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EXPRESSION AND POLIMORPHISM OF *IFN-γ* GENE IN PATIENTS WITH CERVICAL CANCER

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Background: **Cervical cancer, the second most common malignancy in women worldwide, is almost invariably associated with infection by human papillomavirus (HPV). However, although many women are infected with high-risk types of HPV, only a subset of infected women will ever develop cervical cancer. Several studies suggested that immunological components play a key role in the development of cervical cancer. Interferon gamma (IFN-γ) is a cytokine produced by activated T cells and natural killer (NK) cells that enhances cellular immune responses by increasing T-cell cytotoxicity and NK cell activity.** ***Aim:*** **To study single nucleotide polymorphism (SNP), T to A, located at the +874 position and measure IFN-γ messenger RNA (mRNA) at the tumor site.** ***Methods:*** **DNA was isolated from peripheral blood of 200 patients with cervical cancer and 200 healthy controls. The allele polymorphism at position +874 in the *IFN-γ* gene was studied by ARMS-PCR (Amplification Refractory Mutation System) and measured IFN-γ mRNA at the tumor site by means of a semi-quantitative polymerase chain reaction (sqRT-PCR) assay.** ***Results:*** **It was observed that genotypes *AT* and *AA* + *AT* increase the risk of cervical cancer (OR = 3.3, 95% CI — 2.05–5.2, $P \leqslant 0.001$ — OR = 2.9, 95% CI — 1.9–4.6, $P \leqslant 0.001$, respectively). In case of passive smokers same genotypes showed highly significant increased risk of cervical cancer (OR = 5.55, 95% CI = 2.77–11.19 — OR = 5.25, 95% CI = 2.77–10, respectively). Thus, the sqRT-PCR reflected the similar level of mRNA expression of *IFN-γ* gene in patients suffering from cervical carcinoma and healthy controls.** ***Conclusion:*** **This is the first study to provide an evidence for effecting of *IFN-γ* gene on the risk of cervical cancer in north Indian population.**
Key Words: **cervical cancer, expression, polymorphism, *IFN-γ* gene.**

Cervical cancer is the most common female malignancy in India, accounting for 26% of female cancer, with 90,000 women developing the disease each year [1]. The major risk factor for cervical cancer is the infection with specific high-risk types of human papillomavirus (HPV). Although the incidence of genital HPV infections in certain subgroups is very high, most of them regress without intervention, suggesting that other factors are also important determinants of cervical cancer development [2]. Recently, immunologic mechanisms have attracted more attention as important control mechanisms in HPV-associated carcinogenesis. Indeed, cell-mediated immunity is important in controlling both HPV infections and HPV-associated neoplasms. Cell-mediated immunity is regulated by cytokines that are secreted primarily by T-helper (Th) cells and macrophages [3].

IFN-γ is a Th1 cytokine and plays important roles in modulating almost all the immune responses, such as hematopoiesis, T-cell differentiation, antiproliferative, antitumor, and antiviral activities [4]. It is produced during viral infection (secreted by T lymphocytes, natural killer cells and antigen presenting cells) and binds to specific receptor that trigger intracellular events through Janus kinase (JAK) and signal transducers and activators of transcription (STAT) pathways [5]. It promotes the response differentiation of T and B cells, facilitating the progression of CD4+ T cells to a Th1 phenotype, the maturation of CD8+ T cells, and the immunoglobulin class switching in B cells. A single gene mapped to human chromosome 12q24.1 encodes it. The gene consists of four exons with three intervening regions [6]. A single nucleotide polymorphism ((+874T/A) located in the first intron of the human *IFN-γ* gene can putatively influence the secretion of IFN-γ [7]. Thus, high level of IFN-γ production is typically associated with effective host defense against viral infection such as HPV. Moreover, decreased intratumor expression of IFN-γ has been reported to be associated with the poor prognosis in patients with cervical cancer [8]. On the other hand, increased production of IFN-γ in tumour-associated inflammatory cells may contribute to tumor growth and progression [9]. It is also well known that chronic inflammation, such as persistent HPV infection and chronic inflammatory bowel diseases, can predispose an individual sensitivity to cancer [10]. Therefore, the role of IFN-γ in tumor development is cell-dependent and complex. Genetic polymorphisms in the *IFN-γ* gene have been shown to be associated with differing amounts of *IFN-γ* secretion and hence may be of biologic importance [11]. The polymorphic responses of the *IFN-γ* gene in host encountering HPV infection may influence an individual's susceptibility to development of cervical cancer. The IFN-γ level has decreased only in patients with advanced cervical cancer; a pronounced shift from type 1 to type 2 cytokine production is associated with more severe disease [12]. Type 1 cytokines,

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Abbreviations used: AC – adenocarcinoma; CI – confidence interval; IFN – interferon gamma; IL-2 – interleukin-2; HPV – human papillomavirus; NA – not applicable; n^c – number of cases and control; NK – natural killer; OR – odds ratio; ref – reference; RT-PCR – reverse transcriptase polymerase chain reaction; SCC – squamous cell carcinoma; SNP – single nucleotide polymorphism.

such as IFN-γ and interleukin-2 (IL-2), increase T cell-mediated immune responses and are considered to be beneficial for antitumor immunity. Type 2 cytokines, such as IL-4, IL-5, and IL-10, inhibit Type 1 responses and promote humoral responses [13].

Several studies have reported the association between *IFN-γ* gene polymorphism at +874 with the susceptibility and clinical severity of disease, such as tuberculosis, breast cancer, chronic allograft nephropathy and *Helicobacter pylori* disease outcome [14, 15]. However, the results are varied between each ethnic group. The main aim of the present study was to determine the impact of single nucleotide polymorphism +874 of *IFN-γ* gene and its expression profile on the risk of cervical cancer in north Indian population.

MATERIALS AND METHODS

Study subjects. The case -control study involved collection of peripheral blood samples (2–5 ml) of 400 North Indian subjects. 200 cases were newly diagnosed, previously untreated and histologically confirmed as cervical cancer. The samples were collected from the Postgraduate Institute of Medical Education and Research (PGIMER) and Government Medical College (GMC), Chandigarh. The control peripheral blood samples (n = 200) were collected in the same institute from women's visiting the gynecology OPD (out patient department) clinic for routine check up without any past medical history of gynecology diseases including cervical diseases and cancer. The distribution of genotype in patients and controls were in Hardy Weinberg equilibrium. The institutional review boards at PGIMER and GMC approved this study, and all volunteer participants provided informed consent. Detailed data regarding age, education, menarche, and menopausal status, number of children, age at marriage and birth of first child, cigarette smoking history and spouse's smoking history were also obtained. The period of the study was four years from 2003 till 2007.

Polymerase chain reaction. Genomic DNA was extracted from EDTA anti-coagulated peripheral blood samples according to a standard proteinase K digestion and phenol chloroform extraction method [16]. Initial typing of the +874A/T *IFN-γ* polymorphism was performed with an amplification refractory mutation system (ARMS), reaction mixture included 50 ng DNA at 10 ng/μl, 5 μl H_2O,1.5 μl 10 × polymerase chain reaction buffer, 1.5 μl $MgCl_2$, 0.3 μl of 8 mM deoxynucleotide triphosphates (dNTPs), 0.3 μl of 10 μl allele-specific and common primers, and 0.3 μl of 2 μl control primers (human growth hormone), 0.08 μl Taq polymerase. The reaction mixture was subjected to PCR as follows: 95 °C for 1 min, 10 cycles of 95 °C for 15 s, 62 °C for15 s, 62 °C for 50 s, 72 °C for 40 s and 10 cycles of 95°for 20 s, 56 °C for 50 s, 72 °C for 50 s with final extention 70 °C for 10 min. The PCR products were analyzed by electrophoresis on 1% gel. T allele and A allele were identified by 261 bp and human growth hormone was determined by 426 bp (Fig. 1).

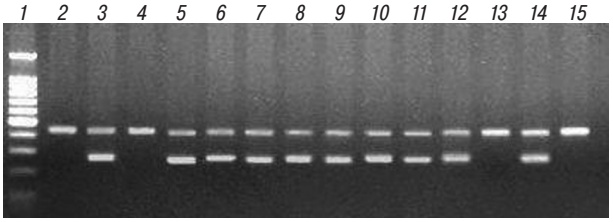

Fig. 1. PCR-ARMS genotype analysis of *IFN-γ* gene. Lane 1 is 100 bp molecular marker, lanes 2–5 (2–3 sample N7 and 4–5 sample N14) are homozygous of +874T. Lanes 6–11 (6–7 sample N9, 8–9 sample N11, and 10–11 sample N17) are heterozygous of +874T/A. Lanes 12–15 (12–13 sample N5 and 4–15 sample N6) are homozygous of +874A

Reverse transcriptase polymerase chain reaction (RT-PCR). Traditionally RT-PCR involves two steps: the RT reaction and PCR amplification. RNA is first reverse transcribed into cDNA using a reverse transcriptase; the resulting cDNA is used as templates for subsequent PCR amplification using primers specific for related genes [17]. In the present study, the TRIZOL method provided satisfactory RNA from most of the biopsied tissue samples of healthy controls [4], and patients [16] of different stages affected with cervical carcinoma in terms of yield and purity. The yield of total RNA, however, varied from 0.50–3.0 μg/μl across the tissue samples. The OD ratio of 260 nm and 280 nm for each of the RNA samples was about 1.8 to 1.9 (A_{260}/A_{280}) indicating high purity of the RNA samples, free from DNA and proteins.

The RNA was extracted from the tissue biopsies using TRIZOL reagent (Invitrogen, USA), in accordance with manufacturer's instructions. After initial optimization of conditions, each cDNA was quantified using nano-drop spectrophotometer so that same amount of starting cDNA could be used for semi-quantitative RT-PCR experiment. Thermal cycle conditions are given in Table 1.

Table 1. Thermal cycling conditions used for amplification of cDNA

Genes	Thermal cycling conditions	Product size
GAPDH	95 °C for 2 min	119 bp
	95 °C for 30 s, 55 °C for 30 s, 72 °C for 30 s – 35 cycles	
	Final extension at 72 °C for 5 min	
IFN-γ	94 °C for 2 min	295 bp
	94 °C for 50 s, 60 °C for 50 s – 35 cycles	
	Final extension at 72 °C for 5 min	

Statistical analysis. The association between polymorphism in *IFN-γ* gene with the risk of cervical cancer was estimated by computing Odds ratio (OR) and 95% confidence intervals (95% CI), using a multivariate logistic regression analysis that included several potential confounding variables. Results were entered into the Epi-Info software (Epi-Info, version 3.2, center for Disease Control and prevention, Atlanta, GA, USA) and the statistical analysis was performed using software SPSS version 10.0 (SPSS, Chicago, IL). Significance was set at $P < 0.05$.

RESULTS

Demographic variables for cases and controls have been summarized in Table 2. The variables have also been categorized for cervical squamous cell carcinoma (SCC) and adenocarcinoma (AC), 175 were identified as SSC and 25 as AC.

Table 2. Demographic characteristics of cervical cancer cases and controls[a]

Variable	Cases (200)	Controls (200)	SCC (175)	AC (25)
Age	48.55 ± 9.43	48.81 ± 9.64	48.39 ± 9.42	49.68 ± 9.64
Age at menarche	14.87 ± 1.14	14.02 ± 1.09	14.90 ± 1.16	14.68 ± 1.00
Age at marriage	16.36 ± 3.03	20.31 ± 3.46	16.68 ± 2.97	14.74 ± 2.56
Age at first birth ± child	18.39 ± 3.39	22.31 ± 4.30	18.61 ± 3.16	16.84 ± 4.45
Children number[b]	4.11	2.50	4.09 ± 1.51	4.21 ± 1.84
Age at menopause ± smoking status	48.31 ± 3.56	48.26 ± 2.39	48.29 ± 3.62	48.44 ± 3.40
- non smoker	110 (55.0)	138 (69.0)	99 (56.6)	11 (44.0)
- active + passive smoker	2 (1.0)	6 (3.0)	2 (1.1)	0
- passive smoker	88 (44.0)	56 (28.0)	74 (42.3)	14 (56.0)
OR	2		1.0	1.3
P	0.002			

Notes: [a]Values are given as mean ± SD or number (percentage) unless otherwise indicated. [b]Values are given as median for the cancer and control groups.

The mean ± SD age was 48.55 ± 9.43 years in the study group and 48.81 ± 9.64 years in the control group. Compared with the controls, the study group had young age at the time of the marriage (16.36 ± 3.03) and of the birth of first child (18.39 ± 3.39) and had a greater median number of children (4.11 *vs* 2.50). Ages at menarche and menopause were found to be comparable between cases and controls.

The distribution of *IFN-γ* genotypes is presented in Table 3. The frequency of *AA* genotype was higher in controls (50.0%), while that of *AT* genotype was more frequent in cancer cases (62.5%) in comparison to the controls (37.5%). There was no difference in *TT* genotype between cases and controls.

Table 3. *IFN-γ* genotypes in cervical cancer and healthy controls[a]

IFN-γ genotype	Case (%) 200	Control (%) 200	OR (95% CI)[b]	*P*
AA	51 (25.5)	100 (50.0)	1.0 (ref)	NA
AT	125 (62.5)	75 (37.5)	3.3 (2.05–5.2)	< 0.001
TT	24 (12.0)	25 (12.5)	1.9 (0.9–3.9)	
AT + TT	149 (74.5)	100 (50.0)	2.9 (1.9–4.6)	< 0.001

Notes: [a]Values are given as number (percentage) unless otherwise indicated. [b]ORs were adjusted for age and smoking status, significance set at $P \leqslant 0.05$. NA – not accessed.

When subdivided histologically, there was highly significant association between patients with SCC and heterozygous *AT* and combined *AT + TT* genotypes of *IFN-γ* (OR = 2.85, 95% CI = 1.78–4.57, $P < 0.001$ and OR = 2.5, 95% CI = 1.6–4.0, $P \leqslant 0.001$, respectively). Unlike decrease in OR of patients with AC was found in those having *AT* and combined *AT + TT* genotypes (OR = 0.42, 95% CI = 0.21–0.82–2.8, $P = 0.001$, OR = 0.37, 95%, CI = 0.20–0.70, $P = 0.001$ respectively) (Table 4).

Table 4. Relation between *IFN-γ* genotype and type of cervical cancer

IFN-γ	Type of cancer	n[c]	OR (95% CI)[a]	*P*
AA	Intact	51/100		NA
AT	SCC	109/75	2.85 (1.78–4.57)	< 0.001
	AC	16/75	0.42 (0.21–0.82)	0.001
TT	SCC	21/25	1.65 (0.80–3.40)	
	AC	3/25	0.32 (0.11–0.95)	0.03
AT + TT	SCC	130/100	2.55 (1.63–4.00)	< 0.001
	AC	19/100	0.37 (0.20–0.70)	0.001

Notes: [a]ORs were adjusted for age and smoking status. Significance set at $P \leqslant 0.05$. [c] – number of cases and control. NA – not accessed.

In case of smoking, significant association was observed for passive smokers with (AT) and combined *AT + TT* genotypes of *IFN-γ*, the increased risk of cervical cancer (OR = 5.5, 95% CI = 2.77–11.19, $P \leqslant 0.001$ — OR = 5.25,95% CI = 2.77–10.0, $P \leqslant 0.001$, respectively). However, the *TT* genotype showed 1.97 folds increased risk (OR = 1.97, 95% CI = 0.6–6.5) (Table 5).

Table 5. Assessments of relation between *IFN-γ* and smoking in cervical cancer and control

IFN-γ genotype	Statue of smoking	Case %	Control %	OR (95% CI)*	*P*
AA	Never smoking	32 (29.1)	63 (39.4)	1.0 (ref)	NA
AA	Passive smoking	18 (20.5)	26 (46.4)	1.36 (0.61–3.03)	
AT	Passive smoking	62 (73.8)	22 (39.3)	5.55 (2.77–11.19)	< 0.001
TT	Passive smoking	8 (9.1)	8 (14.2)	1.97 (0.6–6.5)	
AT + TT	Passive smoking	80 (90.9)	30 (53.6)	5.25 (2.77–10.0)	< 0.001

Notes: *ORs were adjusted for age. Significant set at $P \leqslant 0.05$. NA – not accessed.

Also, the present study was carried out to evaluate the tissue expression level of interferon-γ (IFN-γ) mRNA in patients with different stages (IB, IIB, IIIB, IIA) suffering from cervical carcinoma and their comparison with the healthy control. A total of 16 same cases of cervical cancer patients (53.38 ± 2.02) and 4 healthy controls (46 ± 5.8) were also enrolled for this study.

The comparison of transcript levels was performed, using semi-quantitative reverse transcriptase polymerase chain reaction (RT-PCR). Each transcript was normalized to the level of GADPH transcript, which is a common housekeeping gene and acts as internal control. The normalized values were calculated by dividing the band intensity of test transcript product to the band intensity of GADPH. As expected, the *GAPDH* gene, which was used as an internal control to normalize the expression data, showed similar level of expression in all the samples irrespective of its clinical stages. This validated the efficacy of the employment of semi-quantitative methodology in the present study. Thus the present semi-quantitative analysis reflected the similar level of mRNA expression of *IFN-γ* gene in patients suffering from cervical carcinoma and healthy controls (Fig. 2, 3).

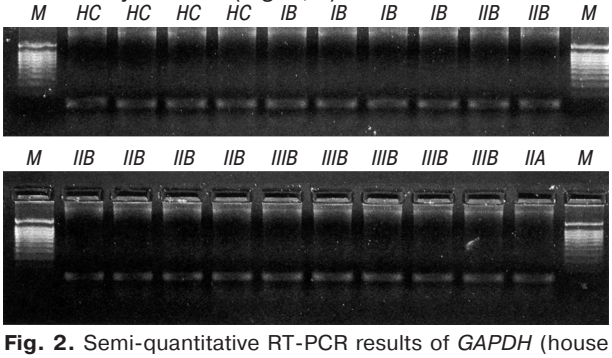

Fig. 2. Semi-quantitative RT-PCR results of *GAPDH* (house keeping) gene expression. In upper row lanes 1 and 12 represent 100 bp ladder (M), lanes 2–5: healthy control (HC), lanes 6–9: patients (IB), lanes 10–11: patients (IIB). In lower row lanes 1 and 12: 100 bp ladder (M), lanes 2–5: patients (IIB), lanes 6–10: patients (IIIB), lane 11: patient (IA)

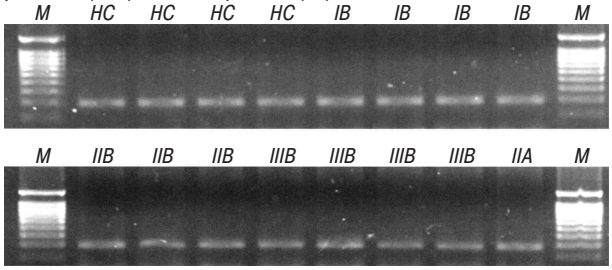

Fig. 3. Semi-quantitative RT-PCR results of *IFN-γ* gene expression. In upper row lanes 1 and 10: represent 100 bp ladder (M), lanes 2–5: healthy control (HC), lanes 6–8: patients (IB), lane 9: patient (IIB). In lower row — lanes 1 and 10: 100 bp ladder (M), lanes 2–4: patients (IIB), lanes 5–8: patients (IIIB), lane 9: patient (IA)

DISCUSSION

A novel single nucleotide polymorphism (SNP), T to A, is located at the +874 position from translation start site in the first intron of *IFN-γ* gene, which coincides with a putative NF-kB binding site that could play a fundamental role in the induction of constitutively high IFN-γ production. The association of +874 alleles *T* to *A* with a low (*AA*), medium (*AT*) and high (*TT*) cytokine production was shown *in vitro* [18]. Govan *et al.* [19] demonstrated a clear correlation between ethnicity and *IFN-γ* polymorphism across different population groups and concluded that differences in ethnicity and gene polymorphism in *IFN-γ* do not influence the development of invasive cervical cancer, but may represent an important susceptibility biomarker for other diseases. Lai *et al.* [20] also suggested that the genomic polymorphism of the *IFN-γ* gene is associated with individual susceptibility to cervical carcinogenesis. Scola *et al.* [21] did not find any association between *IFN-γ* gene polymorphism and breast cancer susceptibility.

Among HPV-infected women, IFN-γ was significantly associated with HPV-16 E6, E7, and high-risk HPV viral load in the uterine cervix. Thus, increased intralesional IFN-γ may be considered to be a prognostic marker for oncogenic potential of high-risk HPV [22]. Recent data have expanded the concept that chronic infection or inflammation is a critical component for carcinogenesis and tumor progression [23, 24]. Cytokines in the microenvironment may provide growth signals and promote genomic instability, malignant transformation and migration, which may partly explain an increased risk of cervical cancer in patients co-infected by herpes virus 2, *Chlamydia*, or other pathogens [25]. Ueda *et al.* [26] showed that SNP creating an IFN-γ response element in the FAS (CD95) promoter is associated with increased risk of cervical cancer. The higher-expression allele of *IFN-γ* gene induces higher or earlier AICD (activation-induced cell death) of lymphocytes resulting in increased risk of cervical cancer requires further investigations.

Tartour *et al.* [27] reported an association between intratumoral IFN-γ mRNA levels (as assessed by a quantitative PCR assay) and clinical outcome in patients with primary invasive cervical carcinoma. Cervical cancer patients who exhibited fewer than 1000 IFN-γ mRNA copies were identified only in the population with high risk of recurrence or low survival. Several studies have indicated a switch in the pattern of cytokine from TH1 (IL2, IFN-γ) to TH2 (IL4, IL5, IL10) groups in cancer patients compared with healthy control subjects, but the clinical prognostic value of this finding has not been determined [28, 29]. Li *et al.* [30] suggested that the major role of IFN-gamma in lung cells is to direct a pro-inflammatory gene expression program rather than having major effects on cell growth or survival or both. Dysregulation of IFN-γ levels occurs early in the course of the disease. Indeed, Pao *et al*. [31] showed that IFN-γ mRNA levels were significantly reduced in cervical intraepithelial neoplasia and cervical cancer tissue as compared with normal cervix. Moreover, the level of IFN-γ production by phytohaemagglutinin-stimulated peripheral blood mononuclear cells was reported to be lower, when the cells were from women with HPV genital infections than when they were from control subjects [32]. A defect in IFN-γ expression at the tumor site may favor tumor progression by various mechanisms. Since the decrease in IFN-γ mRNA expression in a group of cervical cancer patients may not be simply related to the number of infiltrating T or NK cells, other factors could also play a role in this phenomenon. It was shown that a decrease in IL-12 production by macrophages caused by tumor-derived factors such as prostaglandin E2 or phosphatidylserine resulted in impaired IFN-γ production in mammary tumor-bearing mice [33]. An increase in prostaglandin E2 secreted by peripheral blood mononuclear cells has also been reported during the progression of cervical carcinoma [34]. HPV did not seem to play a role in *IFN-γ* gene expression [35].

The present semi-quantitative analysis reflected the similar level of mRNA expression of *IFN-γ* genes in patients suffering from cervical carcinoma and healthy controls.

In future, it would be very pertinent to assess the expression pattern (up- and down regulation) of different cytokines and other candidate genes in patients with cervical carcinoma to understand the involvement of different gene/regulatory factors and dynamics of disease progression. The precise relationship between the altered expression of these genes and cervical tumorigenesis is a matter of great importance. This will also help in elucidating the mechanism of cytokine network that potentially affects the immunological systems during cervical cancer. Apart from mRNA level expression, efforts should also be made to assess the IFN-γ levels in serum for cervical carcinoma patients so as to correlate with their tissue level expression. Immunohistochemical and immunoblotting analysis of affected tissue with cervical carcinoma compared with normal tissue section will also be prudent to ascertain the concentration of tumor-infiltrating immune cells and protein level expression of this cytokine. Considering the fact that another cytokines plays an important role in the interactions among T cells, NK cells and macrophages and induces the IFN-γ production, efforts should also be made to understand the clinical impact of IFN- γ cytokine in patients with solid malignancies, as not much studies have been conducted in cervical carcinoma. However, results of the present study are the initial indicators and in order to validate these results, real time analysis should further be carried out to find out the mRNA copy numbers in absolute terms during different stages of cervical cancer and its comparison with healthy controls. Additionally, apart from this gene, expression of other genes known to be immunologically associated with several types of cancer should also be investigated.

The limitations of the present study are as follows: first, the present study is hospital-based, and exists in environment; therefore, it can't be free from any selection bias. Second, the current study did not include all clustered polymorphism site of *IFN-γ* and associated genes, the haplotypes analysis could not be done, third, so it would be worthwhile to perform further large scale population-based study including the analysis of vari-

ous clustered polymorphisms. In conclusion, in north Indian population, +874 *IFN-γ* genotype is significantly associated with increased risk of cervical cancer. This relationship supports the idea that polymorphism of inflammatory response genes may be host genetic susceptibility to cervical cancer. +874 *IFN-γ* polymorphism should be considered as candidate genetic factor in future study to elucidate the risk of cervical cancer.

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ЭКСПРЕССИЯ И ПОЛИМОРФИЗМ ГЕНА *IFN-γ* У БОЛЬНЫХ РАКОМШЕЙКИ МАТКИ

Рак шейки матки является второй по распространенности опухолью у женщин во всем мире, и почти неизменно ассоциирован с инфицированием вирусом папилломы человека (HPV). Тем не менее, хотя многие женщины инфицированы HPV с высоким риском развития рака шейки матки, только у некоторых из них развивается данное злокачественное заболевание. Несколько проведенных ранее исследований показали, что иммунологические компоненты играют важную роль в развитии рака шейки матки. Гамма-интерферон (IFN-γ) является цитокином, который продуцируется активированными Т-клетками и естественными киллерными клетками (NK), что приводит к повышению эффективности клеточных иммунных ответов, способствуя усилению цитотоксичности Т-клеток и активности NK-клеток. ***Цель:*** **изучить одиночный нуклеотидный полиморфизм (SNP), замену Т на А в положении +874 и оценить уровень экспрессии РНК, кодирующей IFN-γ, в опухоли.** ***Методы:*** **ДНК выделяли из периферической крови 200 больных раком шейки матки и 200 здоровых доноров. Аллельный полиморфизм гена *IFN-γ* в положении +874 изучали с помощью ARMS-PCR (Amplification Refractory Mutation System). Оценку количества кодирующей IFN-γ мРНК в опухоли проводили с помощью полуколичественной обратной полимеразной реакции (sqRT-PCR).** ***Результаты:*** **показано, что генотипы *AT* и *AA* + *AT* повышают риск развития рака шейки матки (OR = 3,3; 95% CI — 2,05–5,2; $P \leqslant 0{,}001$ — OR = 2,9; 95% CI — 1,9–4,6; $P \leqslant 0{,}001$). В случае пассивных курильщиков при тех же генотипах отмечено очень существенное повышение риска развития рака шейки матки (OR = 5,55; 95% CI = 2,77–11,19 — OR = 5,25; 95% CI = 2,77–10). В то же время sqRT-PCR показал, что мРНК IFN-γ экспрессирована на одинаковом уровне у больных раком шейки матки и у здоровых доноров.** ***Выводы:*** **проведено первое исследование, доказывающее вклад полиморфизма гена *IFN-γ* в риск развития рака шейки матки у жительниц северной части Индии.**

Ключевые слова: **рак шейки матки, экспрессия, полиморфизм, ген *IFN-γ*.**