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Association between circulating interleukin-1 beta (IL-1β) levels and IL-1β C–511T polymorphism with cervical cancer risk in Egyptian women

Magdy A. Al-Tahhan · Rasha L. Etewa · Manal M. El Behery

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Abstract Cancer cervix is one of the leading causes of cancer-related mortality among women worldwide. It is believed that the host genetic factors such as inflammation-induced cytokines may play a role in cervical carcinogenesis. The interleukin-1β (IL-1β) gene contains several single nucleotide polymorphisms. One of them, C–511T, which in the promoter region has been associated with increased IL-1β production and with increased risk of developing cancers. We assessed the association between the IL-1β C–511T polymorphism and cervical cancer risk in a case–control study among 100 histopathologically confirmed Egyptian women with cervical cancer and 50 age-matched, cervical cytology negative, healthy controls by polymerase chain reaction-restriction fragment length polymorphism. Plasma levels of IL-1β were assayed by enzyme-linked immunosorbent assay. There was significant increase in the mean plasma IL-1β level in cervical cancer cases (43.40 $\pm$ 25.95 pg/ml) when compared with controls (30.51 $\pm$ 18.28 pg/ml, $P = 0.002$). The plasma levels above the 75th percentile of controls (IL-1$\beta \geq$ 45.74 pg/ml) were significantly associated with a 2.49-fold increased risk of cervical cancer. The significant increase in IL-1β concentration in cervical cancer cases was observed only among cervical cancer cases carrying C–511T variant genotypes. T/T genotype of IL-1β polymorphism was significantly higher in cervical cancer cases compared with controls (57 vs. 38%; OR = 2.16; $P = 0.028$) and the T allele carriage was significantly associated with cervical cancer risk (OR = 2.00, 95% CI = 1.19–3.38, and $P = 0.008$). In conclusion, plasma IL-1β level and IL-1β C–511T polymorphism may be considered as candidate biomarkers for cervical cancer in Egyptian women.

Keywords Cervical cancer · Interleukin 1β gene · C–511T polymorphism

M. A. Al-Tahhan · R. L. Etewa (✉)
Department of Medical Biochemistry,
Zagazig University, Zagazig 44519, Egypt
e-mail: rashalotfi@yahoo.co.uk

M. M. El Behery
Department of Obstetrics and Gynecology,
Zagazig University, Zagazig 44519, Egypt

Introduction

Cancer cervix is one of the leading causes of cancer-related mortality among women worldwide. It occupies either the top rank or second among cancers in women in the developing countries [1]. It is well-known that the infection with human papillomavirus (HPV) plays a central role in the pathogenesis of cervical cancer, as it causes chronic infection of keratinocytes in the cervix [2]. Also, HPV is a well-known oncogenic dsDNA virus linked to cervical cancer, and associated with the high-risk group of viral oncogenes E6 and E7 [3]. Although many women are infected with high-risk types of HPV, only a subset of infected women develops cervical cancer, suggesting that other cofactors must be present for the development of malignancy [4]. These inter-individual differences in cancer susceptibility have been linked to genetic polymorphisms [5].

Cytokines, as the products of host response to inflammation, play an important role in the defense against viral infections [6]. In cervical cancers, a number of previous reports have suggested that chronic inflammation is associated with the precancerous intraepithelial lesion and cancer of uterine cervix [7–9].

Interleukin-1 beta (IL-1β) is a pro-inflammatory cytokine produced mainly by blood monocytes and tissue macrophages and has been implicated in mediating both acute and chronic inflammations [10]. There were several reports supporting the positive association between increased IL-1β secretion and cervical and other cancers risk [11, 12]. We hypothesized that polymorphisms of the IL-1β gene might regulate production and bioactivity of its product, and increase the risk of cervical cancer.

The gene for IL-1β is located on chromosome two (2q14) that contains a cluster of the other IL-1 genes [13]. IL-1β gene contains several single nucleotide polymorphisms. One of them is –511C/T, which is located in the promoter region [14, 15], and it has been associated with increased intracellular IL-1β production [16] and with increased risk of developing cancers [17–20].

The aim of this study was to evaluate the possible association of plasma IL-1β levels and IL-1β C–511T polymorphism with the risk of cervical cancer in Egyptian women in a case–control study.

Subjects and methods

Subjects

One hundred Egyptian women with clinically and histologically confirmed cervical carcinoma were enrolled in this study between January 2008 and June 2010 from various Gynecology clinics at Sharkia, Egypt. Exclusion criteria included patients with previous cancers, other metastasized cancers, and/or previous radiotherapy or chemotherapy. Fifty age-matched cervical cytology negative women with no signs or symptoms of malignancy were randomly selected from various clinics at Sharkia, Egypt; and were taken as controls. Detailed data regarding education, menstrual and reproductive history, hormonal contraception, smoking history, and family history of cancer (any reported cancer in first-degree relatives) were obtained from each participant. Written informed consent was obtained from each participant in the study.

The study protocol was approved by the ethical committee of Faculty of Medicine, Zagazig University.

Blood sampling

For each individual enrolled in the study, 3 ml of venous blood was collected in EDTA-treated tubes for DNA extraction and plasma separation for IL-1β assay. The plasma was separated with the help of centrifugation, coded, and stored at −20°C until further analysis.

DNA extraction

Blood samples from all participants were coded and analyzed in a blind manner for genomic DNA extraction using QIAampDNA Blood Mini Kit supplied by Qiagen GmbH (Hilden, Germany) as described in the user manual. The quality of the genomic DNA was tested using agarose gel electrophoresis.

Cytokine assay

Plasma levels of IL-1β were measured by an enzyme-linked immunosorbent assay using the Quantikine human IL-1β ELISA assay (R and D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. The assay employed the quantitative sandwich enzyme immunoassay technique. The intra- and inter-assay coefficient of variation were <12%.

IL-1β –511 genotype analysis

The IL-1β promoter polymorphism at position –511 was analyzed by polymerase chain reaction amplification followed by restriction fragment length polymorphism (PCR-RFLP) analysis after *Ava*I digestion according to Achyut et al. [21] using: forward primer 5′-TGG CAT TGA TCT GGT TCA TC-3′; reverse primer 5′-GTT TAG GAA TCT TCC CAC TT-3′. The PCR was carried out in a final volume of 25 µl containing 100 ng of template DNA, 25 pmol of each primer (Biosource Europe SA, Germany), and 12.5 ul of 2x Dream *Taq*^{TM} Green PCR Master Mix (MBI Fermentas, Germany).

The amplification protocol was as follow: 94°C for 5 min; then 35 cycles of 94°C for 30 sec, 56°C for 30 s, and 72°C for 30 s; then 72°C for 5 min using thermal cycler PTC-100 machine (MJ Research, Inc., Watertown, MA, USA). 15 µl of the amplified product was digested with 5 U of *Ava*I (New England Biolabs, Beverly, MA, USA) at 37°C for 3 h, then the PCR products were separated in 2% agarose electrophoresis system then visualized with ethidium bromide staining under ultraviolet transillumination with 100 bp-ladder (Pharmacia Biotech, USA) and photographed.

Statistical analysis

The data was processed by the SPSS (SPSS Inc., Chicago, IL, version 11, USA) statistical package. Two-tailed *t*-test was used for continuous variables and Chi-square (χ^2) test was used for categorical variables. Hardy–Weinberg equilibrium analyses were performed to compare observed and expected genotype frequencies using the χ^2 test. The associations between genotypes and cervical cancer risk

were estimated by the odds ratios (OR) and their 95% confidence intervals (CI) from multivariate logistic regression analyses with adjustments for age, smoking, menopausal status, parity, and family history of cancer. P value of <0.05 was considered statistically significant.

Results

Demographic data of the participants

From 100 cancer cervix patients, 89 women had squamous cell carcinoma, 8 women had adenocarcinoma, and 3 women had adenosquamous cell carcinoma. Comparing patients with cervical cancer versus controls; there were no significant differences in the mean age ($P = 0.789$), mean age at menarche ($P = 0.263$), mean age at menopause ($P = 0.560$), use of hormonal contraception ($P = 0.929$), and smoking status ($P = 0.466$). Compared with the controls, the cervical cancer cases were married at a significantly younger age ($P = 0.002$), had a significantly lower age at having first live birth ($P < 0.001$), had a greater number of children ($P = 0.013$), and had higher frequency of family history of any cancers ($P = 0.043$); Table 1.

IL-1β C–511T polymorphism analysis and cervical cancer risk

PCR-RFLP analysis of *Ava*I digestion of the IL-1β C-511T polymorphism is shown in the figure.

The distributions of the genotype and allele frequencies for IL-1β C–511T polymorphism in cancer cervix patients and controls are represented in Table 2. The genotype frequencies were conformed to the Hardy–Weinberg equilibrium in controls ($P = 0.917$) and in patients ($P = 0.932$). In patients with cancer cervix, the frequencies of C/C, C/T, and T/T genotypes were 7, 36, and 57%, respectively; and in controls, the frequencies were 18, 44, and 38%, respectively. As regard the risk of development of cancer cervix, the C/C genotype and C wild allele were taken as references, the logistic regression analysis with adjustment for the age, smoking, menopausal status, parity, and family history of cancer showed that the T/T genotype was significantly associated with an increased risk of cancer cervix (OR 2.16, 95% CI, 1.07–4.33, and $P = 0.028$) and C/T genotype was found to be lower in cases (36%) compared with healthy controls (44%), but difference was not statistically significant (OR 0.72, 95% CI 0.36–1.43, and $P = 0.343$). When the C/T and T/T genotypes were taken together, we found that C/T and T/T genotypes were associated with OR of 2.91 (95% CI was 1.01–8.36 and $P = 0.036$). The frequencies of C and T alleles in cancer cervix patients were 25 and 75%; and in controls were 40 and 60%, respectively. The carriage of T allele was significantly associated with cervical cancer risk (OR 2.0, 95% CI 1.19–3.38, and $P = 0.008$) in cancer cervix patients versus controls.

Plasma IL-1β levels and cervical cancer risk

The mean plasma level of IL-1β was 43.40 ± 25.95 pg/ml in cervical cancer cases, and 30.51 ± 18.28 pg/ml in the controls with significant increase in cervical cancer cases ($P = 0.002$). The plasma IL-1β level of the 75th percentile in controls (45.74 pg/ml) was used as a cutoff value for the calculation of OR. After adjustment for age, smoking status, menopausal status, family history of cancer and parity; 44 out of 100 (44%) of the cervical cancer women and 12

Table 1 Demographic data of cancer cervix patients ($n = 100$) and controls ($n = 50$)

Variables	Cancer cervix patients	Controls	P value*
Age (yrs)			
Range	21–78	20–78	
Mean ± SD	49.31 ± 11.98	48.71 ± 9.64	0.789
Age at menarche, mean ± SD (yrs)	13.87 ± 1.13	13.64 ± 1.28	0.263
Age at marriage, mean ± SD (yrs)	18.36 ± 3.59	20.31 ± 3.46	0.002
Age at menopause[a], mean ± SD (yrs)	48.98 ± 3.54	48.51 ± 2.99	0.560
Age at first birth child[b], mean ± SD (yrs)	18.29 ± 3.38	23.31 ± 3.30	<0.001
Hormonal contraception, n (%)			
Never	31	17	
Past	39	19	
Current	30	14	0.929
Number of children	3.10 ± 1.33	2.55 ± 1.30	0.013
Family history of any cancer, n (%)	29 (29)	7 (14)	0.043
Smoking status, n (%)	7 (7)	2 (4)	0.466

* Two-tailed t-test for continuous variables; Chi-square (χ^2) test for categorical variables

[a] Data available for 55 cases and 26 controls

[b] Data available for 89 cases and 45 controls

Table 2 Genotype distributions and allelic frequencies of IL-1β C–511T polymorphism in cancer cervix patients ($n = 100$) and controls ($n = 50$)

IL-1β C–511T polymorphism	Cancer cervix patients, *n* (%)	Controls, *n* (%)	Odds ratio (95% confidence interval)*	*P* value
Genotypes				
C/C	7 (7)	9 (18)	1 (reference)	–
C/T	36 (36)	22 (44)	0.72 (0.36–1.43)	0.343
T/T	57 (57)	19 (38)	2.16 (1.07–4.33)	0.028
Combined C/T and T/T genotypes	93 (93)	41 (82)	2.91 (1.01–8.36)	0.036
Alleles				
C allele	50 (25)	40 (40)	1 (reference)	
T allele	150 (75)	60 (60)	2.00 (1.19–3.38)	0.008

* Odds ratio and 95% confidence interval were derived from logistic regression analysis with adjustment for the age, smoking, menopausal status, parity, and family history of cancer comparing the homozygous wild-type genotype/allele (C/C for IL-1β) with other genotypes/alleles

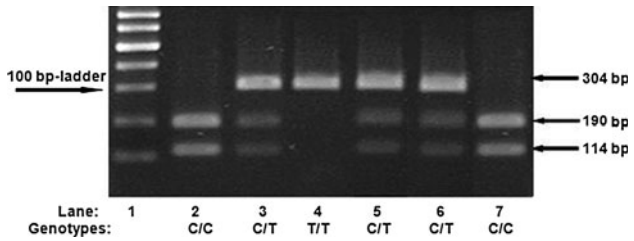

Fig. 1 PCR-RFLP analysis of *Ava*I digestion of interleukin-1β C-511T polymorphism. *Lane 1* 100 bp-ladder; *lanes 2* and *7* C/C genotype, two bands of 114, 190 bp; *lanes 3*, *5*, and *6* C/T genotype, three bands of 114, 190, and 304 bp; *lane 4* T/T genotype, a single band of 304 bp

of the controls (24%) were above this level which significantly associated with cervical cancer (OR 2.49; 95% CI was 1.16–5.32, $P = 0.017$); Table 3.

In the stratified analysis of plasma IL-1β levels on cervical cancer risk by IL-1β C–511T polymorphism; patients with cancer cervix were divided according to the genotypes of IL-1β C–511T; the mean plasma level of IL-1β was highest in patients with cervical cancer with the T/T (44.22 ± 23.26 pg/ml), intermediate in C/T patients (43.10 ± 25.23 pg/ml) and lowest in C/C patients (38.29 ± 27.03 pg/ml). In the controls, the mean plasma level of T/T genotype carriers was 30.37 ± 15.75 pg/ml, of C/T genotype was 28.51 ± 16.78 pg/ml, and of C/C genotype was 35.68 ± 20.42 pg/ml. There was significant increase in IL-1β concentration cervical cancer cases versus controls only among carriers of IL-1β –511T variant genotypes ($P = 0.020$ for C/T and 0.018 for T/T genotype); Table 4.

Discussion

In this study we aimed to evaluate the possible role of plasma IL-1β levels and IL-1β C–511T polymorphism with the risk of cervical cancer. We found significantly elevated plasma levels of IL-1β in cervical cancer cases, and IL-1β –511T variant (combined C/T and T/T) genotypes was significantly associated with increased risk of cervical cancer in Egyptian women; and more importantly, the differences of plasma IL-1β concentrations between cervical cancer patients and controls were observed only among subjects carrying IL-1β variant genotypes. These results support our hypothesis that –511T allele might be associated with increased production of IL-1β and that IL-1β may play a role as host factors promoting cervical carcinogenesis.

By using multivariate analysis and after correction of other factors, we found that plasma IL-1β level is a risk factor for cervical cancer and IL-1β may be involved in early step of cervical carcinogenesis and that inter-individual difference of IL-1β secretion may affect individual susceptibility to cervical cancer progression. In accordance

Table 3 IL-1β levels and cutoff value[a] (75th percentile in controls) in cancer cervix patients ($n = 100$) and controls ($n = 50$)

	Cancer cervix patients	Controls	OR (95% CI)*	*P* value
Plasma IL-1β level (pg/ml) (mean ± SD)	43.40 ± 25.95	30.51 ± 18.28		0.002
Above cutoff value, *n* (%)	44 (44)	12 (24)	–	
Below cutoff value, *n* (%)	56 (56)	38 (76)	2.49 (1.16–5.32)	0.017

* Odds ratio (OR) and 95% confidence interval (CI) were derived from logistic regression analysis with adjustment for the age, smoking, menopausal status, parity, and family history of cancer

[a] 45.74 pg/ml

Table 4 Plasma IL-1β levels in IL-1β C–511T polymorphism carriers in cancer cervix patients ($n = 100$) and controls ($n = 50$)

IL-1β genotypes	Plasma IL-1β levels (pg/ml)		*P* value
	Cancer cervix patients	Controls	
C/C, *n* (mean ± SD)	7 (38.29 ± 27.03)	9 (35.68 ± 20.42)	0.829
C/T, *n* (mean ± SD)	36 (43.10 ± 25.23)	22 (28.51 ± 16.78)	0.020
T/T, *n* (mean ± SD)	57 (44.22 ± 23.26)	19 (30.37 ± 15.75)	0.018

to our results, Qian et al. [22] have also found increased plasma levels of IL-1β in cancer cervix in Chinese women. These results were supported by Tjiong et al. [23] and Behbakht et al. [24] who have found that cytokines, including IL-1β, have been correlated to the risk of cervical cancer and the levels of the IL-1β increased in the cervicovaginal washings of cervical cancer patients. On contrary to these results Majeed et al. [25] have found that women with high and intermediate IL-1β secretor phenotypes may be more susceptible to lower grade lesions and may be protected against cervical carcinoma.

Immune response to HPV infection can be influenced by polymorphisms in cytokine genes modifying the risk of the development of cancer cervix [26, 27]. The most well-known carcinogenic mechanism in cervical cancer is the degradation of the p53 gene by oncogenic HPV E6 protein [28, 29]. Mutations in the p53 gene have been suggested to be associated with cytokines including IL-1β overexpression [30]. Hybertson et al. [31] have found that intratracheal instillation of IL-1 in rats caused hydrogen peroxide production in lung tissue initiating neutrophil influx and stimulating the release of reactive oxygen species. Also, inflammatory cytokines have been shown to induce DNA damage and inhibit DNA repair [32]. Moreover, IL-1β has been shown to reduce apoptosis by changing the ratio of BCL-2/BAX proteins [33]. Therefore, higher production of IL-1β found in our results may lead to increase in p53 mutation load, and the increased level of IL-1β may play a role not only in HPV-related cervical carcinogenesis but also in HPV-nonrelated cervical carcinogenesis.

This study revealed that the carriage of T allele was significantly associated with cervical cancer risk up to twofold increase, and the women with T/T genotype were significantly associated with an increased risk of cancer cervix up to 2.16-fold. In consistence with our results, Kang et al. [4] also have reported that the carriers of –511 C/T or T/T genotypes were at a higher risk of cervical cancer with an OR of 2.42 in Korean women. Also, Singh et al. [5] have reported that IL-1β –511 polymorphism carriers had higher risk of cervical cancer in Indian population (2.8-fold for T/T genotype). Many studies have investigated the association between IL-1β C–511T polymorphism and cancers at different sites, such as the gastric [17, 18], breast [19], lung [20], and liver [34]. However, the results remain controversial in different populations and different disease models.

In this study, we found that –511T/T genotype was associated with higher IL-1β level in the cervical cancer cases. The observed differences between cases and controls were more prominent among variant genotypes (C/T and T/T) carriers (risk carriers). Therefore, variant genotypes of the IL-1β polymorphism may be associated with an increased response to carcinogens (like HPV infection). These results were consistent with the observation that variant genotypes and elevated IL-1β levels were associated with cervical cancer risk. So, inherited genetic polymorphism of IL-1β gene may contribute to cervical cancer susceptibility suggesting that IL-1β could also be an etiological factor. El-Omar et al. [17] have found that IL-1β –511 C>T polymorphism was associated with risk of gastric cancer and they stated that there were no differences in binding activity between IL-1β –511 genotypes, indicating that the effect of IL-1β –511 polymorphism may be mediated by linkage disequilibrium with the TATA box polymorphism (IL-1β –31T/C transition). The T allele of –511 genotype has been reported to be associated with increased transcriptional activities; but it is not simply the case in terms of circulating IL-1β levels [35, 36]. So, there is still some possibility that –511C/T polymorphism may be affecting the cancer susceptibility due to its linkage with some other polymorphism of IL-1 locus, which can directly influence the IL-1β gene expression.

There were several limitations in this study. First, although we observed significant association between both IL-1β C–511T polymorphism and plasma IL-1β levels and cervical cancer risk, the limited sample size restricted us to identify genotype–clinicopathological parameters' correlations. Second, the study did not analyze all clustered polymorphic site of IL-1β and associated genes, the haplotype analysis could not be done. Third, this study lacked the measurement of IL-1β levels in the local environment of cervix.

In conclusion, this study suggests that both plasma IL-1β level and IL-1β C–511T polymorphism may be considered as candidate biomarkers for cervical cancer and IL-1β –511T carriers have elevated risk for cervical cancer in Egyptian women. Studies looking for possible interactions between IL-1β gene polymorphism and environmental factors should

follow this study for better understanding of pathogenesis of cervical cancer, which may in future lead to better prediction of individuals who are at risk of cervical cancer.

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Conflict of interest None.

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