HLA DRB allele polymorphisms and risk of cervical cancer associated with human papillomavirus infection: a population study in China

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Summary

Objective: Persistent infection with high-risk human papillomavirus (HPV) is the main cause of cervical cancer. Environmental, behavioral, and ill-defined genetic factors have also been implicated in the pathogenesis of this disease. To determine whether human leukocyte antigen (HLA) DRB alleles are associated with cervical cancer and HPV infections in the Chinese population, HLA genotypes were examined in 69 cervical cancer patients and 201 controls. *Materials and Methods:* Polymorphisms in HLA-DRB genes were genotyped using oligoneucleotide arrays, and the magnitude of associations was determined by logistic regression analysis. *Results:* HLA-DRB1*13 (OR = 4.01 95% CI, 1.703 - 9.442) and HLA-DRB1*3(17) (OR = 2.661 95% CI, 1.267 - 5.558) were associated with an increased risk of cervical cancer, and DRB1*09012 (OR = 0.182, 95% CI, 0.079 - 0.418 and DRB1*1201 (OR = 0.35 95% CI, 0.142 - 0.863 were associated with a decreased risk. The risk associations of HPV infection were increased in women carrying the HLA-DRB1*09012 (OR = 1.924; 95% CI, 1.08 - 3.427) and DRB3(52)*0101 (OR = 7.527 95% CI, 0.909 - 62.347) alleles. Among cervical cancer patients, the risk associations differed between HPV positive and negative cases for several alleles; increased risk of cervical cancer was associated with DRB3 (52)*02/03 (OR, 12.794; 95% CI, 5.007 - 32.691) and DRB1*3(17) (OR = 3.48; 95% CI, 1.261 - 9.604), and decreased risk was associated with DRB1*09012 and DRB5(51)*01/02. Furthermore, HPV16-containing cervical cancer cases differed from non-HPV16 subjects in their positive association with DRB1*1501 (OR = 4.173; 95% CI, 1.065 - 16.356) and DRB5(51)*0101/0201, and their negative association with DRB4(53)*0101 (OR = 0.329; 95% CI,0.122 - 0.888). *Conclusions:* The present results provide further evidence that certain HLA class II allele polymorphisms are involved in the genetic susceptibility to cervical cancer and HPV infection in the Chinese population from an area with a high incidence of this neoplasia.

Key words: Cervical cancer; Human leukocyte antigens; Human papillomavirus.

Introduction

Cervical cancer (CC) is the second most common cancer among women worldwide. Although population wide screening in most countries has led to a remarkable reduction in the incidence and mortality of CC, it remains a major global health burden with approximately 500,000 new cases and 250,000 cancer-related deaths each year. Human papillomaviruses (HPV) have been identified as the major etiological factor in cervical carcinogenesis [1]. However, most patients with HPV-associated lesions such as cervical intraepithelial neoplasm (CIN) will remain stable or spontaneously regress over time. Only a small proportion of women with persistent oncogenic HPV infection develop malignant cervical lesions. Although oncogenic HPV genes are capable of immortalization and can contribute to the process of transformation, not all non-invasive lesions progress to the full malignant phenotype [2]. Therefore, other genetic or epigenetic events or individual immune responses to HPV infection are likely to be involved in cervical carcinogenesis. The combination of such factors may lead to a series of molecular events that result in the evolution of intraepithelial and invasive disease.

Experimental and clinical evidence demonstrate that the immunological and genetic background of the host plays an important role in the outcome of HPV associated diseases. The human leukocyte antigen (HLA) class I and II molecules play a critical role in the process by which HPV peptides are presented to T-cells. High-affinity engagement of a T-cell receptor with a HPV peptide-HLA complex and a co-stimulatory signal is necessary to activate a T-cell response. HLA Class I molecules (HLA-A,-B,-C) are found in most nucleated cells and present peptides derived from the cytosol to cytotoxic T-cells. HLA class II molecules (HLA-DR,-DQ,-DP) are found in antigen-presenting cells (e.g., dendritic cells and macrophages) and present peptides degraded in intracellular vesicles to helper T-cells [3]. An effective immune response may require optimal peptide presentation by both class I and II molecules to activate efficient helper and effector T-cell responses to HPV. Subtle changes or impairment in T-cell responses may allow escape from immune surveillance, induction of immune allergy, or tolerance to HPV peptides [4].

Although associations between specific HLA alleles and cervical neoplasia have been reported in numerous studies, the alleles and haplotypes associated with disease

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Table 1. — *Relative risk of cervical cancer associated with HLA class II DRB alleles.*

Gene type	Controls (n = 201)	%	Cases (n = 69)	%	OR-adjusted*	95% CI	*p* value
DRB1*0101	11	5.47	5	7.25	1.393	0.466-4.165	0.552
DRB1*04	41	20.4	22	31.88	1.827	0.991-3.367	0.052
DRB1*0701	15	7.46	3	4.35	0.626	0.174-2.249	0.575
DRB1*08	44	21.89	20	28.99	1.518	0.816-2.825	0.186
DRB1*09012	77	38.31	7	10.14	0.182a	0.079-0.418	0
DRB1*1001	9	4.48	0	0	1.047	1.016-1.027	0.118
DRB1*11	25	12.43	8	11.59	1.041	0.446-2.431	0.925
DRB1*1201	43	21.39	6	8.69	0.35a	0.142-0.863	0.018
DRB1*13	18	8.96	14	20.29	2.588	1.209-5.537	0.012
DRB1*13-1	3	1.49	1	1.45	0.007	0.112-10.771	0.935
DRB1*13-2	11	5.47	13	18.84	4.01b	1.703-9.442	0.001
DRB1*1301	4	1.99	0	0	1.02	1-1.041	0.575
DRB1*1405	11	5.47	0	0	1.058	1.023-1.094	0.071
DRB1*1406	18	8.96	5	7.25	0.82	0.292-2.301	0.706
DRB1*15	38	18.91	16	23.19	1.295	0.668-2.509	0.443
DRB1*1601	5	2.49	0	0	1.026	1.003-1.048	0.333
DRB1*3(17)	19	9.45	15	21.74	2.661b	1.267-5.558	0.008
DRB3(52)*0101	8	3.98	3	4.35	1.097	0.283-4.256	1
DRB3(52)*02 /03	107	53.23	31	44.93	0.717	0.414-1.241	0.234
DRB4(53)*0101	120	59.7	32	46.38	0.584	0.337-1.013	0.054
DRB5(51)*0101/0201	43	21.39	16	23.19	1.109	0.577-2.131	0.756

* adjusted for age; a: $p < 0.05$; b: $p < 0.01$.

Table 2. — *Relative risk of HPV infection associated with HLA class II DRB alleles in control subjects.*

HLA-DRB	HPV positive subjects (n = 100)	HPV negative subjects (n = 101)	OR-adjusted*	95% CI	*p* value
DRB1*0101	4	7	0.56	0.159-1.974	0.361
DRB1*0401	20	21	0.952	0.479-1.892	0.889
DRB1*0701	6	9	0.652	0.223-1.906	0.432
DRB1*0801	21	23	0.901	0.462-1.76	0.761
DRB1*09012	46	31	**1.924**	1.08-3.427	0.026
DRB1*1001	4	5	0.8	0.208-3.07	0.745
DRB1*1101	15	10	1.606	0.684-3.769	0.273
DRB1*1201	18	25	0.667	0.338-1.319	0.234
DRB1*13-1	1	2	0.5	0.045-5.604	0.567
DRB1*13-2	8	3	2.841	0.731-11.035	0.117
DRB1*1301	1	3	3.031	0.31-29.639	0.317
DRB1*1405	4	7	0.56	0.159-1.974	0.361
DRB1*1406	9	9	1.011	0.384-2.662	0.982
DRB1*15	21	17	0.761	0.375-1.548	0.45
DRB1*1601	3	2	1.531	0.25-9.364	0.683
DRB1*3(17)	7	12	0.558	0.21-1.482	0.237
DRB3(52)*0101	7	1	7.527	0.909-62.347	0.035
DRB3(52)*02/03	49	58	0.712	0.408-1.242	0.231
DRB4(53)*0101	64	56	1.429	0.811-2.517	0.216
DRB5(51)*0101/0201	24	19	1.429	0.811-2.517	0.37

* adjusted for age.

Table 3. — *Relative risk of HPV-containing CC and control group associated with HLA II DRB alleles.*

Alleles	HPV positive subjects Cases (n = 53)	Control (n = 100)	OR-adjusted*	95% CI	*p* value
DDRB1*0101	5	4	2.5	0.642-9.737	0.277
DRB1*04	13	20	1.3	0.587-2.878	0.517
DRB1*0701	3	6	0.94	0.225-3.919	1
DRB1*08	18	21	1.935	0.919-4.074	0.08
DRB1*09012	5	46	0.122	0.045-0.333	0
DRB1*1001	0	4	1.024	1.001-1.084	0.299
DRB1*11	7	15	0.862	0.328-2.266	0.764
DRB1*1201	6	18	0.582	0.216-1.567	0.28
DRB1*13-1	1	1	1.904	0.117-31.06	0.574
DRB1*13-2	9	8	2.352	0.85-6.509	0.093
DRB1*1301	0	1	1.01	0.99-1.03	0.654
DRRB1*1405	0	4	1.042	1.001-1.084	0.299
DRRB1*1406	5	9	1.503	0.334-3.319	0.572
DRB1*15	15	21	1.485	0.689-3.199	0.311
DRB1*1601	0	3	1.031	0.996-1.067	0.552
DRB1*3(17)	11	7	3.48	1.261-9.604	0.012
DRB3(52)*0101	3	7	0.797	0.197-3.218	0.75
DRB3(52)*02 /03	26	7	12.794	5.007-32.691	0
DRB4(53)*0101	20	49	0.631	0.32-1.245	0.183
DRB5(51)*0101/0201	15	64	0.222	0.108-0.458	0

* adjusted for age.

have varied from study to study in different populations. Some studies have suggested a negative association between HLA class II DRB1*13 alleles and CC [5]. Other studies have failed to confirm this association, but have suggested a positive association between HLA class II DRB1*1501, DQB1*0602 and disease risk [6]. Interestingly, although reports have often been inconsistent with respect to the specific HLA alleles positively associated with cervical disease, many of these studies consistently reported a reduction in risk of disease associated with HLA class II DRB1 alleles.

In the present study, the authors conducted gene chip HPV typing to assess the risk of squamous cell cervical cancer associated with class II HLA-DRB loci in China. Polymorphisms of HLA-DRB genes were analyzed including DRB1-1 DRB1-3 DRB1-4 DRB1-7 DRB1-8 DRB1-9 DRB1-10 DRB1-11 DRB1-12 DRB1- DRB1-14 DRB1-15, DRB1-16, DRB3, DRB4, and DRB5 in a case-control study of women from the county of WuFeng in the Hubei province. This region has one of the highest incidence rates of CC in China.

Table 4. — *Relative risk of cervical cancer and HPV16 associated with HLA class II DRB alleles.*

Gene type	HPV 16 positive cases (n = 40)	HPV 16 negative cases (n = 29)	OR-adjusted*	95% CI	*p* value
DRB1*0101	4	1	3.111	0.329-29.407	0.389
DRB1*04	10	12	0.472	0.169-1.321	0.15
DRB1*0701	2	1	1.474	0.127-17.071	1
DRB1*08	14	6	2.064	0.681-6.256	0.196
DRB1*09012	2	5	0.253	0.045-1.407	0.122
DRB1*1001	0	0	0	0	0
DRB1*11	4	4	0.694	0.159-3.041	0.712
DRB1*1201	4	2	1.5	0.256-8.794	1
DRB1*13	7	7	0.667	0.205-2.166	0.499
DRB1*13-1	1	0	0.975	0.928-1.025	1
DRB1*13-2	6	7	0.555	0.165-1.87	0.338
DRB1*1301	0	0	0	0	0
DRB1*1405	0	0	0	0	0
DRB1*1406	3	2	1.095	0.171-7.008	1
DRB1*15	13	3	**4.173**	1.065-16.356	0.031
DRB1*1601X	0	0	0	0	0
DRB1*3(17)	9	6	1.113	0.347-3.569	0.857
DRB3(52)*0101	0	3	1.115	0.986-1.262	0.07
DRB3(52)*02/03	19	12	1.282	0.488-3.364	0.614
DRB4(53)*0101	14	18	**0.329**	0.122-0.888	0.026
DRB5(51)*0101/0201	13	3	**4.173**	1.065-16.356	0.031

* adjusted for age.

Materials and Methods

Samples

A total of 69 CC cases and 201 out of 1,023 controls were randomly selected from an epidemiological study of CC and HPV infection conducted in mid-western China. The controls were women with normal or non-dysplastic Pap smears. Epidemiological data from all subjects were obtained during a standardized interview carried out by a trained nurse using a structured questionnaire. Information regarding socio-demographic variables, education, sexual behavior, diet, personal hygiene habits, and reproductive history was obtained. The study was approved by the local ethics committee.

After the interview, all subjects were asked to provide a sample of peripheral blood, and DNA was extracted and stored at -80 °C. Aliquots of the purified DNA were used for HLA class II allele typing and HPV detection. A cervical cellular specimen was collected from each control using a cytobrush, and tumor biopsies were obtained from all cancer patients. All specimens were prepared and submitted for cytological or histological examination.

HLA typing

All specimens from CC cases and controls were typed for HLA-DRB1 DRB3 DRB4 DRB5 DRB6 DRB7 and DRB9 genes using a HLA -DRB gene typing chip (UnitedGene, Shanghai, China). The identification and naming of HLA-DRB genes used in this study followed the 12th International Histocompatibility Workshop and Conference recommendations.

HPV typing

HPV detection and typing were performed by polymerase chain reaction (PCR) based amplification of a 450 bp segment in the L1 viral gene with MY09 and MY11 primers. PCR products were dot-blotted onto a nylon membrane and hybridized with individual 32P-labeled oligonucleotide probes specific for HPV types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51-59, 66, and 68. A 268 bp fragment of the b-globin gene was amplified to ensure DNA quality. A negative control tube containing all PCR reagents except template DNA was included in all PCR reactions, and DNA from HeLa cells that harbor HPV18 integrated into the host genome was used as a positive control.

Statistical analysis

The distribution of specific HLA genotypes in CC cases and controls was compared using the 2 test, and the HLA allele frequencies for each group were ascertained. Comparisons of exposure profiles between cases and controls were performed by 2 tests for independent samples. The magnitude of the association between the HLA gene type and the occurrence of CC or HPV infection was measured by OR and the respective 95% CI. Logistic regression analysis was carried out to examine the independent effects of multiple alleles found to be associated with disease. A linear trend was also analyzed using the 2 test when a trend was observed in the association between HLA and disease severity. The correlation between the alleles found to be associated with disease was computed using the Pearson correlation coefficient. The RR, as estimated by the odds ratio, was the measure used to determine the magnitude of the association between HLA and disease, and 95% CIs were calculated to determine the statistical significance of these associations.

Results

To verify whether the specific HLA-DRB1, B3, B4, and B5 alleles were associated with the risk of CC, the ORs and 95% CIs (Table 1) were calculated in 69 CC cases and 201 controls. The proportions of samples carrying HLA-DRB alleles are shown in Table 1. Two class II alleles that were present in > 20% of the cases, HLA-DRB1*13 (OR = 4.01 95% CI, 1.703 - 9.442 $p = 0.001$) and HLA-DRB1*3(17) (OR = 2.661 95% CI, 1.267-5.558 $p = 0.008$) were significantly associated with an elevated risk of CC. HLA-DRB1*13 alleles were analyzed including DRB1*13-1, DRB1*13-2 and other DRB1*13 alleles, but only DRB1*13-2 showed a strong association with an increased risk of CC. The other two class II alleles that were found to confer a decreased risk of CC were HLA-DRB1*09012 (OR = 0.182, 95% CI, 0.079 - 0.418 $p = 0$ and HLA-DRB1*1201 (OR = 0.35 95% CI, 0.142 - 0.863 $p = 0.018$), which were present in 38.31% and 21.39% of controls, respectively. The ORs also remained similar and marginally significant even after adjustment for all covariates.

Of the 201 control subjects included in the analysis, 101 harbored HPV DNA. The authors further examined the association between HLA alleles and HPV infection (Table 2). The OR for the HLA-DRB1*09012 (OR = 1.924; 95% CI, 1.08 - 3.427) and DRB3(52)*0101 (OR = 7.527 95% CI, 0.909 - 62.347 alleles increased in magnitude, and the risk associations of HPV infection for women carrying the two alleles would be increased. No significant negative associations were found in this analysis.

To investigate whether these associations were due to HPV infection, HPV type or to the development of cancer, the analysis was restricted to HPV16 positive control

subjects (n = 100) and HPV-16 positive case subjects (n = 40). HPV DNA was detected in 77% of the 69 tumors tested, and HPV16 was the most frequent oncogenic HPV type in the cases (75.5% of all cases). Firstly, the association between HLA alleles and CC risk was examined on the basis of HPV oncogenic potential, and the ORs for HLA-DR alleles were calculated considering only HPV-positive cancer cases in comparison with HPV positive control subjects (n = 100) (Table 3). A higher proportion of HPV16-positive samples carried the DRB1*15, DRB3 (52), and DRB1*08 alleles compared with control samples (with HPV infection). At the allele-specific level, significant positive associations were found for DRB3 (52)*02/03 (OR = 12.794; 95% CI, 5.007 - 32.691) and DRB1*3(17) (OR = 3.48; 95% CI, 1.261 - 9.604), although a risk trend was also observed for DRB1*13. On the other hand, two alleles, DRB1*09012 (OR = 0.122; 95% CI, 0.045 - 0.333) and DRB5 (51)*01/02 (OR = 0.222; 95% CI, 0.108 - 0.458), showed significant negative associations with the risk of CC in this analysis. Secondly, the risk estimates for specific alleles associated with CC were totally different when the case group was restricted to HPV-16-positive case subjects (n= 40), compared with HPV-16-negative case subjects (n = 29). The risks of CC infected with HPV-16 were statistically significantly different from those of HPV-16-negative cases, and two positive association DRB1*1501 (OR = 4.173; 95% CI, 1.065 - 16.356) and DRB5(51)*0101/0201 (OR = 4.173; 95% CI, 1.065 - 16.356) and a negative association with DRB4(53)*0101 (OR = 0.329; 95% CI, 0.122 - 0.888) were found (Table 4).

Discussion

In this population-based study, the authors analyzed the proportions of HLA class II DRB polymorphisms in 69 cases with CC and 201 control women from a high incidence area in the mid-west of China. The association between HLA class II alleles and increased or decreased risks of CC has been previously reported. The present results supported the hypothesis that certain HLA class II DRB alleles affect the risk of invasive CC. In this study, there were four HLA class II alleles significantly associated with CC after correction for multiple comparisons. The presence of the HLA DRB1*09012 and DRB1*1201 alleles was associated with a decreased risk of CC, and the strongest negative association was between DRB1*09012 and CC.

In the present study, the authors detected certain associations, that to their knowledge have not been reported previously, such as an increased risk of CC associated with HLA DRB3(17) and decreased risks associated with the DRB1*09012 and DRB1*1201 alleles. A significant positive association was found between the HLA DRB1*13 group and HLA DRB3(17) and an increased risk for CC. The strongest associations involved HLA DRB1*13-2, while other DRB1*13 alleles, although present, tended to be less frequent among CC cases. A decreased risk of cervical neoplasia associated with the HLA DRB1*13 has been previously reported [7, 8]. Although the DRB1*13 allele has been associated with a decreased risk of CC in several population studies throughout the world [8], the authors found positive associations between CC and the DRB1*13 allelic group. The strongest associations involved DRB1*13-2, which was associated with a four-fold increased risk of CC (OR = 11.5; 95% CI, 3.5 - 38.5 in Table 1). The reason for these conflicting findings between different studies is not clear, but it is possible that a direct association between DRB1*13 and cervical disease is not always present, and differences between the ethnically distinct populations in each study or the presence of diverse HPV types in different regions could be responsible for the discrepancies. These studies, which showed a positive association, were conducted among Mongolian populations in China. Although the associations detected in different populations frequently involve the same HLA groups, there is no consensus regarding the specific HLA alleles that contribute to the risks of CC in any particular population. Contradictory results could be an indication that such populations have intrinsic features that are determinants of risk, and suggest the possible role of differences in the interaction between environmental and host factors in the risk of CC.

It is likely that only women persistently infected with oncogenic HPV types are prone to developing malignant cervical lesions. Furthermore, persistent HPV infections associated with a high viral load are considered to be risk factors for the development of cervical lesions [9]. The outcomes of HPV infection are the result of a combination of features intrinsic to some HPV types (particularly those of the high-risk types) and interactions between HPV and the host [10, 11]. The authors investigated the associations between HLA class II alleles and HPV infection in a control population from the Wufeng region, which has one of the highest rates of incidence of CC and HPV infection in China. Significant associations were found between the HLA DRB1 *09012 and DRB3(52)*0101 alleles and an increased risk for HPV infection. The DRB3(52)*0101 allele was associated with a seven-fold increased risk of HPV infection (Table 2), showing the strongest relationship in the study. There were no alleles showing negative associations in the present study. However, the analysis was based on HPV measurements obtained at a single point in time, and therefore the interactive relationship between HLA polymorphisms, HPV infection persistence, and development of malignant lesions cannot be confirmed. The fact that DRB3(52)*0101 and DRB1*09012 were associated with increased risks for HPV positivity in this population may indicate the importance of HLA polymorphisms in directing the course of HPV infections. Genetic susceptibility may influence the persistence of HPV infections and high viral loads, augmenting the risk for development of malignant lesions of the cervix.

In addition, there was a nearly 13-fold increase in the risk of CC associated with the DRB3(52)*02/03 allele in this study (Table 3). The prevalence of this polymorphism

in China suggests that the presence of this allele could be considered a risk for the development of malignant lesions of the cervix in cases of oncogenic HPV16 infection. DRB1*3(17) had similar effects on the development of CC. DRB1*09012 (OR = 0.122; 95% CI, 0.045 - 0.333) and DRB5(51)*01/02 (OR = 0.222; 95% CI, 0.108 - 0.458) showed significant negative associations in this analysis, which have not been reported previously. However, the presence of the DRB1*09012 allele was associated with decreased risks for CC in the absence of HPV16 infection, but it was associated with increased HPV positivity among the control population. This indicates that the DRB1*09012 allele may be a significant HLA allele in carcinogenesis of the cervix regardless of the HPV infection status. Taken together, these findings suggest that different HLA II alleles may contribute differently to the development of CC and HPV infection in our population.

To better understand the mechanism by which HLA class II alleles affect the development of CC in the presence or absence of HPV infection, HPV-16 positive cases were compared to HPV16 negative cases and the results are shown in Table 4. The authors identified specific HLA alleles that increased or decreased the risk of cervical disease. The risks for CC in cases on oncogenic HPV were different (although not significantly) from those of non-HPV-16-containing tumors in association with DRB1*1501 and DRB5 (51)*0101/0201, which were associated with at least a four-fold increased risk of CC in the presence of HPV16 infection. These results indicated that these two alleles may play important roles in the development of CC induced by HPV16. DRB4(53)*0101 displayed a negative association with the risk of CC, and the presence of this allele prevented the development of CC in cases of persistent oncogenic HPV infection. However, it should be noted that DRB5(51)*0101/0201 decreased the risk of HPV containing cervical cancer (OR = 0.222, 95% CI: 0.108 - 0.458). These results suggest that, regardless of HPV type, there might be a decreased risk of cervical cancer associated with DRB5(51)*0101/0201, whereas a strong positive association is detected in the presence of HPV16 infection in cervical cancer tissues.

Although HPV infection is considered a major risk factor for the development of CC, it is not the only causative factor. There is increasing evidence of the essential role of cellular immune responses in HPV infection clearance and the development of CC [12-14]. The identification of an increasing number of risk associations for combinations of MHC genes may help explain some of the discrepancies regarding HLA-related susceptibility among individuals. Studies addressing the relationship between HLA and HPV-16 have found an increased risk of CC that contain certain HPV types associated with special DRB1 alleles [15-18]. Viral factors, such as type and variant, and viral load may promote cervical carcinogenesis in the context of the host's HLA type. The small sample size of the present study may have limited the detection of significant differences between HPV16 containing and non-HPV16 containing tumors . In addition, the HLA alleles may directly affect other tumor-associated antigens, rather than HPV peptides, or the relevant epitopes could be conserved across HPV types. Nevertheless, the possibility that these alleles play an important role in HPV infection susceptibility cannot be discounted.

Previous studies suggested that the risk of CC may depend on specific HLA alleles or HLA-linked genes. In addition, studies have indicated that the cellular immune response is essential in HPV infection clearance [12, 13]. Different combinations of HLA class II molecules and antigenic peptides may influence cytokine production during the early stages of the immune response against an HPV infection [19, 20]. As genotyping of the HLA region has become more precise, observations of associations between HLA and CC have also become more refined. A decreased susceptibility to cervical dysplasia was associated with the haplotype DRB1*0101 in British women [21]. Several studies have examined the association between the risks of cervical neoplasia and the presence of these alleles [7, 22, 23]. Some recent studies conducted in the eastern United States and Costa Rica with high-resolution typing across A-B-DR alleles reported that there were no HLA haplotypes significantly associated with cervical neoplasia [24]. However, less consistent results for different HLA alleles similar to those of the present study have been previously reported and may represent population-specific or even chance findings because of the polymorphic nature of the HLA region genes. Although different populations frequently exhibit associations involving the same HLA alleles, there is no consensus regarding the specific HLA alleles that contribute to the risks of CC or HPV infection in any particular population [7, 19-22].

In conclusion, the present results suggest that HLA polymorphisms play a role in the genetic susceptibility to CC and HPV infection in the Chinese population. In particular, the authors found an increased risk for CC associated with the HLA DRB1*13-2, HLA DRB3(17) and DRB3(52)*0201/03 alleles. Individuals that carry the HLA DRB1*09012, DRB1*1201 and DRB4(53)*0101 alleles were found to have decreased risks for CC. An increased risk for HPV positivity was associated with DRB3(52)*0101. A better understanding of these associations may help clarify the role of HLA molecules in the immune responses against HPV infections and subsequent CC pathogenesis in the Chinese population, and would be of value for the design of strategies for the prevention and treatment of CC through vaccination and immunotherapy.

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