

# Evaluation of the Association between Genetic Polymorphism of Interleukin-1 Beta (-511C/T and +3953C/T) and Cervical Cancer Susceptibility

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### Abstract



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Cervical cancer (CC) is the leading cause of cancer-related mortality among women, primarily caused by persistent human papillomavirus (HPV) infection, especially in developing countries. A proinflammatory cytokine, emerging as a major facilitator of carcinogenesis, is termed interleukin-1 beta (IL-1 $\beta$ ), which characterizes host-environment interactions. Numerous epidemiological studies have revealed that IL-1 $\beta$  gene polymorphisms have been associated with numerous malignancies, but in the context of CC, results of these studies were inconclusive. Thus, our study aimed to explore the relationship between IL-1 $\beta$  polymorphisms (-511C/T and +3953C/T) and CC susceptibility. Genotyping was conducted on 192 CC patients and 200 healthy controls through polymerase chain reaction-restricted fragment length polymorphism. HPV analysis was done through real-time polymerase chain reaction, and the serum concentration of IL-1 $\beta$  was measured by enzyme-linked immunosorbent assay. Women with CT and TT genotypes of IL-1 $\beta$  -511C/T had a threefold increased risk of CC (odds ratio [OR], 3.60; 95% confidence interval [CI], 2.132-6.063;  $p < 0.001$  vs. OR, 3.34; 95% CI, 1.952-5.713;  $p < 0.001$ ) compared to controls. Women with the T allele of IL-1 $\beta$  -511C/T polymorphism were associated with increased CC susceptibility (OR, 2.00; 95% CI, 1.51-2.66;  $p = 0.0001$ ) compared to controls. No significant difference was found between patients and controls in the genotype or allele frequencies of IL-1 $\beta$  +3953C/T polymorphism (OR, 0.93; 95% CI, 0.56-1.55;  $p = 0.86$  vs. OR, 0.95; 95% CI, 0.72-1.26;  $p = 0.74$ ). There was no significant association found between IL-1 $\beta$  -511C/T promoter (OR, 2.41; 95% CI, 0.46-12.76;  $p = 0.28$  vs. OR, 1.64; 95% CI, 0.13-21.10;  $p = 0.7$ ) and +3953C/T (OR, 3.76; 95% CI, 0.44-31.82;  $p = 0.19$  vs. OR, 0.21; 95% CI, 0.01-3.92;  $p = 0.25$ ) polymorphisms in tobacco chewers and smokers compared to

### Keywords

- ▶ ELISA
- ▶ gene polymorphism
- ▶ HPV
- ▶ PCR-RFLP
- ▶ RT-PCR

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controls. The level of serum concentration of IL-1 $\beta$  was significantly higher in cases compared to controls. Our results conclude that IL-1 $\beta$  -511C/T polymorphism is associated with CC susceptibility.

## Introduction

Cervical cancer (CC) is the second most prevalent gynecological malignancy after breast cancer, and it is one of the major causes of cancer-related mortality in females around the world. As per 2020 GLOBOCAN, it is the fourth most commonly diagnosed cancer and the leading cause of cancer death in women, with an estimated 604,127 new cases and 341,831 fatalities.<sup>1</sup> Epidemiological studies have demonstrated that the human papilloma virus (HPV) is officially designated as the main cause of CC, primarily HPV-16 and HPV-18.<sup>2</sup> HPV-16 was found to be highly significant in tissues from CC patients, followed by HPV-18.<sup>3</sup> According to the molecular mechanism of CC, HPV deoxyribonucleic acid (DNA) was integrated into the host's genome which prompted keratinocytes to change the uterine cervix into cancer.<sup>4</sup> The uterine body and vagina are connected via the cervix. The area of the cervix closest to the uterine body is termed the endocervix. The exocervix is the region of the uterus that is located nearest to the vagina. The cells that line the cervix, also known as the uterine cervix, the lowest portion of the uterus, are where CC first develops.<sup>5</sup> The glandular cells and the squamous cells, which coat the cervix, are primarily two cell types. The "transformation zone" is the location where these two subtypes of cells collide. As a person gets older and after giving birth, the transition zone's location changes. The transition zone is a common place where CC develops.<sup>5</sup>

CC is caused by a multitude of factors, including multiple sexual partners, age at first sexual intercourse, parity, heavy cigarette smoking, immune suppression, tobacco and alcohol use, and coinfection with other sexually transmitted agents.<sup>6</sup> The immune system is crucial in suppressing or encouraging cancer by activating a variety of immunological components, especially cells and cytokines. The antigen presentation response, which is downregulated in CC and has a negative impact on cellular and humoral responses, appears to alter carcinogenesis.<sup>7</sup> As a result of the dynamic interactions between environmental exposure and host genetic background, it is widely regarded as a complex disease. Polymorphisms in the human genome are now acknowledged as a fundamental cause of the disease.

Interleukin (IL)-1 is a proinflammatory cytokine primarily produced by macrophages, monocytes, and epithelial cells that has a role in inflammation, immunological response, and angiogenesis of tumor or tumor initiation.<sup>8</sup> The interleukin-1 alpha (IL-1 $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), and IL-1 receptor antagonist genes are located in the 2q13-21 gene family and encode IL-1 $\alpha$ , IL-1 $\beta$ , as well as the anti-inflammatory cytokine IL-1RA.<sup>9</sup> Breast, lung, colon, and melanomas are solid tumors in which IL-1 $\beta$  production has a poor prognosis.<sup>10</sup> Polymorphisms in the IL-1 $\beta$  gene have been linked to susceptibility to a variety of cancers, according to research.<sup>11,12</sup> To the best of our knowledge, only a few studies

have investigated the association between IL-1 $\beta$  gene polymorphism and CC risk, but results were inconclusive. As a result, the purpose of this study was to look into the relationship between IL-1 $\beta$  -511C/T and +3953C/T gene polymorphisms and CC susceptibility.

## Materials and Methods

### Study Design: Case–Control Study

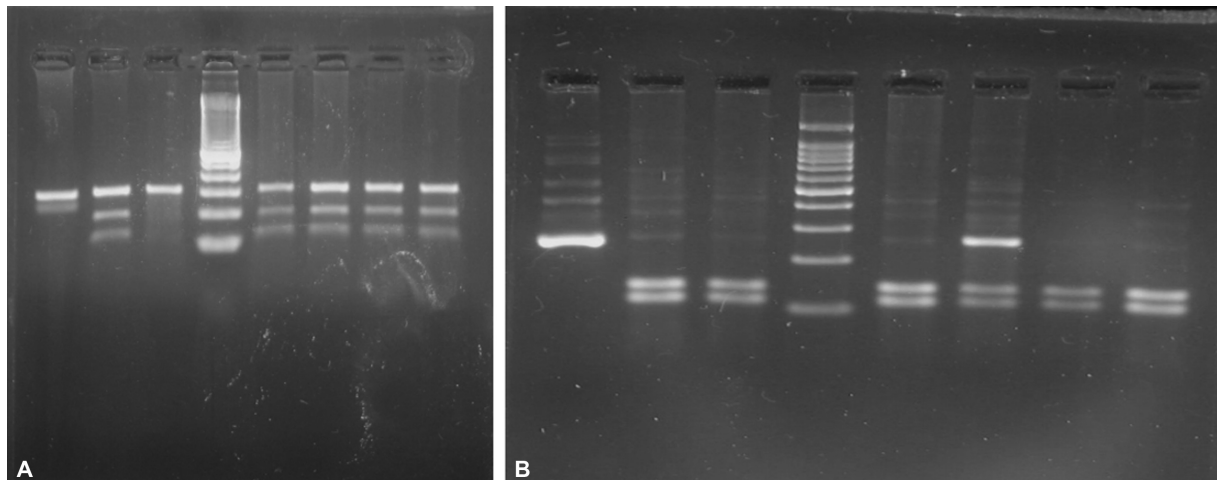
#### Patients and Sample Collection

For this case–control study, 192 women with CC and 200 healthy controls were recruited from the outpatient department (OPD) of the Department of Obstetrics and Gynaecology, Era's Lucknow Medical College and Hospital, Lucknow, Uttar Pradesh, India. All patients had recently been diagnosed, histopathologically verified, and staged as per International Federation of Gynaecology and Obstetrics (FIGO) criteria. The institutional ethics committee gave its approval, and each subject gave their informed consent. Patients with history of cancer or who had received radiotherapy or chemotherapy were excluded. Controls were recruited from the same department as those attending OPD, confirmed to be cervical cytology negative in the pathology department, and ascertained to have no history of cancer, infection, or any acute or chronic pathology. Each subject's peripheral blood (5 mL) was collected into tubes containing ethylenediamine tetraacetic acid and plain vials prior to radiation therapy and/or chemotherapy at the time of the initial diagnosis. Each participant's blood and serum samples were kept at  $-70^{\circ}\text{C}$  until further use.

#### Genomic DNA Extraction and Genotyping

The PureLink® Genomic DNA extraction kit was used to extract genomic DNA from each subject according to the manufacturer's instructions. To determine the IL-1 $\beta$  promoter polymorphism at position -511C/T gene, polymerase chain reaction-restricted fragment length polymorphism (PCR-RFLP) method<sup>13</sup> was used with the following specific primer sequence: 5'-TGGCATTGATCTGGTTCATC-3' forward, and 5'-GTTTAGGAATCTTCCCACTT-3' reverse. For each sample, PCR was carried out in a final volume of 20  $\mu\text{L}$  including 2  $\mu\text{L}$  of genomic DNA, 25 mM of Deoxynucleotide triphosphates (dNTP), 1 mmol/L of MgCl<sub>2</sub>, 1.5 units of Taq, that is, DNA polymerase (Fermentas, Thermo Fisher Scientific, BIO-RAD, USA), and 5  $\mu\text{L}$  of buffer with annealing at 58 $^{\circ}\text{C}$ .

The amplified product, that is, 15  $\mu\text{L}$  was digested with 5 U of Aval (New England Biolabs, Beverly, Massachusetts, United States) at 37 $^{\circ}\text{C}$  overnight, then the products were separated on 3% agarose gel electrophoresis with EtBr (Invitrogen Life Technologies, Carlsbad, California, United States) and visualized under ultraviolet light with a 100 base pair ladder (**–Fig. 1A**).



**Fig. 1** (A) Agarose gel picture showing interleukin (IL)-1 $\beta$  (-511C/T) gene polymorphism: Lanes 1 and 3, TT genotype; Lanes 2 and 5–8, CT genotype; Lane 4, molecular marker 100 bp. (B) Agarose gel picture showing IL-1 $\beta$  +3953 C/T gene polymorphism: Lane 1, TT genotype; Lanes 2, 3, 5, 7, and 8, CC genotype; Lane 6, CT genotype; and Lane 4, molecular marker 100 bp.

For genotyping of the IL-1 $\beta$  polymorphism at position +3953, PCR amplification was followed by RFLP analysis.<sup>14</sup> Using the primer sequence 5'-GTT GTC ATC AGA CTT TGA CC-3' forward and 5'-TTC AGT TCA TAT GGA CCA GA-3' reverse, the target DNA sequence in exon 5 of the IL-1 $\beta$  gene was amplified with annealing at 59°C. The amplified product was digested with 2.5 U Taq 1 at 37°C overnight and separated on 3% agarose gel electrophoresis and under ultraviolet light (**Fig. 1B**).

The concentration of IL-1 $\beta$  in human serum samples was measured by enzyme-linked immunosorbent assay (ELISA) using the Human IL-1 $\beta$  Diaclone ELISA Kit as per the manufacturer's protocol (Cat. No.850.006.096).

### Statistical Analysis

The SPSS v. 21.0 tool (SPSS Inc., Chicago, Illinois, United States) was used to analyze the data. For continuous variables, the two-tailed *t*-test was employed, and for categorical variables, the Chi-square ( $\chi^2$ ) test was utilized. Using the  $\chi^2$  test, Hardy-Weinberg equilibrium studies were used to compare observed and anticipated genotype frequencies. The odds ratio (OR) and their 95% confidence interval (CI) from multivariate logistic regression analysis were used to determine the correlations between genotypes and CC risk. A statistically significant *p*-value of 0.05 was used.

### Results

The demographic characteristics of cases and controls are summarized in **Table 1**. The mean age of cases was 49.8 years on average, while controls were 44.9 years old. Histopathological distribution of CC was keratinizing squamous cell carcinoma (85.42%) and adenocarcinoma (4.16%), as shown in **Table 1**. Staging of all the cases was scrutinized through FIGO criteria. Among them, majority of the cases (57.30%) were diagnosed with stage II. Between patients and controls, there was a significant difference in serum IL-1 $\beta$  levels.

### IL-1 Beta Polymorphism -511C/T Polymorphism

Genotype distribution of IL-1 $\beta$  polymorphism -511C/T in the promoter region among CC patients and controls is summarized in **Table 2**. Overall, three genotypes (CC, CT, and TT) and two alleles (C and T) were seen in this study. Genotype

**Table 1** Clinicopathological characteristics of women with cervical cancer

Cases (n = 192)			Controls (n = 200)	
Age (years)	n	%	n	%
o 21–30	10	5.2	6	3
o 31–40	32	16.67	62	31
o 41–50	76	39.59	102	51
o 51–60	44	22.92	16	8
o 61–70	26	13.54	10	5
o >70	4	2.08	4	2
o Mean age	49.8 years		44.9 years	
Histopathological analysis				
o Nonkeratinizing SCC	20	10.42	N/A	N/A
o Keratinizing SCC	164	85.42	N/A	N/A
o Adenocarcinoma	8	4.16	N/A	N/A
FIGO staging				
o Stages I	42	21.87	N/A	N/A
o Stages II	110	57.3	N/A	N/A
o Stages III	30	15.62	N/A	N/A
o Stages IV	10	5.21	N/A	N/A
Tobacco chewing	96	50	57	28.5
Smoking	36	18.75	16	8

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics; N/A, not available; SCC, squamous cell carcinoma.

**Table 2** Distribution of genotype and allele of interleukin-1 $\beta$  (-511C/T and +3953 C/T) single nucleotide polymorphism in cervical cancer and control samples

IL-1 $\beta$ -511 C/T	Genotype frequencies				Association analysis	
	Patients		Controls		Patients vs. controls	
Genotype	n = 192	%	n = 200	%	OR (95% CI)	p-Value
Codominant model						
o CC	32	16.67	82	41	Reference	Reference
o CT	87	45.31	62	31	3.60 (2.132–6.063)	<0.001
o TT	73	38.02	56	28	3.34 (1.952–5.713)	<0.001
Dominant model						
o CC	32	16.66	82	41	Reference	Reference
o CT + TT	160	83.34	118	59	3.47 (2.17–5.57)	<0.001
Recessive model						
o CC + CT	119	61.98	144	72	Reference	Reference
o TT	73	38.02	56	28	1.58 (1.03–2.41)	0.034
Allele						
o C	151	39.33	226	56.5	Reference	Reference
o T	233	60.67	174	43.5	2.00 (1.51–2.66)	0.0001
IL-1 $\beta$ +3953 C/T						
Codominant model						
o CC	69	35.94	67	33.5	Reference	Reference
o CT	71	36.98	79	39.5	0.87 (0.54–1.38)	0.565
o TT	52	27.08	54	27	0.93 (0.56–1.55)	0.865
Dominant model						
o CC	69	35.94	67	33.5	Reference	Reference
o CT + TT	123	64.06	133	61.5	0.90 (0.59–1.36)	0.612
Recessive model						
o CC + CT	140	72.92	146	73	Reference	Reference
o TT	52	27.08	54	27	1.00 (0.64–1.57)	0.985
Allele						
o C	209	54.42	213	53.3	Reference	Reference
o T	175	45.58	187	46.8	0.95 (0.72–1.26)	0.741

Abbreviations: CI, confidence interval; IL, interleukin; OR, odds ratio.

frequencies in cases were (CC, CT, and TT) 16.67%, 45.31%, and 38.02% versus 41, 31, and 28% as compared to controls. The allele frequencies were 0.61 for the C allele (ancestral allele) and 0.60 for T allele (variant allele) in the cases while in the controls 0.56 and 0.43 for C and T alleles, respectively. Statistical analyses for genotype and allele frequencies included codominant, dominant, and recessive models, as summarized in **Table 2**. C/T and T/T genotype frequencies were higher in cases as compared to controls ( $p < 0.001$ ). As compared to controls, CC patients had a higher frequency of C/T + T/T genotype ( $p < 0.001$ ). Frequency of T allele was higher in cases as compared to controls ( $p = 0.0001$ ). Women with the C/T genotype (OR, 3.60; 95% CI, 2.132–6.063), T/T genotype (OR, 3.34; 95% CI, 1.952–5.713), C/T + T/T genotypes (OR, 3.47; 95% CI, 2.17–5.57), and T allele (OR, 2.00; 95%

CI, 1.51–2.66) were more likely to develop CC. The polymorphism of IL-1 $\beta$  -511C/T has been linked significantly to CC.

#### IL-1 $\beta$ +3953C/T Polymorphism

IL-1 $\beta$  +3953C/T polymorphism frequency distribution between CC cases and controls is summarized in **Table 2**. In this study, three genotypes and two allele were observed. Frequencies of genotypes were C/C 35.94%, C/T 36.98%, and T/T 27.08% in CC patients group and 33.50%, 39.50%, and 27% in the control group, respectively. In the controls, the allele frequencies for alleles C (ancestral allele) and T (variant allele) were 53.3% and 46.80%, respectively, whereas in the cases, the allele frequencies for alleles C and T were 54.42% and 45.58%, respectively. When compared to the controls, there was no significant association found ( $p > 0.05$ ).

Data confirming whether IL-1 $\beta$  (-511C/T and +3953C/T) polymorphism is associated with tobacco chewing and smoking are summarized in **Table 3**. On the comparison to controls there was no association found among genotype and allele frequencies between tobacco chewers and smokers ( $p > 0.05$ ). In context of -511C/T polymorphism, in the individuals carrying C/T and T/T genotypes (OR, 1.79; 95% CI, 0.91–3.54;  $p = 0.09$  and OR, 2.41; 95% CI, 0.46–12.76;  $p = 0.28$ ), T allele (OR, 1.58; 95% CI, 0.93–2.68;  $p = 0.09$ ) was not associated with CC susceptibility in tobacco chewers

**Table 3** Distribution of genotype and allele frequency of interleukin-1 $\beta$  (-511C/T and +3953 C/T) single nucleotide polymorphism with tobacco chewing and smoking versus controls

IL-1 $\beta$ -511 C/T	Genotype frequencies				Association analysis	
	Patients		Controls		Patients vs. controls	
Tobacco chewing	<i>n</i> = 96	%	<i>n</i> = 57	%	OR (95% CI)	<i>p</i> -Value
Genotype						
o CC	41	42.71	33	57.89	Reference	Reference
o CT	49	51.04	22	38.6	1.79 (0.91–3.54)	0.09
o TT	6	6.25	2	3.51	2.41 (0.46–12.76)	0.28
o CT + TT	55	57.31	24	42.1	1.84 (0.95–3.58)	0.06
Allele						
o C	131	68.23	88	77.19	Reference	Reference
o T	61	31.77	26	22.81	1.58 (0.93–2.68)	0.09
Smoking	<i>n</i> = 36	%	<i>n</i> = 16	%	OR (95% CI)	<i>p</i> -Value
Genotype						
o CC	11	30.56	9	56.25	Reference	Reference
o CT	23	63.89	6	37.5	3.14 (0.89–11.04)	0.06
o TT	2	5.55	1	6.25	1.64 (0.13–21.10)	0.7
o CT + TT	25	69.45	7	43.75	2.92 (0.87–9.86)	0.07
Allele						
o C	45	62.5	24	75	Reference	Reference
o T	27	37.5	8	25	1.80 (0.71–4.57)	0.21
IL-1 $\beta$ +3953 C/T						
Tobacco chewing	<i>n</i> = 96	%	<i>n</i> = 57	%	OR (95% CI)	<i>p</i> -Value
Genotype						
o CC	49	51.04	23	40.35	Reference	Reference
o CT	39	40.62	33	57.89	0.55 (0.28–1.09)	0.08
o TT	8	8.34	1	1.76	3.76 (0.44–31.82)	0.19
o CT + TT	47	48.96	34	59.65	0.65 (0.33–1.26)	0.2
Allele						
o C	137	71.35	79	69.3	Reference	Reference
o T	55	28.65	35	30.7	0.91 (0.55–1.50)	0.7
Smoking	<i>n</i> = 36	%	<i>n</i> = 16	%	OR (95% CI)	<i>p</i> -Value
Genotype						
o CC	24	66.67	5	31.25	Reference	Reference
o CT	11	30.56	10	62.5	0.23 (0.06–0.83)	0.2
o TT	1	2.77	1	6.25	0.21 (0.01–3.92)	0.25
o CT + TT	12	33.34	11	68.75	0.23 (0.06–0.80)	0.01
Allele						
o C	59	81.95	20	62.5	Reference	Reference
o T	13	18.05	12	37.5	0.37 (0.14–0.93)	0.03

Abbreviations: CI, confidence interval; IL, interleukin; OR, odds ratio.

**Table 4** Genotype and allele frequencies of interleukin-1 $\beta$  -511C/T and +3953C/T gene and their association with stages of cervical cancer and controls

IL-1 $\beta$ -511 C/T	Controls		Cervical cancer with stages I and II (%)		Odds ratio (95% CI)	p-Value	Cervical cancer with stages III and IV (%)		Odds ratio (95% CI)	p-Value
	n = 200	%	n	%			n	%		
Genotype frequency										
o CC	82	41	21	17.36	Reference	Reference	11	15.51	Reference	Reference
o CT	62	31	54	44.63	3.40 (1.86–6.21)	0.0005	33	46.47	3.97 (1.86–8.47)	0.0002
o TT	56	28	46	38.01	3.21 (1.73–5.95)	0.0001	27	38.02	3.59 (1.65–7.83)	0.0008
o CT + TT	118	59	100	82.64	3.31 (1.91–5.73)	0.0001	60	84.5	3.79 (1.88–7.65)	0.0001
Allele										
o C	226	56.5	96	39.67	Reference	Reference	55	38.73	Reference	Reference
o T	174	43.5	146	60.33	1.98 (1.43–2.73)	0.0003	87	61.27	2.05 (1.39–3.04)	0.0002
IL-1 $\beta$ +3953 C/T										
o CC	67	33.5	35	35.35	Reference	Reference	34	36.56	Reference	Reference
o CT	79	39.5	36	36.36	0.87 (0.49–1.54)	0.637	35	37.64	0.87 (0.49–1.55)	0.642
o TT	54	27	28	28.29	0.96 (0.52–1.77)	0.889	24	25.8	0.88 (0.46–1.65)	0.681
o CT + TT	133	61.5	64	64.65	0.92 (0.56–1.53)	0.75	59	63.44	0.87 (0.52–1.46)	0.608
Allele										
o C	213	53.25	106	53.54	Reference	Reference	103	55.37	Reference	Reference
o T	187	46.75	92	46.46	0.99 (0.70–1.39)	0.947	83	44.63	0.92 (0.65–1.30)	0.63

Abbreviations: CI, confidence interval; IL, interleukin.

and smokers as compared to controls, as presented in **Table 3**.

As shown in **Table 4**, a strong correlation between the genotypes of the IL-1 $\beta$  -511C/T polymorphism and the clinical stage of CC patients who met FIGO criteria was confirmed. Individuals carrying C/T (OR, 3.40; 95% CI, 1.86–6.21;  $p = 0.0005$ ), T/T (OR, 3.21; 95% CI, 1.73–5.95;  $p = 0.0001$ ), and C/T + T/T genotypes (OR, 3.31; 95% CI, 1.91–5.73;  $p = 0.0001$ ) along with T allele (OR, 1.98; 95% CI, 1.43–2.73;  $p = 0.0003$ ) of IL-1 $\beta$  -511C/T were significantly associated with stages I and II of CC. Similarly, C/T, T/T, and C/T + T/T genotypes and T allele of IL-1 $\beta$  -511C/T polymorphism were also significantly associated with stages III and IV: (OR, 3.97; 95% CI, 1.86–8.47;  $p = 0.0002$ ), (OR 3.59; 95% CI, 1.65–7.83;  $p = 0.0008$ ), and (OR 3.79; 95% CI, 1.88–7.65;  $p = 0.0001$ ); and (OR 2.05; 95% CI, 1.39–3.04;  $p = 0.0002$ ). However, there is no correlation between CC patients' clinical stage and the IL-1 $\beta$  +3953C/T genotypes, as shown in **Table 4**.

## Discussion

CC is still a major public health issue in both developed and developing nations. CC is mostly caused by high-risk HPV, according to several prior epidemiological studies.<sup>15</sup> CC is widely recognized to be a multifaceted disease wherein genetic and environmental factors also play key roles in development. Environmental variables include lifestyle, exposure to tobacco-derived carcinogens, and kitchen smoke,

whereas genetic variables include inheritance of genetic traits or gene variations related to carcinogenesis.<sup>16</sup>

Production of proinflammatory cytokines such as IL-18 and IL-1 $\beta$  triggers by multiprotein oligomer inflammatory.<sup>17</sup> The elevated level and or expression of IL-1 $\beta$  may induce an inflammatory cascade that results in cancer-related inflammation including chemotaxis, angiogenesis, and adhesiveness.<sup>18</sup> Polymorphisms in cytokine genes can influence the immune response to HPV infection, altering the risk of CC development.<sup>19</sup> The p53 gene degradation by the oncogenic protein HPV E6 is the most well-known carcinogenic pathway in CC.<sup>20</sup> Inflammatory cytokines have also been found to cause DNA damage and prevent DNA repair.<sup>21</sup>

Our study revealed that in IL-1 $\beta$  -511C/T polymorphism, T allele was significantly linked with CC risk with up to twofold increase ( $p < 0.0001$ ). The women with C/T and/or T/T genotype were strongly related with an increased CC risk of up to 3.60–3.34 folds ( $p < 0.001$ ). Kang et al establish that carriers of the IL-1 $\beta$  -511 C/T or T/T genotypes had a greater risk of CC with an OR of 2.42 in Korean women, which is consistent with our findings.<sup>22</sup> Singh et al also have reported that women with T/T genotype of IL-1 $\beta$  -511 C/T polymorphism were strongly linked with an increased CC risk in Indian population.<sup>23</sup> Numerous studies have revealed the link between IL-1 $\beta$  -511C/T gene polymorphism and cancers including gastric,<sup>24</sup> liver,<sup>25</sup> breast,<sup>26</sup> and lung.<sup>27</sup> However, the results remain inconclusive in different populations and various disease models.

Our study revealed that IL-1 $\beta$  -511C/T and T/T genotypes were associated with increased risk of CC as compared to controls ( $p < 0.001$ ). As a result, genotypes of the IL-1 $\beta$  polymorphism may be linked to a higher reactivity to carcinogens (like HPV infection). Therefore, inherited genetic variations in the IL-1 $\beta$  gene may play a significant role in CC susceptibility, also indicating that IL-1 $\beta$  could potentially be a cause for CC. El-Omar et al reported that polymorphism in IL-1 $\beta$  -511C/T was associated with susceptibility to gastric cancer and also stated the T allele has been reported to be linked with increase in transcriptional activities.<sup>28</sup> So, due to its association with another polymorphism of the IL-1 locus, which can directly alter the IL-1 $\beta$  gene expression, the -511C/T polymorphism may still be influencing cancer susceptibility. Wu et al revealed that T/T versus C/C, C/T versus C/C, and C/T+T/T versus C/C of IL-1 $\beta$  -511C/T polymorphism have considerably enhanced the risk of CC in the Asian group.<sup>29</sup> We contribute to these data, showing that susceptibility to CC risk linked to the C/T, T/T, and C/T+T/T genotypes becomes more significant in cases as compared to controls and also in tumor stage, which resembles with Wu et al. However, the findings of subgroup analysis revealed contrary effects of IL-1 $\beta$  -511C/T polymorphism with CC. According to Zidi et al, C/C genotype was associated with enhanced risk of development of CC among Tunisian women, while T/T genotype and T allele of IL-1 $\beta$  -511C/T polymorphism may be protective factor against CC development.<sup>30</sup> In contrast, findings of Al-Tahhan et al demonstrated that individuals carrying T/T genotype and T allele of IL-1 $\beta$  -511C/T polymorphism may be acknowledged as candidate biomarkers for CC development among Egyptian women.<sup>31</sup>

The results of our investigation showed a strong correlation between the polymorphism of IL-1 $\beta$  -511C/T and vulnerability to CC. The allele analysis supported the connection between carrying the T allele and an elevated risk of CC in women with the C/T, T/T, and C/T+T/T genotypes. Our findings also showed the necessity to expand prevention efforts regarding the disease's relevance and promote gynecological follow-ups due to the high prevalence of and death due to CC. A potential strategy for determining CC risk is to create a susceptibility framework that includes both individual traits that raise the likelihood of the disease's occurrence and genetic biomarkers like the IL-1 $\beta$  -511C/T polymorphism.

## Conclusion

In summary, this is preliminary experimental research to investigate the relationship between putatively functional genetic variations of the IL-1 $\beta$  gene and CC risk. Our findings add to the growing body of evidence linking IL-1 $\beta$  gene variation to CC susceptibility. Our findings could shed fresh light on proinflammatory cytokines, inflammation, and the etiology of CC. Elevated serum levels are linked to a higher chance of developing CC as compared to controls.

## Limitations of the Study

However, these findings should be interpreted with caution, and additional research with a bigger sample size and various demographics should be done to confirm our findings.

### Authors' Contributions

Pushpendra D. Pratap conceived the study design, participated in data collection, and carried out the laboratory work. Syed Tasleem Raza, Ghazala Zaidi, and Shipra Kunwar revised the manuscript. Ale Eba and Muneshwar Rajput assisted for technical support. All authors read and approved the final manuscript.

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### Conflict of Interest

None declared.

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