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RESEARCH

Contribution of *IL12A* and *IL12B* Polymorphisms to the Risk of Cervical Cancer

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Abstract We studied the contribution of the *IL12A* 3′UTR G>A (rs568408) and *IL12B* 3′UTR A>C (rs3212227) polymorphisms to the risk of cervical cancer. These polymorphisms were genotyped in four hundred-five patients with cervical cancer and four hundred fifty unrelated healthy females from the Polish population. Logistic regression analysis adjusting for age, pregnancy, oral contraceptive use, tobacco smoking, and menopausal status revealed that the *IL12B* 3′UTR A>C polymorphism could be a genetic risk factor for cervical cancer. The adjusted odds ratio (OR) for patients with the A/C genotype vs A/A genotype was 1.557 (95 % CI=1.173–2.066, p=0.0178) and adjusted OR for the C/C or A/C genotype vs the A/A genotype was 1.635 (95 % CI=1.241–2.153, p=0.0125). However, logistic regression analysis did not show an association of the *IL12A* 3′UTR G>A polymorphism with cervical cancer development in the studied Polish population. Our studies confirmed that the *IL12B* 3′UTR A>C polymorphism may be a genetic risk factor for cervical cancer.

Keywords Cervical carcinoma · *IL12A* and *IL12B* · Polymorphisms

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Introduction

Cervical malignancy is among the most frequently occuring cancers in women worldwide. In the European Union, 34, 000 women were diagnosed with cervical cancer in 2004, with more than 16, 000 deaths resulting from these tumors [1]. Refractory infection with human papilloma virus (HPV) oncogenic subtypes is considered a crucial contributing factor to the development of a cervical tumor and its precursor lesion, cervical intraepithelial neoplasia (CIN) [2, 3]. However, epidemiological studies have shown that HPV infection is not a definitive indicator that a patient will develop a cervical malignancy [4]. Only a minority of HPV infected women demonstrate CIN or cervical tumor, which suggests a strong contribution of other host or environmental components in the development of this disease [4]. The host components may include genetic and behavioral risk factors, such as hormonal contraceptive use and smoking [5–8].

It has been demonstrated that cell-mediated immunity supported by type 1 helper T cells (Th1) is one of the crucial host defenses against HPV-associated tumorigenesis [9, 10]. The maturation of Th1 cells from the naive CD4+ T cell pool is regulated by interleukin-12 (IL-12) [11, 12]. IL-12 exhibits an immunoregulatory impact on T- and NK-cells by inducing IFN-γ biosynthesis from both cell types, augmenting their proliferation and cytotoxicity [11, 12]. This interleukin is primarily biosynthesized by antigen-presenting

cells (APCs), including dendritic cells, monocytes/macrophages, B-lymphocytes, and other cell types such as neutrophils and keratinocytes [13–15]. By promoting Th1 adaptive immunity and cytotoxic T-lymphocyte responses, IL-12 has been shown to exhibit antitumor activity that is also directed against cervical cancer [9, 12, 16]. Moreover, IL-12 displays anti-angiogenic activity, which may antagonize the pro-angiogenic signals whose presence has been demonstrated during the progression of malignancies [17, 18].

IL-12 is a heterodimeric proinflammatory cytokine composed of a 35 kDa light chain and a 40 kDa heavy chain [19]. The light and heavy chains are encoded by the *IL12A* and *IL12B* genes, respectively [19]. Several molecular epidemiologic studies have been conducted to determine how various *IL12A* and *IL12B* single nucleotide polymorphisms (SNPs) affect the risk of Kaposi sarcoma, malignant melanoma, non–Hodgkin lymphoma, and the developments of gastric, colorectal, lung, nasopharyngeal, and hepatocellular carcinomas [20–29]. Recently, the SNPs *IL12A* G>A (rs568408) and *IL12B* A>C (rs3212227), located in the 3′ untranslated region (3′UTR), have demonstrated an association with cervical cancer in some Asian populations [30–32]. Therefore the aim of our study was to evaluate whether the *IL12A* 3′UTR G>A and *IL12B* 3′UTR *A>C* polymorphisms can be genetic risk factors of cervical cancer in the Polish population.

Patients and Methods

Patients and Controls

The patient group included four hundred five women with histologically confirmed cervical carcinoma according to the International Federation of Gynecology and Obstetrics (FIGO). All women were enrolled between April 2007 and March 2011 at the Department of Radiotherapy, Greater Poland Cancer Center in Poznan, Poland (Table 1). The controls were composed of four hundred fifty unrelated healthy female volunteers who were matched by age to the patients (Table 1). Information about pregnancy, oral contraceptive use, tobacco smoking, and menopausal status was obtained during the clinic interview. All individuals were Caucasian, enrolled from the Wielkopolska area of Poland. Patients and controls provided written informed consent. The study was approved by the Local Ethical Committee of Poznan University of Medical Sciences.

Genotyping

DNA was isolated from peripheral leucocytes using a salting out procedure. The *IL12A* 3′UTR G>A (rs568408) DNA fragment was amplified using the primers 5′ ATGAG GAAACTTTGATAGGATG 3′ and 5′TTCCCTTCTTAG CAATTCATTC 3′. This polymorphism was then genotyped by high-resolution melting curve analysis (HRM) on the Light Cycler *480* system (Roche Diagnostics, Mannheim, Germany). Identification of the *IL12B* 3′UTR A>C (rs3212227) polymorphic variant was conducted by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). PCR was carried out using the primer pair 5′ TTAAAGACACAACGGAATAGAC 3′and 5′ TGCTTTATCAACACCATCTCC 3′. The PCR-amplified fragment of *IL12B* was 557 bp length and was isolated and digested with endonuclease TaqI (T/CGA) (New England Biolabs, Ipswich, USA). The *IL12B* 3′UTR C allele was cleaved into 454 bp and 103 bp fragments, whereas the *IL12B* 3′UTR A allele remained uncut. DNA fragments were separated by electrophoresis on 2 % agarose gel and

Table 1 Clinical and demographic characteristics of patients and controls

Characteristic	Patients (n=405)	Controls (n=450)
[a]Mean age (years) ± SD	52.2±9.7	52.4±10.0
Tumor stage		
IA	51 (12.6 %)	
IB	52 (12.8 %)	
IIA	54 (13.3 %)	
IIB	45 (11.1 %)	
IIIA	141 (34.8 %)	
IIIB	52 (12.8 %)	
IVA	6 (1.5 %)	
IVB	4 (1.0 %)	
Histological grade		
G1	71 (17.5 %)	
G2	128 (31.6 %)	
G3	89 (22.0 %)	
Gx	117 (28.9 %)	
Histological type		
Squamous Cell Carcinoma	351 (86.7 %)	
Adenocarcinoma	41 (10.1 %)	
Other	13 (3.2 %)	
Pregnancy		
Never	42 (10.4 %)	45 (10.0 %)
Ever	363 (89.6 %)	405 (90.0 %)
Oral contraceptive pill use		
Never	223 (55.1 %)	251 (55.8 %)
Ever	182 (44.9 %)	199 (44.2 %)
Tobacco smoking		
Never	264 (65.2 %)	305 (67.8 %)
Ever	141 (34.8 %)	145 (32.2 %)
Menopausal status		
Premenopausal	142 (35.1 %)	172 (38.2 %)
Postmenopausal	263 (64.9 %)	278 (61.8 %)

[a] age at first diagnosis

visualized by ethidium bromide staining. The *IL12A* 3′UTR G>A and *IL12B* 3′UTR A>C polymorphisms were verified by commercial sequencing analysis.

Statistical Analysis

The differences in genotypic and allelic prevalence between patients and controls and their genotype deviation from Hardy-Weinberg (HW) equilibrium were evaluated by Chi-square test. All polymorphisms were tested for association with cervical cancer incidence using the Chi-square test for trend (p_{trend}). Moreover, the Odds Ratio (OR) and 95 % Confidence Intervals (95 % CI) were calculated. Unconditional logistic regression analysis was used to adjust for the effect of confounders such as age, pregnancy, oral contraceptive use, tobacco smoking, and menopausal status. A p-value of <0.05 was considered statistically significant.

Results

The p values for HW equilibrium of the *IL12A* 3′UTR G>A genotypes in patients and controls were 0.3620 and 0.4034, respectively. For *IL12B* 3′UTR A>C genotype, the p value for HW equilibrium was 0.0798 and 0.1605 in patients and control groups, respectively.

Distribution of *IL12A* 3′UTR G>A Polymorphism in Women with Cervical Cancer

There was a 1.5-fold times higher frequency of the *IL12A* 3′ UTR A/A genotype in patients than controls (Table 2). The *IL12A* 3′UTR A/G heterozygote frequency in women with cervical cancer was also increased compared to healthy individuals and amounted to 0.32 and 0.28, respectively (Table 2). The *IL12A* 3′UTR A allele frequency was higher in patients compared to healthy individuals, and amounted to 0.22 and 0.18, respectively (Table 2). The p value of the Chi-square test of the trend observed for the *IL12A* 3′UTR G>A polymorphism was not statistically significant (p_{trend}=0.0700).

Logistic regression analysis did not reveal a significant association of the *IL12A* 3′UTR G>A polymorphism with cervical cancer (Table 2). The adjusted OR for patients with the G/A genotype vs G/G genotype was 1.249 (95 % CI= 0.924–1.688, p=0.4643), the adjusted OR for the A/A genotype vs the G/G genotype was 1.194 (95 % CI= 0.864–1.651, p=0.0267), and the adjusted OR for the G/A or A/A genotype vs the G/G genotype was 1.118 (95 % CI= 0.837–1.494, p=0.7650) (Table 2).

Distribution of the *IL12B* 3′UTR A>C Polymorphism in Women with Cervical Cancer

The frequency of the *IL12A* 3′UTR C/C genotype was 2.5-fold times higher in patients than controls (Table 2). The *IL12A* 3′UTR A/C heterozygous genotype frequency was also higher in women with cervical cancer than in healthy individuals and amounted to 0.43 and 0.34, respectively (Table 2). The *IL12A* 3′UTR C allele frequency was increased in patients compared to controls and amounted to 0.26 and 0.19, respectively (Table 2). The p value of the Chi-square test of the trend observed for the *IL12B* 3′UTR A>C polymorphism was statistically significant (p_{trend}= 0.0002). Logistic regression analysis showed that the the *IL12B* 3′UTR A>C polymorphism was significantly associated with an increased risk of cervical cancer (Table 2). The

Table 2 Contribution of the *IL12A* 3′UTR G>A (rs568408) and *IL12B* 3′UTR A>C (rs3212227) polymorphisms to cervical cancer

Gene	rs no.	Genotype	Patients (frequency)	Controls (frequency)	Odds ratio (95 % CI)	p[a]	Adjusted Odds ratio (95 % CI)[b]	p[a]
IL12A	rs568408	GG	253 (0.62)	306 (0.68)	Referent	–	Referent	–
		GA	128 (0.32)	125 (0.28)	1.239 (0.920–1.668)	0.1584	1.249 (0.924–1.688)	0.4643
		AA	24 (0.06)	19 (0.04)	1.528 (0.818–2.853)	0.1809	1.194 (0.864–1.651)	0.0267
		GA + AA	152 (0.38)	144 (0.32)	1.277 (0.963–1.693)	0.0896	1.118 (0.837–1.494)	0.7650
	Minor allele frequency		0.22	0.18	1.255 (0.989–1.593)	0.0610		
IL12B	rs3212227	AA	212 (0.52)	289 (0.64)	Referent	–	Referent	–
		AC	174 (0.43)	151 (0.34)	1.571 (1.186–2.081)	0.0016	1.557 (1.173–2.066)	0.0178
		CC	19 (0.05)	10 (0.02)	2.590 (1.180–5.685)	0.0143	1.544 (1.028–2.320)	0.0880
		AC + CC	193 (0.48)	161 (0.36)	1.634 (1.242–2.150)	0.0004	1.635 (1.241–2.153)	0.0125
	Minor allele frequency		0.26	0.19	1.511 (1.202–1.900)	0.0004		

[a] Chi-square analysis

[b] ORs were adjusted by age, pregnancy, oral contraceptive use, tobacco smoking, and menopausal status.

Significant results are highlighted in bold font

adjusted OR for patients with the A/C genotype vs A/A genotype was 1.557 (95 % CI=1.173–2.066, p=0.0178) and adjusted OR for the C/C or A/C genotype vs the A/A genotype was 1.635 (95 % CI=1.241–2.153, p=0.0125) (Table 2). However, we did not find statistical significance for the C/C genotype vs the A/A genotype. In this case, the adjusted OR was 1.544 (95 % CI=1.028–2.320, p=0.0880).

Discussion

The role of IL-12 in immunoregulation of cell-mediated immunity has been well demonstrated in the regression of various malignancies in murine models [17, 33, 34]. An elevated IL-12 production has been observed in HPV-positive women without cervical dysplasia as compared to HPV-negative individuals [35]. Moreover, cell-mediated immune response to the HPV E7 oncoprotein has been shown to be associated with clearance of HPV infection and regression of CIN [36]. The possible use of IL-12 in anticancer therapy of cervical malignancies has also been considered [37–39]. Jin et al. (2005) showed that immunization with vectors carrying *IL-12* and *HPV E7 oncoprotein* augmented the immunity response to HPV 16-associated tumors in animal models [37]. Furthermore, peritumoral administration of an IL-12-producing cellular vaccine can also restore the diminished cytotoxic and proliferative responses of tumor infiltrating lymphocytes in women with HPV 16-associated cancers [38]. Recently, Mikyšková et al. (2011) demonstrated that genetically modified cancer vaccines producing IL-12 increased the efficiency of gemcitabine chemotherapy for HPV16-associated malignancies in the murine model [36]. These findings suggest that genetic factors which may reduce *IL-12* expression may play a marked role in cervical cancer susceptibility.

We found a significant association between the *IL12B* 3′ UTR A>C polymorphism and cervical cancer development in the studied sample of the Polish population. Our observations are similar to those of Chen et al. (2009), who showed a markedly increased risk of cervical cancer occurrence in carriers of *IL12B* 3′UTR AC/CC genotypes in the Chinese population [30]. Kordi-Tamandani et al. (2009) also reported that women with the *IL12B* 3′UTR AC/CC genotypes displayed an increased risk of cervical cancer incidence in the Hindu population [31]. Studies conducted by Han et al. (2004) demonstrated an association of the *IL12B* 3′UTR AC/CC genotypes with cervical cancer in Korean women, but this effect was not statistically significant, probably due to that study′s small sample size [32].

To date, the *IL12B* 3′UTR A>C polymorphism has been associated with the risk of nasopharyngeal cancer, asthma, pulmonary tuberculosis, age of onset of type I diabetes, psoriasis and psoriatic arthritis [29, 40–44]. Moreover, this polymorphism may contribute to the severity of malaria and survival prediction in patients with follicular lymphoma [45, 46].

The effect of the *IL12B* 3′UTR A>C polymorphism on *IL12B* expression is still controversial [47–50]. Morahan et al. (2001) showed an association of the A/A genotype with markedly increased *IL12* expression in EBV-transformed human cell lines [47]. This observation was confirmed by Davoodi-Semiromi et al. (2002), who demonstrated that A allele expression is approximately 50 % higher than C allele expression in peripheral lymphocytes from *IL12B* 3′UTR A/C heterozygous individuals [48]. However, these findings were not confirmed in other studies [49, 50].

We did not observe a significant contribution of the *IL12A* 3′UTR G>A polymorphism to cervical cancer. By contrast, Chen et al. (2009) observed a significantly increased risk of cervical cancer in women with *IL12A* 3′ UTR GA/AA variant genotypes in the Chinese population [30]. These differences in the involvement of this polymorphism on the incidence of cervical cancer may be due to this disease's heterogeneity, which often confounds the studies of complex multigenic diseases. Moreover, environmental factors may also modulate the contribution of the *IL12A* 3′ UTR G>A polymorphism to cervical cancer development. To date, the *IL12A* 3′UTR A>C polymorphism has been found to be a genetic risk factor for asthma, Graves' disease, and hepatocellular carcinoma, and to modify the relationship between body mass index and the risk of non-Hodgkin lymphoma [40, 51–53].

Our study shows an association of the *IL12B* 3′UTR A>C polymorphism, but not of the *IL12A* 3′UTR G>A polymorphism, with cervical cancer in a sample of the Polish population. Our genetic study is the first in a Caucasian cohort and should be further replicated in other independent cohorts.

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