원저

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No association between genetic polymorphisms of the *Interleukin-4 Receptor α* gene and cervical cancer in Korean population

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Objective : Genetic variants of *IL-4Rα* polymorphisms of Ile50Val were known to upregulate receptor response to IL-4. IL-4 was found in cervical cancer cell lines and known to promote cervical carcinogenesis and the progression from cervical intraepithelial neoplasia to cervical cancer. So, we aim to explore whether the Ile50Val polymorphisms of *Interleukin-4 receptor α (IL-4Rα)* gene increase cervical cancer risk, which could serve as useful genetic markers for assessing the risk of the development and progression of cervical cancer in Korean population.

Methods : The blood samples of 228 cervical cancer patients who were diagnosed at Seoul National University Hospital from 1999 to 2002 and 204 subjects who had screened at the health care system of Seoul National University Hospital and confirmed as non-cancer controls, were obtained. PCR amplification and TagMan assay were used. We used the chi-square test to evaluate whether the distribution of genotypes varied significantly between cervical cancer and controls. Odds Ratio and 95% confidence intervals were calculated using logistic regression test after age adjusting.

Results : The distribution of homozygotes and heterozygotes closely approximated the expected values under Hardy-Weinberg equilibrium in cases and controls (p=0.33, chi-square=0.94; p=0.15, chi-square=2.04). In cervical cancer group, allele frequency of Ile was 46.1%, in comparison with 43.4% in control group which showed no significant difference statistically (p=0.52). Using subject with the Val/Val homozygote as a reference group, we found no association between the Ile/Val and Ile/Ile genotypes and the risk of cervical cancer with age adjusted regression analysis ($_a$OR=1.09, 95% CI=0.70-1.72, p=0.7; $_a$OR=1.21, 95% CI=0.67-2.19, p=0.52). Subanalyses of the cervical cancer according with clinical stage, histologic type, lymph node status and parametrial invasion status showed no statistically significant association with these polymorphisms.

Conclusion : The polymorphisms of the *IL-4Rα* gene are neither associated with increasing risk of cervical cancer nor more vulnerable for cervical cancer progression in Korean population.

Key Words : IL-4, *IL-4Rα* gene, Ile50Val polymorphisms, Cervical cancer

INTRODUCTION

Cervical cancer is a major cause of death, and the second most frequent cancer in women worldwide.[1] Many studies have indicated a causal relation between genital human papillomavirus (HPV) infections and cervical cancer. High risk HPV genotypes have been detected in almost 100% of all cervical cancers, and the process of HPV mediated carcinogenesis has been partly clarified.

Because HPV infections are so widespread in the general population and because HPV-immortalized cell lines are generally not tumorigenic, other factors in addition to HPV infections, such as the host immune response to HPV infections, are thought to have a role in controlling both HPV infections and HPV-related neoplasm.[2] This is supported by the observation that an ineffective cellular immune response, as immunocompromised individuals with human immunodeficiency virus, is associated with an in-

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creased incidence of HPV-related disorders.[3]

Type 1 cytokines, such as interferon gamma and IL-2, increase 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.[2,4] Of these Type 2 cytokines, IL-4 is intriguing in that high affinity IL-4R is expressed on a variety of solid tumor cells, including renal cell carcinoma, squamous cell carcinoma of head and neck, lung, and gastric carcinoma.[5-9] IL-4 was found in cervical cancer cell lines and known to promote cervical carcinogenesis and overexpressed parallel to the progression from cervical intraepithelial neoplasia to cervical cancer.[2,10] Signaling through the receptors of IL-4 has been suggested to have some biologic effects on theses tumor cells, such as production of IL-6.[5-8]

IL-4Ra gene has several types of polymorphic sites. Genetic variants of *IL-4Ra* polymorphisms of Ile50Val were known to upregulate receptor response to IL-4 which is associated with atopy.[11] The result supports the idea that Ile50Val polymorphisms of *IL-4Ra* gene may be associated with the cervical cancer progression through the increased response of IL-4R to IL-4, which could serve as useful genetic markers for assessing the risk of the development and progression of cervical cancer. The aim of this study was to explore an association between the Ile50Val polymorphisms of *IL-4Ra* gene and cervical cancer in Korean population.

MATERIALS AND METHODS

1. Subjects

The blood samples of 228 cervical cancer patients who underwent surgery or concurrent chemoradiotherapy at Seoul National University Hospital from 1999 to 2002 were collected. Final diagnoses were made on the basis of pathology reports of the specimens obtained by diagnostic biopsy or surgery. As a control, blood samples of 204 subjects, who had screened at the health care system of Seoul National University Hospital and confirmed as non-cancer controls, were also obtained. All of the subjects in the control group took cervical cytology examination in order to confirm the lack of cervical intraepithelial neoplasia.

Cervical cancer group and control group were all Korean meaning the same ethnics. Informed consent and 10 ml of peripheral blood were obtained from each of them.

2. PCR Amplification

Amplification reactions (5µl) were carried with 50ng of template DNA, 1×TagMan Universal Master Mix buffer (Applied Biosystems, Foster City, CA), 20 pM of each primer, and 5 pM of each fluorogenic probe. Thermal cycling was initiated with 2 minutes incubation at 50°C, followed by first denaturation step of 10 minutes at 95°C, and then by 40 cycles of 15 seconds at 95°C and 1 minute at 60°C.

3. TagMan assay

The sequences of the primer and probe used in this study are listed in Table 1. Primer and probe were designed using the Primer Express software version 1.5 (Applied Biosystems, Foster City, CA). Detection system was ABI PRISM 7900 HT.

Table 1. Sequences of primer and probe

Name	Sequence and fluorescence labels of probe
Sense primer	CCTAACCCAGCCCCTGTGT
Anti sense primer	CCATGAGCAGGTGGCACA
IL-4R-I50V-G	FAM-AGCCCACACGTGTGTCCCTGAGA-TAMRA
IL-4R-I50V-A	VIC-AGAGCCCACACGTGTATCCCTGAGAA-TAMRA

4. Statistical Analysis

We used the chi-square test to evaluate whether the distribution of genotypes varied significantly between cervical cancer group and controls. Odds Ratio (OR) and 95% confidence intervals (CI) were calculated using logistic regression test after age adjusting. Clinicopathological parameters were dichotomized as follows: stage (stage Ia vs Ib-IV), nodal statu (>1 vs no positive lymph node), and parametrial invasion status (involvement vs no involvement).

Table 2. Clinicopathological characteristics of the cervical cancer patients

	No. of the patients (%)
Clinical stage	
Ia	58 (25.4)
Ib	130 (57.0)
II	39 (17.1)
IV	1 (0.4)
Histology	
Squamous cell carcinoma	181 (79.4)
Adenocarcinoma	40 (17.5)
Squamoadenocarcinoma	3 (1.3)
Small cell carcinoma	3 (1.3)
Lymphoma	1 (0.4)
Lymph node status	
No	172 (75.4)
>1	34 (14.9)
Unknown	22 (9.6)
Parametrial invasion	
No	196 (86.0)
Yes	22 (9.7)
Unknown	9 (3.9)

RESULTS

In cancer group, 58 patients were stage Ia, 130 patients were stage Ib, 39 patients were stage II, and 1 patient was stage IV. Concerning the histology, 181 patients (79.4%) were squamous cell carcinoma, 40 (17.5%) were adenocarcinoma, 3 (1.3%) were squamousadenocarcinoma, 3 (1.3%) were small cell carcinoma, and 1 (0.4%) were lymphoma. Thirty four patients showed lymph node metastasis and 172 patients did not. Twenty two patients showed parametrial invasion and 196 patients did not (Table 2). Age distribution was significantly different in the cervical cancer group and control group, 53.1±11.1 (range, 30-79) years in cervical cancer group and 47.6±10.6 (range, 21-77) years in control group (p=0.00).

The distribution of homozygotes and heterozygotes closely approximated the expected values under Hardy-Weinberg equilibrium in cases and controls (p=0.33, chi-square=0.94; p=0.15, chi-square=2.04). In cervical cancer group, allele frequency of Ile was 46.1%, in comparison with 43.4% in control group which showed no significant di-

Table 3. Allele frequency and genotype distribution in cervical cancer patients and controls

Genotype	Cervical Cancer (n=228)	Controls (n=204)	$_a$OR (95% CI)*	p
Allele frequency				
Val	246 (53.9)	231 (56.6)	1	
Ile	210 (46.1)	177 (43.4)	1.10 (0.83-1.15)	0.52
H-W†	NS	NS		
Genotype distribution				
Val/Val (%)	61 (26.8)	62 (30.4)	1	
Ile/Val (%)	124 (54.4)	107 (52.5)	1.09 (0.70-1.72)	0.70
Ilel/Ile (%)	43 (26.8)	35 (17.2)	1.21 (0.67-2.19)	0.52
Ile/Val or Ilel/Ile (%)	167 (81.2)	142 (69.7)	1.12 (0.73-1.73)	0.60

*Age adjusted odds ratio with 95% confidence interval, † Goodness of fit to the Hardy-Weinberg equilibrium for genotype distribution (NS, not significant)

Table 4. Association of Ile/Val or Val/Val genotype with clinical parameters in cervical cancer patients

Clinical parameter	Val/Val	Ile/Val or Ile/Ile	p-value
Clinical stage			
Ia	13	44	0.47
Ib-IV	48	123	
Histologic type			
Squamous cell carcinoma	46	135	0.55
Others	14	33	
Lymph node status			
0	49	123	0.55
>1	8	26	
Parametrial invasion			
No	49	147	0.11
Yes	9	13	

fference statistically (p=0.52). Using subject with the Val/Val homozygote as a reference group, we found no association between the Ile/Val and Ile/Ile genotypes and the risk of cervical cancer with age adjusted regression analysis ($_a$OR=1.09, 95% CI=0.70-1.72, p=0.70; $_a$OR=1.21, 95% CI=0.67-2.19, p=0.60). The prevalence of Ile50Val was higher in cervical cancer group (81.2%) than in control group (69.7%) without significance (Table 3).

Subanalyses of the patients with cervical cancer were conducted according with clinical stage, histologic type, lymph node status, and parametrial invasion status (Table 4). There was no statistically significant interaction between these polymorphisms and these parameters.

DISCUSSION

Although we sought to determine whether *IL-4Ra* gene polymorphisms of Ile50Val influenced cervical cancer risk, we did not observe any association of Ile50Val with cervical cancer risk.

Some studies have showed the association of IL-4 and cervical cancer. A shift in cytokine, especially IL-4, production patterns was reported to occur during the progression from CIN to invasive cervical cancer.[12] An increased immunohistochemical expression of intratumoral IL-4 in HGL compared with LGL or normal cervix, and IL-4 mRNA was more expressed in cervical cancer biopsies than in normal or CIN biopsies without significant.[13,14] In many cancers, including cervical cancer, ovarian cancer, renal cell carcinoma or colorectal carcinoma, IL-4 expression is also detected in biopsies.[4,15-17]

With respect to serum concentrations of interleukins, median serum IL-4 in healthy women was higher than in patients with cervical cancer.[10] The serum level of IL-4 was not different between patients with CIN and the healthy women.[18,19] However, serum IL-6, IL-8, and IL-10 were elevated in patients with cervical cancer and correlate with progression of the disease.[20] However, the production of IL-6 may be associated with the signaling through the receptors of IL-4.[5-8]

The switch form type 1 to type 2 cytokines described in many human cancers mainly depends on upregulation of IL-6 and IL-10 and not IL-4.[21] In CIN, the level of IL-10 was increased compared to the controls.[17,22] The increased serum level of IL-6 was observed both in CIN and cervical cancer. Furthermore, IL-6 itself has a role in carcinogenesis of uterine cancer.[23,24]

The Hardy-Weinberg equilibrium suggested no deviation in recruiting the controls. However, the result of this study had low calculation power and large numbers of samples were needed to confirm the lack of association of polymorphisms of *IL-4Ra* and risk of cervical cancer. Comparing the equilibrium of Ile50Val between the controls of this study and those of Japanese and German studies, we found different genotype distributions of Val/Val, Val/Ile, and Ile/Ile (p=0.06; p=0.00).[5,25] However, the genotype distribution of this study did not show difference in comparison with other Korean population study (p=0.89).[26] Ethnic difference could make disappointed results of this study.

In addition to the ethnic difference which influences the genetic distribution, other risk factors are also important to the vulnerability of cervical cancer. Although HPV infection is a key factor of cervical cancer, especially squamous cell carcinoma, other environment factors such as cigarette smoking or other immunocompromised status must be thought as causes of cervical cancer.

Smoking itself can suppress the immune system and alter the cytokine expression. Smoking was thought to modulate immune response by a direct effect on the cells that produce the type 2 cytokines involved in asthma and allergy, including IL-4. Evidence for this mechanism is supported by the findings of higher level of IL-4 in smokers compared to nonsmokers and in endothelial cell lines stimulated by cigarette smoke condensate.[27,28] However, no significant differences in IL-4 level by cigarette consumption were observed in the study with nonasthmatic monozygotic twins.[29] Concerning the IL-4, changes of the level of IL-4 after exposure to smoking were not constant. Increased level of IL-6 was observed in the cell line study and the production of IL-6 may be stimulated by smoking in the cervix.[29,30] Coinfection of HIV and HPV could alter the cytokine expression compared to HPV infection alone, which increased numbers of cells expressing IL-4, IL-6, and IL-8.[31] Analyzing the significance of genetic variants of *IL-4Ra* polymorphisms of Ile50Val without considering above factors could lead false results.

There was no association between variants of genotypes and clinical parameters such as stage, histology types, lymph node involvement, and parametrial invasion. Therefore, with these results, we may postulate that polymorphisms of *IL-4Ra* did not promote the progress of cervical cancer. In a previous study, although no clear correlation was observed between the levels of *IL-4* mRNA expression and the clinical stage of patients with detectable cytokine mRNA expression, patients with undetectable cytokine mRNA expression more often presented with advanced stage cervical carcinoma. Down regulation of IL-4 in advanced stage cancers was considered to be a tumor escape mechanism.[4]

Ile50Val can signal increased Stat 6-dependent transcriptional activity, which is known to be correlated with an increased risk of atopic disease.[11,32] Aberrant activation of Stat-signaling gives rise to different pathological event. Generally, one group of Stat proteins including Stat 2, Stat 4, and Stat 6, is thought to be activated by a small number of cytokines and play a distinct role in the development of T-cells and in IFNγ signaling. The other group including Stat 1, Stat 3, and Stat 5, plays an important role in controlling cell-cycle progression and apoptosis and thus contributes to oncogenesis.[33,34] However, in the viewpoint of immunosurveillance of tumor, Stat 6-deficiency was suggested as a potent strategy for immunotherapy.[35]

This is the first article which explored the association between the polymorphisms of *IL-4Ra* gene, Ile50Val, and cervical cancer. In summary, we did not provide any evidence that Korean women with the polymorphisms of Ile50Val in *IL-4Ra* genes had an altered risk of development and progression of cervical cancer.

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Interleukin-4수용체α 유전자 다형성과 자궁경부암 발생위험도 및 임상인자 사이의 연관성 분석

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목적 : *Interleukin (IL)-4수용체α*의 다형성인 Ile50Val 유전 변이는 IL-4에 대한 IL-4수용체의 반응을 증가시킨다. IL-4는 자궁경부세포주에서 발현되고 자궁경부상피내암에서 자궁경부암으로의 진행하는 발암과정에 작용을 하는 것으로 알려져 있다. 따라서, 우리는 본 연구를 통해서 IL-4수용체α 유전자의 Ile50Val 다형성이 한국 여성의 자궁경부암의 발생과 진행의 위험을 증가시키는지의 여부를 알아보고자 하였다.

연구 방법 : 1999년부터 2002년까지 서울대학교병원에서 자궁경부암을 진단받은 228명과 서울대학교병원 강남센터에서 자궁경부암이 없는 것을 확인한 204명의 대조군의 혈액을 사용하였다. 그리고 PCR 증폭과 Taqman 분석을 이용하였다. 자궁경부암과 대조군의 유전형이 차이를 보기 위해서 chi-square 검사를 하였다. 나이를 보정한 후에 선형회귀분석을 통해서 교차비와 95%신뢰구간을 계산하였다.

결과 : 동종접합체와 이형접합체의 분포는 환자군과 대조군에서 Hardy-Weinberg 평형을 이루었다(p=0.33, chi-squre=0.94; p=0.15, chi-square=2.04). 자궁경부암환자에서 Ile 대립유전자의 빈도가 46.1%이고, 대조군에서는 43.4%로 의미있는 차이를 보이지 않았다(p=0.52). Val/Val 동종접합체를 참고로 비교하면, 연령보정 선형회귀분석을 통해 Ile/Val와 Ile/Ile 유전자가 자궁경부암의 발생위험과 관련이 없다는 것을 알 수 있었다($_a$OR=1.09, 95% CI=0.70-1.72, p=0.7; $_a$OR=1.21, 95% CI=0.67-2.19, p=0.52). 자궁경부암을 임상병기, 조직병리, 림프절 전이, 자궁방 침범의 상태에 따라서 분석을 했을 때, 이러한 유전자의 다형성과 관련이 없었다.

결론 : *IL-4수용체α* 유전자의 다형성은 한국인에서 자궁경부암의 발생 위험을 증가시키지 않고 자궁경부암의 진행에 영향을 주지 않는다.

중심단어 : IL-4, *IL-4수용체α* 유전자, Ile50Val 다형성, 자궁경부암