0.033; OR= 0.35; 95%CI= 0.13-0.94). COX-2 765 GG genotype distribution was significantly different in the control group compared to the patient group (χ^2= 16.29; p= 0.000; OR= 3.10; 95%CI=1.77-5.41) COX-2 765 CG genotype distribution was significantly different in the control group compared to the patient group (χ^2= 7.83; p= 0.45; OR= 0.45;95%CI= 0.26-0.79).

These findings were significantly different between the control and patient groups (Table 2).

3.3. COX-2 1195A → G genotype distributions

COX-2 1195A → G genotype distributions in control and patient groups are summarized in Table 3. COX1195 AA genotype distribution was significantly different in the patient group compared to the control group (χ^2= 8.78; p= 0.003; OR= 2.35; 95%CI= 1.33-4.14). COX1195 GG genotype distribution was significantly different in the patient group compared to the control group (χ^2= 3.96; p= 0.064; OR= 1.03; 95%CI= 1.00-1.07) COX1195 AG genotype distribution was significantly different in the patient group compared to the control group (χ^2= 12.78; p=0.000; OR= 0.35; 95%CI= 0.19-0.62)

3.4. NF-ĸB genotype distributions

Genotype distributions of NF-κB genes were found significantly different between control and patient groups (Table 4). NF-κB WW genotype distribution was significantly different in the patient group compared to the control group (χ^2= 5.73; p= 0.017; OR= 0.51; 95%CI= 0.29-0.88) NF-κB DD genotype distribution was significantly different in the patient group compared to the control group (χ^2= 34.11; p= 0.000; OR= 8.94; 95%CI= 3.96-20.2) NF-κB WD genotype distribution was significantly different in the patient group compared to the control group (χ^2= 8.23; p= 0.004; OR= 0.43; 95%CI= 0.24-0.77)

3.5. COX-2 765: 1195 Haplotype frequency

Haplotype frequencies of COX-2 765: 1195 were shown in Table 5. Despite the fact that the association between endometrial cancer disease parameters and statistically significant polymorphisms is analyzed in Table 6, there is no statistically significant relationship between disease parameters and polymorphisms.

Table 2. *COX-2 765 C → G genotype distributions in control and patient groups*

COX-2 *765 C→G* Genotypes	Control N:106		Patient N:109		P value	χ^2	OR	95% CI
	N	%	N	%				
CC	15	14.1	6	5.5	0.03*	4.55	0.35	0.13-0.94
GG	36	34	67	61.5	0.000**	16.29	3.10	1.77-5.41
CG	55	51.9	36	33.0	0.005**	7.83	0.45	0.26-0.79
Alleles								
C	85	40.1	48	22.02	0,000**	16.43	0.32	0.18-0.56
G	127	59.9	170	77.98				

*OR: odd ratio, CI: confidence interval, (one asterisk * indicates for p<.05; two asterisks ** indicate for p<.01).*

Table 3. *COX-2-1195A → G genotype distributions in control and patient groups*

COX-2-*1195A→G* Genotypes	Control N:106		Patient N:109		P value	χ^2	OR	95% CI
	N	%	N	%				
AA	56	52.8	79	72.5	0.003*	8.78	2.35	1.33-4.14
GG	0	0	4	3.7	0.064	3.96	1.03	1.00-1.07
AG	50	47.2	26	23.8	0.000**	12.78	0.35	0.19-0.62
Alleles								
A	162	76.42	184	84.4	0.03*	4.36		
G	50	23.58	34	15.6				

*OR: odd ratio, CI: confidence interval, (one asterisk * indicates for p<.05; two asterisks ** indicate for p<.01).*

Table 4. *NF-ĸB genotype distributions in control and patient groups*

NF-ĸB Genotypes	Control N:106		Patient N:109		P value	χ^2	OR	95% CI
	N	%	N	%				
WW	51	48.1	35	32.1	0.017*	5.73	0.51	0.29-0.88
DD	8	7.5	46	42.2	0.000**	34.11	8.94	3.96-20.2
WD	47	44.4	28	25.7	0.004**	8.23	0.43	0.24-0.77
Alleles								
W	149	70.28	98	44.96	0.0000**	28.20		
D	63	29.72	120	55.04				

*OR: odd ratio, CI: confidence interval, (one asterisk * indicates for p<.05; two asterisks ** indicate for p<.01).*

Tablo 5. *COX-2 765:1195 haplotype frequencies*

Haplotype	Frequency				
	Total	Patients	Controls	χ^2	*p* – value
COX-2 765:1195					
GA	0.530	0.638	0.418	21.019	$4.54.10^{-6}$ **
CA	0.275	0.206	0.347	10.691	0.0011**
GG	0.161	0.141	0.181	1.27	0.2598
CG	0.034	0.014	0.054	5.189	0.0227*

*(one asterisk * indicates for p<.05; two asterisks ** indicate for p<.01).*

Tablo 6. *Relationship between endometrial cancer disease parameters and statistically significant polymorphisms*

Polymorphism Type	*COX-2 755 G+*	*COX-2 765 GG*	*COX-2 1195 AA*	*NF-κB D+*	*NF-κB DD*
Endometrial Cancer Clinicopathological parameter					
Type1 and Type2	**0.59**	**0.87**	**1.00**	**0.35**	**0.54**
Presence of deep invasion	**0.42**	**0.99**	**0.95**	**0.75**	**0.61**
Early Stage (1-2) vs Advanced Stage (3-4)	**0.50**	**0.73**	**0.43**	**0.44**	**1.00**
Presence of lymphovascular area invasion	**1.00**	**0.49**	**0.64**	**0.71**	**0.35**

(results are given as p value, all results were found as statistically not significant; p <.05)

4. DISCUSSION

In our study, it was found that NF-κB-94ins / del polymorphisms increased the risk for endometrial cancer in patients carrying the del allele. Besides, the susceptibility to endometrial cancer was higher in COX-2 765 C> G gene polymorphism in individuals carrying homozygous GG or G allele and in COX-2 1195 A> G gene polymorphism for homozygous AA individuals. One of the strengths of our study is that the patients used in our study had well-characterized data and that the age range determined for the patient and control group was kept close. The endometrium patients determined for the patient group consisted of patients who are diagnosed with endometrium because of pathology.

One of the weaknesses of this study may be the low number in the patient and control groups. In our study, we found no difference in both NF-κB and COX-2 polymorphism rates in type 1 and type 2 endometrial cancer groups. This shows that polymorphisms are more related to the occurrence of cancer itself than the type of endometrial cancer. It has been reported that NF-κB suppression is associated with a decrease in tumor incidence and small tumor size in animal model studies (14). It is possible to interpret that the incidence of cancer may be affected by NF-κB gene polymorphisms. Andersen et al (15) stated in their study that NF-κB-94del polymorphism increased the risk for colorectal cancer 1.45 times. When compared with our study, it is seen that the results are consistent with each other, those carrying the Del allele in the NF-κB gene are thought to be riskier in terms of endometrial cancer. The relationship between NF-κB and endometrial cancer was first demonstrated in the study of Vaskivuo et al (16). NF-κB is a regulator with shown antiapoptotic function in many cells (17). NF-κB is also present in the endometrium during the normal menstrual cycle and increased NF-κB levels have been shown to suppress apoptosis. Increases in IL-1beta and COX2 transcription, induced by increased levels of NF-κB, have been reported to suppress the proapoptotic properties of TNF alpha (17,18). It can be thought that increased levels of NF-κB due to NF-κB polymorphisms may cause loss of control of cell proliferation and subsequently cancer by creating an antiapoptotic environment. In the period following cancer formation, NF-κB stimulates the increase of matrix metalloproteinases in malignant cells and accelerates the processes of tumor invasion, metastasis, and neovascularization (19,20). Vaskivuo et al (16) found that NF-κB levels in individuals with endometrial cancer decreased in their study and suggested that NF-κB did not have an important role in the spread of endometrial cancer. In our study, a relationship was found between NF-κB polymorphisms and the incidence of endometrial cancer, but when this relationship was evaluated in terms of clinicopathological data of the disease, no significant difference was found between disease types (16). PTEN inactivations have also been shown to trigger an increase in NF-κB activity (11).

The relationship between COX-2 gene polymorphisms and cancer has also been investigated in some studies. In a study conducted on individuals with colorectal cancer, it was found that individuals carrying the A allele at 1195 G> A polymorphism had a higher risk of cancer (21). In another study conducted with colorectal cancer patients, it was shown that the distribution of the 765GG genotype was high in patients (22). While COX-2 expression is seen in colorectal cancer tissue, the absence of expression in surrounding normal tissue is a sign that COX-2 plays an active role in tumor development (23). Nevertheless, some publications are stating that 1195 A> G polymorphisms are not associated with colon cancer (24). Our study is original in that it is the first study evaluating the relationship between endometrial cancer and COX-2 1195 G> A polymorphisms, and as a result, 1195 AA genotype was found to be significantly higher in the patient group. In studies conducted with other cancer types, the high incidence of cancer due to COX-2 1195 A> G has been found responsible for the increase in COX-2 gene transcription (21). COX-2 overexpression has been associated with its potential for resistance to apoptosis, adhesion, angiogenesis, and metastasis. Increased cancer susceptibility can be seen with the change caused by the mutation in the COX-2 gene. Another study that supports the results of our study is the decrease in cancer risk seen in the presence of the G allele (22). It has been suggested that the result of changes in the COX-2 gene may have different consequences in Europe, mixed races, and Chinese; for example, esophageal cancer has increased in the Chinese but does not change in Europeans (22,23). In our study, the significantly higher detection of COX-2 1195 A> G and COX-2

765 C> G polymorphisms in women with endometrial cancer indirectly supports the role of COX-2 in the development of this cancer.

Although we showed the connection between the detected NF-κB and COX-2 polymorphisms with endometrial cancer, no significant relationship was found between these polymorphisms and type 1 and 2 endometrial cancer. Likewise, no significant difference was found between these polymorphisms and the presence of deep invasion-lymphovascular area invasion or in terms of the frequency of early-advanced stage cancer. This brings to the fore the idea that NF-κB and COX-2 polymorphisms have a role in the development of type 1 or type 2 endometrial cancer, but do not directly affect the invasion degree or stage of cancer. Since these clinicopathological parameters we mentioned are also related to the aggressiveness of the disease, it can be suggested that the presence of these polymorphisms does not affect the aggressiveness of the disease. As a result, increased NF-κB and COX-2 activity has been demonstrated in colon cancer so far, and the relationship between endometrial cancer and NF-κB and increased COX-2 has been suggested (11,24-26). NF-κB and COX-2 activation may give the endometrium cancer cell a survival advantage, and it appears to do so by regulation of apoptosis (4). NF-κB may be providing this regulation through different mechanisms, since no link was found between NF-κB and absence of PTEN, kRAS mutation, and beta-catenin changes in these studies. The significant relationship between endometrial cancer and NF-κB-94 ins / del ATTG polymorphism, COX-2 765C> G and COX-2 1195A> G polymorphisms we found in our study support the mentioned findings and mechanisms. Some of the studies in the literature investigating the COX and NF-κB relationship with endometrium cancer, have showed that polymorphisms contributing the endometrium cancer development (27,28). Cavalcanti et al (29) showed that – 765G polymorphism of the COX-2 gene was associated with an increased risk for endometriosis in Brazilian fertile women, and also increased expression of COX-2 relative to the control group was shown in the patient group.

5. CONCLUSION

Our study is the first study to reveal the relationship between these polymorphisms and endometrial cancer. The absence of a significant relationship between polymorphisms and the clinicopathological parameters of the disease suggests that these polymorphisms are more important in terms of cell cancer, and they have less effect on the spread of the disease after cancer.

Acknowledgment/Funding: This work was supported by Scientific Research Projects Coordination Unit of Istanbul University. Project number : 15987

Conflict of interest: The authors declare that they have no conflict of interest.

Authors' Contributions: ACI: writing, sample collection and experimental process; BE: writing and experimental process; ESI: experimental process and statistical analysis; BC: statistical analysis and supervising.

REFERENCES

[1] Gultekin M, Kucukyildiz I, Karaca MZ, Dundar S, Boztas G, Turan SH, Hacikamiloglu E, Keskinkilic B. Trends of gynecological cancers in Turkey: Toward Europe or Asia? Int J Gynecol Cancer. 2017; 27 (7): 1525-1533. DOI: 10.1097/IGC.000.000.0000001026.

[2] Hall M, Peters G. Genetic alterations of cyclins, cyclin-dependent kinases, and Cdk inhibitors in human cancer. Adv Cancer Res 1996;68:67–108. DOI: 10.1016/s0065-230x(08)60352-8.

[3] Prat J, Oliva E, Lerma E, Matias-Guiu X. Uterine papillary serous adenocarcinoma. A 10-case study of p53 and c-erbB-2 expression and DNA content. Cancer 1994;74 (16):1778–1783.

[4] Feldman I, Feldman GM, Mobarak C, Dunkelberg JC, Leslie KK. Identification of proteins within the nuclear factor-kappa B transcriptional complex including estrogen receptor-alpha. Am J Obstet Gynecol. 2007;196(4):394.e1-11; discussion 394.e11-3. DOI: 10.1016/j.ajog.2006.12.033.

[5] Modugno F, Ness RB, Chen C, Weiss NS. Inflammation and endometrial cancer: A hypothesis. Cancer Epidemiol Biomarkers Prev 2005;14 (12):2840–2847. DOI: 10.1158/1055-9965.EPI-05-0493.

[6] Pallares J, Martínez-Guitarte JL, Dolcet X, Llobet D, Rue M, Palacios J, Prat J, Matias-Guiu X. Abnormalities in the NF-kappaB family and related proteins in endometrial carcinoma. J Pathol. 2004;204(5):569-577. DOI: 10.1002/path.1666.

[7] Oh JH, Kim JH, Ahn HJ, Yoon JH, Yoo SC, Choi DS, Lee IS, Ryu HS, Min CK. Syndecan-1 enhances the endometrial cancer invasion by modulating matrix metalloproteinase-9 expression through nuclear factor kappaB. Gynecol Oncol. 2009;114(3):509-515. DOI: 10.1016/j.ygyno.2009.05.027.

[8] Tong BJ, Tan J, Tajeda L, Das SK, Chapman JA, DuBois RN, Dey SK. Heightened expression of cyclooxygenase-2 and peroxisome proliferator-activated receptor-delta in human endometrial adenocarcinoma. Neoplasia. 2000; 2(6): 483-490. DOI: 10.1038/sj.neo.7900119.

[9] Lambropoulou M, Alexiadis G, Limberis V, Nikolettos N, Tripsianis G. Clinicopathologic and prognostic significance of cyclooxygenase-2 expression in endometrial carcinoma. Histol Histopathol. 2005;20(3):753-759. DOI: 10.14670/HH-20.753.

[10] Lambropoulou M, Papadopoulos N, Tripsianis G, Alexiadis G, Pagonopoulou O, Kiziridou A, Liberis V, Kakolyris S, Chatzaki E. Co-expression of survivin, c-erbB2, and cyclooxygenase-2 (COX-2): prognostic value and survival of endometrial cancer patients. J Cancer Res Clin Oncol. 2010; 136 (3): 427-435. DOI: 10.1007/s00432.009.0673-6.

[11] St-Germain ME, Gagnon V, Parent S, Asselin E. Regulation of COX-2 protein expression by Akt in endometrial cancer cells is mediated through NF-kappaB/IkappaB pathway. Mol Cancer. 2004 11;3:7. DOI: 10.1186/1476-4598-3-7.

[12] Domenyuk VP, Litovkin KV, Verbitskaya TG, Dubinina VG, Bubnov VV. Identification of new DNA markers of endometrial cancer in patients from the Ukrainian population. Exp Oncol. 2007;29(2):152-155.

[13] Gonzalez-Ramos R, Defrere S, Devoto L. Nuclear factor-kappaB: A main regulator of inflammation and cell survival in

endometriosis pathophysiology. Fertil Steril. 2012;98(3):520-528. DOI: 10.1016/j.fertnstert.2012.06.021.

[14] Elwood PC, Gallagher AM, Duthie GG, Mur LA, Morgan G. Aspirin, salicylates, and cancer. Lancet 2009;373 (9671) :1301-1309. DOI: 10.1016/S0140-6736(09)60243-9.

[15] Andersen V, Christensen J, Overvad K, Tjonneland A, Vogel U. Polymorphisms in NF-κB, PXR, LXR and risk of colorectal cancer in a prospective study of Danes. BMC Cancer 2010;10:484. DOI: 10.1186/1471-2407-10-484.

[16] Vaskivuo TE, Stenback F, Tapanainen JS. Apoptosis and apoptosis related factors Bcl-2, Bax, Tumor necrosis factor alfa, and NF-kB in human endometrial hyperplasia and carcinoma. Cancer 2002;95(7):1463-1471. DOI: 10.1002/cncr.10876.

[17] de Martin R, Schmid JA, Hofer-Warbinek R. The NF-kappaB/rel family of transcription factors in oncogenic transformation and apoptosis. Mutat Res 1999;437 (3): 231-243. DOI: 10.1016/s1383-5742(99)00089-7.

[18] Nagata S. Apoptosis by death factor. Cell 1997;8 (3)8 :355-365. DOI: 10.1016/s0092-8674(00)81874-7.

[19] Kalkoven E, Wissink S, van der Saag PT, van der BB. Negative interaction between the RelA(p65) subunit of NF-kappaB and the progesterone receptor. J Biol Chem. 1996;271(11): 6217-6224. DOI: 10.1074/jbc.271.11.6217.

[20] Higgins KA, Perez JR, Coleman TA, Dorshkind K, McComas WA, Sarmiento UM, Rosen CA, Narayanan R. Antisense inhibition of the p65 subunit of NF-kappa B blocks tumorigenicity and causes tumor regression. Proc Natl Acad Sci U S A. 1993; 1;90(21):9901-9905. DOI: 10.1073/pnas.90.21.9901.

[21] Tang Z, Nie ZL, Pan Y, Zhang L, Gao L, Zhang Q, Lili Qu, Bangshun He, Song G, Zhang Y and Wang S. The Cox-2 1195G>A polymorphism and cancer risk: A meta-analysis of 25 case-control studies. Mutagenesis 2011;26(6):729-734. DOI: 10.1093/mutage/ger040.

[22] Hoff JH, te Morsche RHM, Roelofs HMJ, van der Logt EMJ, Nagengast FM, Peters WHM. COX-2 polymorphisms 765G>C and 1195A>G and colorectal cancer risk. World J Gastroenterol 2009;15(36):4561-4565. DOI: 10.3748/wjg.15.4561.

[23] Zhang X, Miao X, Tan W, Ning B, Liu Z, Hong Y, Song W, Guo Y, Zhang X, Shen Y, Qiang B, Kadlubar FF, Lin D. Identification of functional genetic variants in cyclooxygenase-2 and their association with risk of esophageal cancer. Gastroenterology 2005;129 (2):565-576. DOI: 10.1016/j.gastro.2005.05.003.

[24] Fujiwaki R, Iida K, Kanasaki H, Ozaki T, Hata K, Miyazaki K. Cyclooxygenase-2 expression in endometrial cancer: correlation with microvessel count and expression of vascular endothelial growth factor and thymidine phosphorylase. Hum Pathol. 2002;33(2):213-219. DOI: 10.1053/hupa.2002.31292.

[25] Liang JT, Huang KC, Jeng YM, Lee PH, Lai HS, Hsu HC. Microvessel density, cyclooxygenase 2 expression, K-ras muıtation and p53 overexpression in colonic cancer. Br J Surg 2004;91(3):355-361. DOI: 10.1002/bjs.4447.

[26] Yoshimatsu K, Golijanin D, Paty PB, Soslow RA, Jakobsson PJ, DeLellis RA, Subbaramaiah K, Dannenberg AJ. Inducible microsomal prostaglandin E synthase is overexpressed in colorectal adenomas and cancer. Clin Cancer Res. 2001; 7(12):3971-3976.

[27] Ma X, Hui Y, Lin L, Wu Y, Zhang X, Liu P. Clinical significance of COX-2, GLUT-1 and VEGF expressions in endometrial cancer tissues. Pak J Med Sci. 2015;31(2):280-284. DOI: 10.12669/pjms.312.6604.

[28] Lupi LA, Cucielo MS, Silveira HS, Gaiotte LB, Cesário RC, Seiva FRF, de Almeida Chuffa LG. The role of Toll-like receptor 4 signaling pathway in ovarian, cervical, and endometrial cancers. Life Sci. 2020;15; 247:117435 DOI:10.1016/j.lfs.2020.117435.

[29] Cavalcanti V, Ponce TG, Mafra FA, André GM, Christofolini DM, Barbosa CP, Bianco B. Evaluation of the frequency of G-765C polymorphism in the promoter region of the COX-2 gene and its correlation with the expression of this gene in the endometrium of women with endometriosis. Arch Gynecol Obstet. 2016;293(1):109-115. DOI: 10.1007/s00404.015.3808-9.

How to cite this article: Iyibozkurt AC, Ertugrul B, Iplik ES, Cakmakoglu B. NF-κB and COX-2 Relation Between Endometrial Cancer and the Clinicopathological Parameters. Clin Exp Health Sci 2022; 12: 1025-1031. DOI: 10.33808/clinexphealthsci.1049382