

# HLA and Susceptibility to Cervical Neoplasia

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**ABSTRACT:** The association between cervical neoplasia and certain HLA phenotypes observed in different studies has not been consistent. By serological typing, the association between HLA antigens, cervical carcinoma and cervical intraepithelial neoplasia (CIN) was studied in a group of 172 and 116 patients, respectively. We demonstrated an increased frequency of B63 in patients with HPV types other than HPV 16 or 18, and B55 in patients that were negative for all HPV types. The association between cervical carcinoma and DQ3, described in various populations, was not observed in the present study. However, we confirmed other previously observed associations between cervical cancer and class II antigens, i.e., a positive correlation with DR15 irrespective of the HPV

status, with DR3 in patients harboring HPV types other than HPV 16 or 18, and with DR11 among HPV 16 positive patients. In contrast, a negative correlation between DR13 and HPV positive cervical cancer was observed which suggests protection of this antigen against HPV-associated cervical cancer. A slight increase of DR15 and DQ4 antigens was observed in CIN patients, suggesting that these specific HLA antigens may be important in determining the risk of CIN. *Human Immunology* 60, 337–342 (1999). © American Society for Histocompatibility and Immunogenetics, 1999. Published by Elsevier Science Inc.

**KEYWORDS:** cervical neoplasia, HLA, HPV

## ABBREVIATIONS

CIN cervical intraepithelial neoplasia  
HLA human leucocyte antigen

HPV human papillomavirus

## INTRODUCTION

Cervical carcinoma is one of the most common cancers among women worldwide, particularly in developing countries [1, 2]. From recent years, there is compelling evidence that infection with human papillomavirus is a major etiologic factor in the development of cervical intraepithelial neoplasia (CIN) and cervical carcinoma [3–5]. As in most virus induced diseases, an adequate immune response is likely to play a key role in clearance of HPV infections and HPV-related lesions. This assumption is borne out by both epidemiological studies and animal models. Immune compromised patients such as HIV infected women, organ transplant recipients, and

patients suffering other forms of malignancies, are at higher risk of developing CIN lesions and invasive cervical cancer [6–9]. Moreover, several studies establish the existence of natural HPV E7-specific CTL immunity in humans [10–12].

Only a minority of women infected with oncogenic HPV types develop CIN or cervical cancer. Indeed, the majority of CIN lesions do not progress or even regress to normal cytology, indicating that other factors such as an inadequate immune function are necessary for the development of progressive CIN lesions and cervical carcinoma [13].

The immune response against HPV antigens mediated by T lymphocytes is HLA restricted. Consequently, the HLA class I and II phenotype may be correlated with an effective immune response against HPV associated cervical lesions. Studies by different groups on associations between certain HLA alleles and susceptibility to, or protection against CIN lesions and cervical carcinoma, reveal varying conclusions [14] and warrant further research.

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In the present study we examined the HLA class I and II associations among caucasoid women with cervical neoplasia. We HLA-typed 172 cervical cancer patients and 116 CIN patients from a caucasoid population by HLA serology and compared HLA antigen frequencies with a local control group consisting of 1161 healthy random unrelated Dutch caucasoid female blood donors. Carcinomas were also analyzed for presence and type of HPV DNA to study possible HPV type specific HLA associations.

## MATERIAL AND METHODS

### Patients and Controls

The study population consisted of 172 patients with invasive cervical carcinoma and 116 patients with cervical intraepithelial neoplasia, treated at the Leiden University Medical Center, The Netherlands, between 1989 and 1995. Sixty-three of the carcinoma patients, 25 of which came from Germany, were enrolled through their participation in a phase I/II immunotherapy trial for recurrent disease that had insufficiently responded to conventional treatment (surgery, radiotherapy). Control subjects were 1161 healthy random unrelated Dutch caucasoid female blood donors typed by the Leiden University Medical Center [15]. HLA phenotype frequencies of the German patients were compared to the Dutch patient group using Haldane's modification of Woolf's method [16, 17] revealing no significant differences in antigen distribution among the different populations which permitted inclusion of these patients in the analyses. Patient blood samples and tumor biopsies of the patients were obtained during outpatient clinic visits. Histological classification was performed according to standard procedures and established criteria [18].

### HLA Typing

All individuals were typed for HLA-A and -B using the standard microcytotoxicity technique and for DR and DQ using the propidium iodide staining and automated reading method [19].

### HPV Detection

Formalin-fixed, paraffin-embedded sections were used for DNA extraction. HPV detection in the tumor samples was performed using the consensus primers CP-I and CP-IIIG directed against the E1 open reading frame, which is highly conserved among the HPV genome and enables the detection of a broad spectrum of different HPV types [20]. Direct sequence analysis was performed on HPV positive products.

### Statistical Analysis

HLA phenotype frequencies of patients and controls were compared using Haldane's modification of Woolf's method [16, 17]. P-values were corrected (where necessary) for the number of comparisons according to Edwards [21]. For associations previously described by other authors, no formal adjustment of *P* values for multiple comparisons were made.

## RESULTS

Patients who have failed conventional treatment and experience residual or recurrent disease are more likely to have poor cellular immunity against HPV associated lesions compared to patients with a better prognosis. Therefore, we compared HLA antigen frequencies between cervical carcinoma patients enrolled in the immunotherapy trial for residual or recurrent disease unresponsive to conventional treatment and patients at first diagnosis, primarily treated for cervical carcinoma. No HLA specificities were significantly different in frequency between the two patient groups after correction. Given this result, the two patient groups were combined in subsequent analyses.

Table 1 shows that no significant differences between patients and healthy control individuals were found for any HLA class I antigen distribution. In order to analyze a possible relationship between HLA type and HPV infection, patients were categorized further according to whether their tumor contained HPV 16 DNA, HPV 18 DNA, HPV DNA of other types, or whether no HPV DNA was detected. In the 162 samples eligible for study of HPV presence and genotype, 86% were HPV positive. The prevalence of HPV 16, HPV 18, and other HPV types was 58%, 13%, and 15% respectively. The B63 antigen was significantly more frequent in patients with tumors with HPV types other than HPV 16 or HPV 18 compared to control individuals and the B55 antigen showed an increased frequency in the group of patients in which no HPV DNA could be detected in the tumor specimens compared to controls.

Table 2 shows the HLA class II antigen frequencies in cervical carcinoma patients versus controls. The frequency of the DR15 antigen was increased when all patients, irrespective of their HPV status, were compared with controls.

DR3 also showed an increased frequency over controls in the group patients with tumors positive for HPV types other than HPV 16 and HPV 18.

The frequency of DR11 was increased compared with controls in patients with HPV 16 positive tumors.

DR9 was increased in the patient group with HPV-negative tumors compared with controls. Among the DQ antigens, only DQ4 was increased in patients irre-

**TABLE 1** Frequency (%) of HLA class I antigens in cervical carcinoma patients versus controls

HLA A (n)	All						HLA B	All					
	pts (172)	HPV 16 (94)	HPV 18 (21)	Other types (24)	HPV neg (23)	Contr (1161)		pts (172)	HPV 16 (94)	HPV 18 (21)	Other types (24)	HPV neg (23)	Contr (1161)
A1	27	24	38	33	17	30	B51 (5)	14	15	10	8	22	11
A2	53	59	48	50	57	52	B52 (5)	1	0	0	0	0	1
A3	29	29	19	29	35	29	B7	26	23	38	29	17	27
A9	22	16	33	21	30	20	B8	24	18	33	38	26	23
A23 (9)	2	1	0	4	<b>9</b>	3	B44 (12)	26	33	10	33	13	24
A24 (9)	19	15	<b>33</b>	13	22	18	B45 (12)	1	1	0	0	0	1
A10	6	7	0	0	13	7	B13	2	3	0	4	0	4
A25 (10)	0	0	0	0	0	2	B14	3	4	0	4	0	3
A26 (10)	5	5	0	0	<b>13</b>	4	B62 (15)	13	12	19	<b>0</b>	26	15
A34 (10)	0	0	0	0	0	0	B63 (15)	2	1	0	<b>8<sup>a</sup></b>	0	1
A66 (10)	1	1	0	0	0	0	B38 (16)	2	1	0	0	9	4
A11	12	11	0	17	13	11	B39 (16)	4	2	<b>10</b>	8	4	3
A29 (19)	6	5	<b>14</b>	4	4	5	B57 (17)	6	7	5	4	4	4
A30 (19)	2	2	5	4	0	3	B58 (17)	1	0	<b>5</b>	<b>4</b>	0	1
A31 (19)	9	<b>12</b>	10	4	4	6	B18	5	5	5	0	4	6
A32 (19)	7	<b>12</b>	0	4	0	6	B49 (21)	1	0	<b>5</b>	0	<b>4</b>	1
A33 (19)	2	1	0	<b>8</b>	0	1	B50 (21)	1	1	5	0	0	2
A28	9	11	10	8	4	10	B55 (22)	5	3	0	0	<b>22<sup>b</sup></b>	4
							B56 (22)	1	1	0	<b>4</b>	0	1
							B27	6	7	0	4	4	7
							B35	15	14	19	21	9	17
							B37	6	4	14	8	0	3
							B60 (40)	16	19	19	8	13	16
							B61 (40)	1	2	0	0	0	3
							B41	<b>3</b>	<b>3</b>	0	4	0	1
							B47	1	2	0	0	1	0
							B53	1	0	0	0	4	1
							B70	1	0	0	4	0	2

Bold printed numbers: frequency differences significant before correction;

<sup>a</sup>  $p = 0.02$  after correction; RR = 13.4;

<sup>b</sup>  $p = 0.007$  after correction; RR = 7.0.

spective of the HPV status of the tumor, and in the group of HPV 16-positive tumors. However, the associations with DR9 and DQ4 have not been reported before and need to be confirmed.

Decreased frequencies were observed for DR13, DR52, DQ1, and DQ6 antigens in patients over controls. DR13 was decreased in patients with HPV-positive tumors. The DR13 frequency in patients with HPV-negative tumors was comparable with the frequency in controls. The decreased frequency of DQ6 was observed in patients with HPV 16-positive tumors and in patients with tumors with HPV types other than 16 or 18 but not in HPV 18 positive or in HPV negative cases.

To analyze the correlation between HLA antigens and CIN lesions, we compared HLA class I and II antigen frequencies of 116 tissue typed CIN patients with controls. There was no association with any of the class I antigens. Table 3 shows the frequencies of the different class II antigens categorized in three groups; all CIN lesions, CIN I/II (mild to moderate dysplasia) and CIN III (severe dysplasia). There was a considerable difference

in DR2 frequency between CIN I/II patients and controls but not between CIN III patients and controls.

DR14 and DR8 frequencies were also higher in CIN patients compared with controls, in particular in CINI/II patients, while DQ4 frequencies were increased in both mild to moderate as well as in severe dysplasia patients. The observed differences were not statistically significant after correction for the number of tests performed.

## DISCUSSION

It has been suggested that certain HLA types may influence the prognosis of cervical cancer patients [22, 23]. Therefore, we initially compared HLA antigen frequencies between patients enrolled in this study via an immunotherapy protocol for patients who have failed conventional treatment and experienced residual or recurrent disease in an advanced stage, with patients with first diagnosis of cervical carcinoma. Since this analysis did not reveal significant differences in antigen frequencies we combined the two groups in subsequent analyses.

**TABLE 2** Frequencies (%) of HLA class II specificities in cervical carcinoma patients versus controls

	All patients (169)		HPV 16 (92)		HPV 18 (21)		Other HPV types (24)		HPV neg (24)		Controls (1133)	
		p	RR	p	RR	p	RR	p	RR	p	RR	
DR												
DR1	20			20			24	29			17	20
DR2	34			32			38	25			38	27
DR15 (2)	31	0.05	1.4	29			33	25			33	24
DR16 (2)	2			2			5	0			4	2
DR3	25			21			29	46	0.02	2.5	25	25
DR4	33			32			33	29			33	28
DR11 (5)	17			21	0.05	1.7	19	8			13	14
DR12 (5)	4			1			10	8			4	5
DR13 (6)	19	0.003	0.5	20	0.04	0.6	19	8	0.03	0.3	29	30
DR14 (6)	5			4			0	8			9	5
DR7	16			21			10	13			8	19
DR8	7			9			10	4			0	5
DR9	3			3			0	0			<b>8</b>	n.s. 4.8
DR10	2			2			0	4			4	4
DR103	1			1			0	0			0	1
DR51	31			29			33	27			29	23
DR52	<b>58</b>	n.s.	0.6	58			60	57			63	70
DR53	43			45			38	38			42	46
DQ												
DQ1	<b>63</b>	n.s.	0.7	60			65	54			79	71
DQ5 (1)	27			26			25	33			35	35
DQ6 (1)	42			<b>39</b>	n.s.	0.6	50	<b>29</b>	n.s.	0.4	57	51
DQ2	34			29			38	54			30	38
DQ3	55			60			52	46			54	51
DQ7 (3)	34			37			35	29			25	28
DQ8 (3)	18			17			16	17			25	20
DQ9 (3)	8			11			0	4			9	8
DQ4	<b>8</b>	n.s.	2.6	<b>10</b>	n.s.	3.3	10	8			0	3

Bold printed numbers were not significant (n.s.) after necessary correction (see Materials and Methods).

There were no significant differences in serologically defined HLA class I antigen frequencies when all cervical cancer patients were compared with controls. To investigate HPV type-specific associations, we categorized patients by HPV group (e.g., patients with tumors positive for HPV 16, HPV 18, other HPV types, and tumors in which no HPV DNA could be detected). Eighty-five percent of the cervical cancer specimens were HPV positive. This result is compatible with the hypothesis that only a small proportion of invasive cervical cancer do not contain HPV DNA. Moreover, the HPV negative tumor samples may represent conditions of decreased detectability [24]. Interruptions or deletions at the primer binding site during the process of integration of HPV DNA may prevent HPV detection [25, 26].

The B63 antigen frequency was increased in the group of patients with tumors with HPV types other than HPV 16 or HPV 18 while the frequency of B55 was increased in the group of patients with HPV-negative tumors. However, the patient groups are small and the findings need to be confirmed since they have never been reported before.

Studies on the association of HLA class II antigens and cervical cancer revealed inconsistent results. The described association of cervical cancer with HLA DQ3 and in later studies with the corresponding DQB1\*03 alleles was not observed in this study [22, 27–29]. However, this is in agreement with other studies in different populations in which this association was also not shown [30–32]. Wank *et al.* also described an association with DR5 which was suggested to be caused by the linkage disequilibrium with HLA-DQ3. Duggan-Keen *et al.* described higher frequencies of DRB1\*11, a molecular split of the DR5 serogroup, in a sub-group of patients with high-stage disease while Syrjänen *et al.* showed increased frequencies of the DR5 antigen in CIN lesions and in women harboring HPV 16 [23, 27, 33]. In our study, the frequency of DR11 was higher in patients with HPV 16-positive tumors compared with controls suggesting a weak association which seems independent of the occurrence of the DQ3 phenotype. DR3 antigen frequencies were increased compared to controls in cervical cancer patients with tumors containing HPV types other than HPV 16 or HPV 18 ( $p$ -value = 0.02, RR =

**TABLE 3** Frequencies (%) of HLA class II specificities in CIN patients versus controls

(n)	CIN (116)	RR	CIN I/II (39)	RR	CIN III (77)	RR	Controls (1100)
DR							
DR1	19		18		19		20
DR2	34		<b>44</b>	(2.1)	29		27
DR15 (2)	31		<b>38</b>	(2.0)	28		24
DR16 (2)	3		<b>5</b>	(3.9)	1		2
DR3	19		21		19		25
DR4	28		23		30		28
DR11 (5)	13		3		18		14
DR12 (5)	2		3		1		5
DR6	38		32		41		35
DR13 (6)	30		24		33		30
DR14 (6)	<b>10</b>	(2.1)	<b>13</b>	(2.8)	9		5
DR7	19		23		18		19
DR8	<b>11</b>	(2.2)	<b>15</b>	(3.3)	9		5
DR9	2		0		3		2
DR10	2		0		3		4
DR103	0		0		0		1
DR51	32		43		27		23
DR52	66		55		72		70
DR53	42		36		44		46
DQ							
DQ1	76		79		75		71
DQ5 (1)	32		29		34		35
DQ6 (1)	55		60		53		51
DQ2	35		38		33		38
DQ3	46		33		52		51
DQ7 (3)	26		21		29		28
DQ8 (3)	17		11		19		20
DQ9 (3)	6		3		8		8
DQ4	<b>10</b>	(3.3)	<b>13</b>	(4.5)	<b>9</b>	(2.9)	3

Bold printed numbers, although increased, were not significantly different from controls after correction (see Materials and Methods).

2.5). This result confirms the positive association of DRB1\*03 with cervical cancer observed in French patients [34]. We found an increased frequency of DR15 antigens in patients compared to controls irrespective of their HPV status ( $p = 0.05$ , RR = 1.4). In support of this observation, it is noted that DR15 is part of the DR2 serogroup and a trend for an increase in DR2 has been observed among HPV 16-positive caucasoid carcinoma patients [30]. Apple *et al.* described in Hispanic CIN and carcinoma patients increased DRB1\*1502-DQB1\*0602 haplotype frequencies. The results reported here therefore appear applicable to different populations [31, 35].

In our study DR13 frequencies were decreased in patients with HPV positive tumors but not in the patient group with HPV negative tumors. This result confirms the reported negative association of this antigen with HPV infection and cervical cancer as described in different populations [27, 31, 34]. Therefore, it is highly

suggestive that the DR13 phenotype is protective against HPV infection and subsequent HPV related lesions.

The observed decrease of DR52, DQ1, and DQ6 antigens in this study has not been reported before and since the decrease was not significant after correction, the importance of this finding is unclear.

As cervical carcinoma is preceded by a period of cervical intraepithelial neoplasia, HLA associations with CIN lesions may help to elucidate the role of immunological factors in the progression from CIN to invasive cancer. An increase of DR15 antigens in CIN I/II patients and DQ4 antigens in all CIN patients was observed. DR15 and DQ4 are antigens which were also increased in patients with invasive cervical cancer in this study. Therefore, patients with these antigens may be less likely to clear HPV infections and/or HPV related lesions. Subsequent studies, including HPV status of the CIN patients, may elucidate possible associations with particular HPV types.

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