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Research Article

Association of IL10-1082 and IFN-γ+874 Polymorphisms with Cervical Cancer among Tunisian Women

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Objective. The aim of this study was to investigate the role of IL10-1082 and IFN-γ+874 polymorphisms in susceptibility to cervical cancer among Tunisian women. *Study Design*. The IL10-1082 and IFN-γ+874 polymorphisms were analyzed by ARMS-PCR in 160 healthy women and 122 with cervical cancer. The search for associations between those polymorphisms and cervical cancer was based on the χ^2 test or Fisher's exact test. *Results*. The IFN-γ+874 polymorphism showed significant increased frequency of T allele in healthy controls compared with patients (OR = 0.71, 95% CI = 0.50–1.01, and $P = 0.0459$) and individuals with homozygote IFN-γ+874 T/T genotype were at lesser risk of cervical cancer (OR = 0.53, 95% CI = 0.31–0.92, and $P = 0.015$). However, carriers of allele have higher risk for developing cervical cancer (OR = 1.88, 95% CI = 1.09–3.24, and $P = 0.015$). At the polymorphic nucleotide in position 1082 of the IL10 promoter, no differences were found between patients and controls subjects. *Conclusion*. Our study shows that the T/T genotype polymorphism of IFN-γ+874 T>A is a protective factor for cervical cancer among Tunisian women.

1. Introduction

Worldwide, cervical cancer (CC) is the second most common malignancy in women, with approximately 80% of cases arising in developing countries [1]. The major risk factor for this tumour is infection with specific high-risk types of human papillomavirus (HPV) [2]. However, only a minority of women who have persistent infection with high-risk types of HPV develop CC. Therefore, other factors including genetics factors appear to play a role in the susceptibility and the development of cervical malignancy [3, 4].

Several studies have identified polymorphisms in cytokine gene regulatory regions that correlated with intraindividual variations in cytokine production [5, 6]. In addition, cytokine gene polymorphisms have been implicated in various human diseases [7], such as Epstein-Barr virus associated gastric carcinoma [8], Alzheimer's [9], and rheumatoid arthritis [10], and in patients presenting with severe sepsis after trauma [11], ovarian cancer [12] and the risk of CC [13–18].

One of the polymorphisms that are associated with low, medium, or high production of IL10 corresponds to an A to G transition which is situated in the promoter region of the gene at position 1082 (rs1800896) [19]. The T to A change in the +874 (rs2430561) position from the translation start site in the first intron of IFN-γ gene increases *in vitro* transcription of IFN-γ and may affect disease susceptibility [20]. The aim of the present study was to evaluate the impact of IL10-1082 G>A and IFN-γ+874 T>A polymorphisms on susceptibility to CC among Tunisian women.

2. Materials and Methods

2.1. Subjects: Cases and Controls. In a retrospective study from October 2010 to April 2012, 122 Tunisian cases with invasive CC confirmed by cervical biopsy were consecutively

Table 1: Primer sequences used in polymerase chain reactions with specific sequence primers for the detection of cytokine gene polymorphisms.

Cytokine polymorphisms		Gene sequence
Interferon-gamma (intron1 +874)	Common primer	5′-TCA ACA AAG CTG ATA CTC CA-3′
	T allele primer	5′-TTC TTA CAA CAC AAA ATC AAA TCT-3′
	A allele primer	5′-TTC TTA CAA CAC AAA ATC AAA TCA-3′
Interleukin-10 (promoter –1082)	Common primer	5′-CAG TGC CAA CTG AGA ATT TGG-3′
	G allele primer	5′-CTA CTA AGG CTT CTT TGG GAG-3′
	A allele primer	5′-CTA CTA AGG CTT CTT TGG GAA-3′
Internal control	Primer1	5′-GCC TTC CCA ACC ATT CCC TTA-3′
	Primer2	5′-TCA CGG ATT TCT GTT GTG TTT C-3′

recruited from the Salah Azeiz Oncology Institute (SAI, Tunisia). Cancer diagnosis was established by clinical examination and biopsy, confirmed by two senior pathologists of the SAI. Clinical data were obtained by questionnaire, personal interviews, and review of case records.

Tumours were staged according to the FIGO classification (International Federation of Gynecology and Obstetrics, http://www.figo.org/) [21]. Controls (160) were cancer-free women unrelated and matched for age and ethnicity. They also present negative cervical cytology and were recruited from three medical centres: Tunisian Military Hospital, Regional Hospital of Nefta, and Disponsor of Ettadhamen City. Informed consent was obtained from all participants, and the study was approved by the local ethical committee of SAI.

2.2. Blood Collection. Five milliliters of venous blood with EDTA, as an anticoagulant, was collected from each woman. For patients, the blood was obtained prior to radiation therapy or chemotherapy. Genomic DNA was extracted using QIAamp DNA blood Mini Kit (Qiagen GmbH, Hilden).

2.3. Genotyping. The polymorphisms IFN-γ+874 T>A (rs2430561) and IL10-1082 G>A (rs1800896) were genotyped in subjects using amplification refractory mutation system polymerase chain reaction method (ARMS-PCR) [22].

This reaction was performed in a total volume of 15 μL; 0.25 mM each deoxynucleotide triphosphates, 1X PCR buffer containing 10 mM Tris-HCl, pH 8.6, 50 mM KCl, 1.5 mM $MgCl_2$, 0.1 μL of genomic DNA, 0.1 units of Taq polymerase, 0.25 μL of generic primer and 0.25 μL of specific primer, 0.25 μL of control primers by which a 426 base pair human growth hormone sequence was amplified were used to confirm successful PCR amplification.

The sequences of those primers are listed in Table 1 [23]. The final volume was adjusted up to 15 μL with sterile water. The reaction conditions were as follows: 95°C for 1 min; 10 cycles at 95°C for 15 s, 60°C for 50 s, and 72°C for 40 s; and 25 cycles at 95°C for 20 s, 56°C for 50 s, and 72°C for 50 s, with a final extension of 5 min at 72°C in the last cycle. The PCR products were separated by electrophoresis on a 2% agarose gel stained with ethidium bromide (0.5 mg/mL) and visualized with ultraviolet light.

2.4. Statistical Analysis. Allele and genotype frequencies of IFN-γ+874 T>A and IL10-1082 G>A polymorphisms were calculated by direct counting. The distribution of these two polymorphisms in patients with cervical cancer and healthy controls was compared using χ^2 test or the Fisher exact test. A P value <0.05 was considered to be statistically significant. The strength of the association of individual alleles or genotypes with risk of invasive CC was measured by calculating the odds ratios (OR) and 95% confidence intervals (95% CI) using the Epi info 6 package program (http://wwwn.cdc.gov/epiinfo/html/downloads.htm).

3. Results

The median age of the 122 patients with CC was 52 years, with a range of 30–81 years. Diagnoses of squamous cell carcinoma were confirmed by histopathological examination as the International Federation of Gynecology and Obstetrics; the distribution of the sample according to the FIGO stage is as follows: stage I (21.31%), stage II (38.52%), stage III (25.41%), and stage IV (6.56%).

The median age of the 160 healthy controls was 52 years, with a range of 30–80 years. According the menopausal status of women, our sample is divided into two groups; 30 (24.59%) patients and 75 (46.88%) healthy controls are premenopausal, and 92 (75.41%) patients and 85 (53.12%) healthy controls are postmenopausal (Table 2).

Tables 3 and 4 present the allele and genotype distribution of IFN-γ+874 and IL-10-1082 polymorphisms within patients with CC and healthy controls, respectively.

The allelic frequencies of IFN-γ+874 polymorphism were altered among patients and controls. T and A allele frequency were, respectively, 61% and 39% in controls, 54% and 46% of patients. With regard to the allele, the frequency distributions differ significantly from those of the controls and patients. We showed a higher prevalence of the T allele in healthy women compared with patients with CC (OR = 0.71, 95% CI = 0.50–1.01, and P = 0.0459) (Table 3).

Table 2: Demographic and tumour characteristics of the studied population.

	Patients *n* (%)	Controls *n* (%)
All women	122	160
Age on diagnostic (year)		
30–40	9 (7.38)	65 (40.62)
41–50	33 (27.05)	60 (37.5)
51–60	34 (27.86)	24 (15)
61–70	24 (19.67)	10 (6.25)
71–80	21 (17.24)	1 (0.63)
81	1 (0.80)	0 (0)
Status of menopause		
Premenopausal	30 (24.59)	75 (46.88)
Postmenopausal	92 (75.41)	85 (53.12)
Tumour stage (FIGO)		
Stage I	26 (21.31)	
Stage II	47 (38.52)	
Stage III	31 (25.41)	
Stage IV	8 (6.56)	
ND	10 (8.2)	

ND: not determined; FIGO: International Federation of Gynecology and Obstetrics.

The frequency of IFN-γ+874 T/T genotype was significantly higher in controls (40%) compared with cases with CC (26.23%). Women with homozygote IFN-γ+874 T/T genotype were at lesser risk of cervical cancer (OR = 0.53, 95% CI = 0.31–0.92, and $P = 0.015$). Carriers of allele A have an increased risk for developing CC (OR = 1.88, 95% CI = 1.09–3.24, and $P = 0.015$).

Taking into account that the T allele is much more frequent than the A allele in healthy controls, therefore, it is a protective factor for CC.

At the polymorphic nucleotide 1082 of the IL10 promoter, the G and A allele frequencies of the control group were 55% and 45% and those of patients were 49% and 51%, respectively.

No significant difference was found in allelic frequencies of IL10-1082 G>A polymorphism between patients with cervical cancer and healthy controls (Table 3).

At genotype level, IL-10-1082 polymorphism showed a higher prevalence of women carrying a homozygous AA genotype in cases (18%) than in controls (11.25%). However, this result did not reach statistical significance ($P = 0.105$).

In addition, when grouping the population considering individuals as being carriers or not carriers of a specific allele, no differences were found between patients and control subjects ($P > 0.05$) (Table 4).

4. Discussion

It is well established that individual genetic variations may affect the host's response to malignant tumours [24]. As cytokine gene polymorphisms play a role in the immune response, several studies have investigated the association between cytokine gene polymorphisms and cancers. However, the results vary between population groups [25–27].

Given the role of TNF-γ and IL10 in the immune response to tumor cells and cancer pathogenesis, this study evaluated the effect of two polymorphisms IFN-γ+874 and IL10-1082 on susceptibility to CC among Tunisian women.

IFN-γ is a Th1 proinflammatory cytokine which plays a pivotal role in the induction of immune-mediated inflammatory responses and the defence against viruses and intracellular pathogens [28]. Defective IFN-γ production may be associated with increased disease severity in cancer patients [29]. The IFN-γ+874 polymorphism, located in the first intron of human IFN-γ gene, is a single nucleotide polymorphism (SNP) +874 changing a thymine (T) to an adenine (A). The specific sequence of the +874 T allele provides a binding site for the transcription factor nuclear factor kB (NFkB) correlates with high IFN-γ expression, whereas the A allele correlates with low expression [20, 30, 31].

IFN-γ+874 T>A gene polymorphism has been shown to be associated with chronic immune diseases [32, 33]. In fact, it is possible that low IFN-γ production may impair the antiviral response against tumour progression, rendering these individuals more susceptible to this viral infection. The present study found that carriers of allele A (being to genotypes A/A and A/T) present an increased risk for developing CC, and the IFN-γ+874 T/T genotype may protect against the development of CC. In agreement with our results, a recent study carried out by Wang et al. in a Chinese population revealed that the IFN-γ+874 A/A genotype may increase the risk for developing CC while the IFN-γ+874 T/T genotype is a protective factor for this tumoral pathology [18]. Two studies carried out successively by Tamandani et al. and Gangwar et al. in two populations of Indian women reported, respectively, that genotypes A/T and A/A+A/T increase the risk of CC and that the AA genotype was more common in cases with CIN than controls [34, 35]. In concordance with these results the A/A genotype was associated with increased susceptibility to CC in Swedish women [36]. However, Govan et al. found no association between the IFN-γ+874 alleles and/or genotypes susceptibility to CC in South African women [37]. No association was found between the IFN-γ+874 TA genotype and susceptibility to HPV-related cervical lesions in Brazilian women [38]. In order to prove a more precise estimation of IFN-γ+874 T>A polymorphism in CC, two meta-analyses were recently performed. The first including 17 case-control studies, from which four were carried out on CC, showed a significant increased risk of this tumour for heterozygous A/T cases [39]. The second was based on 32 case-control studies on different cancer types. Of these studies, seven include CC type. This meta-analysis did not show any association between IFN-γ+874 A>T polymorphism and different cancer types [25].

All these studies are pertinent; however, they offer conflicting results which could be explained by differences in linkage disequilibrium and population structure. Therefore, further well-designed larger studies are warranted in order to better evaluate the association between IFN-γ+874 T>A polymorphism and CC.

IL10 is a multifunctional cytokine implicated in inflammation, immunity, and cellular organization. It was also proposed to play an important role in cancer biology [40].

Table 3: Allele frequencies of IFN-γ+874 and IL-10 polymorphisms in cases and controls and risk analysis for cervical cancer.

SNPs	Allele	Controls n (%)	Cases n (%)	OR (95% CI)	P value
IFN-γ+874 T>A	T	196 (61)	129 (54)	0.71 (CI = 0.50–1.01)	**0.0459**
	A	124 (39)	115 (46)		
IL-10-1082 G>A	G	176 (55)	119 (49)	0.78 (CI = 0.55–1.1)	0.1422
	A	144 (45)	125 (51)		

SNP: single nucleotide polymorphism; OR: odds ratio; nominal value of comparison; $P > 0.05$: no significant association; degree of freedom = 1. Value in bold is statistically significant at the 5% level.

Table 4: Frequency distribution of the IFN-γ+874, IL-10-1082 genotypes among cases and controls and risk analysis for cervical cancer.

SNP	Genotype	Controls n (%)	Cases n (%)	OR (95% CI)	P value
IFN-γ+874 T>A	T/T	64 (40)	32 (26.23)	0.53 (CI = 0.31–0.92)	**0.015**
	T/A	68 (42.5)	65 (53.27)	1.54 (CI = 0.93–2.55)	0.072
	A/A	28 (17.5)	25 (20.5)	1.22 (CI = 0.64–2.31)	0.524
	Carrier A	96 (60)	90 (73.77)	1.88 (CI = 1.09–3.24)	**0.015**
IL-10-1082 G>A	G/G	34 (21.25)	19 (15.6)	0.68 (CI = 0.35–1.32)	0.226
	G/A	108 (76.5)	81 (66.4)	0.95 (CI = 0.56–1.62)	0.844
	A/A	18 (11.25)	22 (18)	1.74 (CI = 0.84–3.59)	0.105
	Carrier A	126 (87.75)	103 (84.4)	1.46 (CI = 0.76–2.85)	0.226

SNP: single nucleotide polymorphism; OR: odds ratio; nominal value of comparison; $P > 0.05$: no significant association; degree of freedom = 1. Values in bold are statistically significant at the 5% level.

It has been reported that several polymorphic sites in the IL10 gene may influence the transcription and expression level of IL10 and consequently play a role in susceptibility to cancer [41].

Indeed, the effect of IL10-1082 G>A polymorphism and the risk of CC which has been investigated in a several variety of case-control studies. Nevertheless, the obtained results are controversial. In fact, this polymorphism has been found to be associated with an increased risk of CC in populations from Zimbabwe and Japan [42], while studies in South Africa [37], Netherlands [43], Hungary [44], Argentine [45], and Tunisia (present study) did not find any association. A meta-analysis was recently performed on eight studies for IL-10-1082 G>A polymorphism in CC and showed no effect on cervical cancer risk in the overall analysis [26]. So, the implication of the IL10-1082 G>A polymorphism in the susceptibility to CC is still ambiguous.

In conclusion, this study evaluated two cytokine gene polymorphisms IFN-γ+874 and IL10-1082 that may modulate the susceptibility to cervical cancer among Tunisian women. The data suggest that there is no association between the risk of CC and IL10-1082 polymorphism. However, carriers of IFN-γ+874 T/A and A/A genotypes present an increased risk for the development of CC, while the homozygous IFN-γ+874 T/T cases have a decreased risk for this malignancy. These results need to be verified by further studies involving larger numbers of patients and healthy controls. Furthermore, larger investigations are needed in order to better evaluate the involvement of these polymorphisms in the oncogenesis of CC.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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