# Genetic susceptibility to HPV infection and cervical cancer

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## Abstract

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Squamous cell carcinoma of the cervix (SCCC) is one of the leading causes of death in developing countries. Infection with high-risk human papillomavirus (HPV) is the major risk factor to develop malignant lesions in the cervix. Polymorphisms of the MHC and p53 genes seem to influence the outcome of HPV infection and progression to SCCC, although controversial data have been reported. MHC are highly polymorphic genes that encode molecules involved in antigen presentation, playing a key role in immune regulation, while p53 is a tumor suppressor gene that regulates cell proliferation. The HPV E6 protein from high-risk types binds p53 and mediates its degradation by the ubiquitin pathway. The role of these polymorphisms in genetic susceptibility to HPV infection and to SCCC remains under investigation.

## Carcinoma of the uterine cervix and human papillomavirus

Squamous cell carcinoma of the cervix (SCCC) is one of the most frequent carcinomas affecting women, predominantly in developing countries (1). SCCC and its precursor lesions (cervical intraepithelial neoplasias or CINs) behave as sexually transmitted diseases. Epidemiological and molecular studies have implicated human papillomavirus (HPV) as the major risk factor to develop malignant lesions in the uterine cervix (2). HPV DNA is found in more than 90% of the samples from patients with SCCC, with HPV16 being the type most frequently found (3). SCCC and HPV infections share several risk factors related to sexual behavior, including age at first intercourse and increas-ing number of sexual partners in a lifetime (4).

Papillomaviruses are epitheliotropic viruses present in the skin and mucosa of several animals. In humans, more than 70 types have been described (5). Mucosal and genital HPVs, consisting of about 30 types, are divided into low-risk (HPVs 6, 11, 42, 43, and 44) and high-risk (HPVs 16, 18, 31, 33, 35, 45, 51, 52 and 56), according to their presence in malignant lesions of the cervix (6).

The genome of these viruses is a double-stranded DNA molecule of about 8000 bp. Three genomic regions have been identified: a late region (L), an early region (E), and a long control region (LCR). The early genes E1 and E2 encode proteins involved in viral DNA replication and control of viral tran-

scription (5). The products of genes E6 and E7 are essential in the process of HPV-induced cellular immortalization and transformation (7,8). The late genes L1 and L2 encode the viral capsid proteins (5).

HPV genomes are found as episomes in the nucleus of infected cells of the normal cervix, where infective viral particles can be isolated. However, in some low-grade and in most of the high-grade lesions of the uterine cervix, including cancer, HPV genomes are found integrated into the host genome (9). A disruption of the E1-E2 region is required for HPV genome integration. This event results in an increased expression and stabilization of the E6 and E7 transcripts (10).

The E6 protein from high-risk HPVs binds cellular p53 (11), promoting the degradation of p53 by the cellular ubiquitin proteolysis system (12). The E7 protein interacts with pRB and inactivates this cellular protein (13). As a consequence, E2F transcription factor is released from pRB-E2F complex, leading to transcriptional activation of several genes involved in cell proliferation (14). Such interactions of HPV E6 and E7 proteins interfere with two major pathways involved in the control of the cell cycle.

## Persistence of HPV infections

Infection with high-risk HPV types is frequent among sexually active women, with incidence ranging from 15 to 40% (2). When additional cervical specimens are taken from these women in follow-up surveys, the majority of the infections are found to be transient (15). However, a small proportion of infected women has persistent infection with high-risk HPV types. Previous reports have demonstrated that women persistently infected with oncogenic HPV types are more likely to develop malignant cervical lesions (16) and progressive dysplasia (17). Furthermore, persistent HPV infections associated with a high viral load are considered to be risk factors for persistent cervical lesions

(18,19). This could be explained by intrinsic features of some HPV types, particularly those of the high-risk type, but very little is known in this respect.

It is also likely that the genetic background of the host influences the persistence of HPV infection. Among genetic factors that could participate in the susceptibility to SCCC and disease outcome, polymorphic genes of the major histocompatibility complex (MHC), as well as a particular polymorphism in the p53 gene have been intensely investigated.

## MHC genes and cervical cancer

MHC genes are highly polymorphic genes that encode proteins implicated in antigen presentation to T cells. The MHC class I genes (HLA-A, HLA-B and HLA-C, in humans) are expressed in all nucleated cells and their products present antigenic peptides to CD8^{+} T cells (cytotoxic T cells). The expression of MHC class II genes is restricted to professional antigen-presenting cells (APCs) and activated lymphocytes. Class II molecules (HLA-DR, HLA-DQ and HLA-DP, in humans) present antigenic peptides to CD4^{+} T cells (helper T cells) (20). The MHC genes play a key role in the regulation of the immune response (21).

Some studies have indicated a role for MHC genes in immunological events related to papillomavirus infection, such as wart regression and response to HPV epitopes (22,23). Furthermore, it has been reported that MHC class II genes are involved in genetic susceptibility to cervical cancer in humans. Positive and negative associations between HLA alleles and SCCC or HPV infection have been described. Table 1 lists the results obtained in several studies (see Refs. 24-42) carried out on different populations. These findings show that the associated MHC class II alleles may change according to the population analyzed. On the other hand, some associations are frequently

Table 1 - HLA associations with HPV-associated cervical intraepithelial neoplasia (CIN) and squamous cell carcinoma of the cervix (SCCC).

[a]Positive associations are indicated by OR values above 1, and negative associations by values lower than 1. [#]Allele frequencies in the control group were obtained from International Histocompatibility Workshops. [*]Control group is not from the same population. CIS - Carcinoma in situ; LSIL - low-grade squamous intraepithelial lesion; HSIL - high-grade squamous intraepithelial lesion.

| Disease | Patients | Controls | Population | Associations[a] | Reference |
|---|---|---|---|---|---|
| SCCC | 66 | 109 | German | DQ3 (OR = 7.1) | 24 |
| | | 2019[#] | | DR6 (OR = 0.07) | |
| SCCC | 65 | 857 | British | No associations found | 25 |
| SCCC | 213 | 181 | Norwegian | DQ3 (OR = 2.0) | 26 |
| CIN III | 30 | 99 | British | DQB1*03 (CIN III: OR = 2.5) | 27 |
| CIN I/CIN II | 24/21 | 323 | Belgian | DQB1*03 (CIN I-II: OR = 2.6) | 28 |
| SCCC | 22 | 387[*] | Tanzanian | DQB1*0602 (positive association) | 29 |
| HPV infection | 95 | 78 | British | DQ3 (OR = 2.0) | 30 |
| SCCC | 98 | 220 | Hispanic | DRB1*1501-DQB1*0602 (all cases: OR = 2.9; HPV16-positive cases: OR = 4.8) | 31 |
| | | | | DRB1*0407-DQB1*0302 (HPV16-positive cases: OR = 2.6) | |
| | | | | DRB1*0405-DQB1*0302 (other HPV-positive cases: OR = 4.2) | |
| | | | | DR13 haplotypes (all cases: OR = 0.29; HPV16-positive cases: OR = 0.26) | |
| | | | | DR14 haplotypes (other HPV-positive cases: OR = 0.15) | |
| SCCC | 66 | 214 | African-American | DQB1*0303 (OR = 2.7) | 32 |
| | | | | DQB1*0604 (OR = 5.2) | |
| | | | | DQB1*0201 (OR = 0.57) | |
| | | | | DQB1*0301/*0501 heterozygous (OR = 0.1) | |
| SCCC | 23 | 307[#] | Japanese | DQ3 (OR = 6.9) | 33 |
| CIN III/CIS | 73 | 220 | Hispanic | DRB1*1501 (HPV16-positive cases: OR = 4.7) | 34 |
| | | | | DRB1*1501-DQB1*0602 (HPV16-positive cases: OR = 3.0) | |
| | | | | DRB1*0407-DQB1*0302 (HPV16-positive cases: OR = 2.7) | |
| | | | | DRB1*0701-DQB1*0201 (HPV16-positive cases: OR = 2.3) | |
| | | | | DQA1*0501-DQB1*0301 (HPV16-positive cases: OR = 0.2) | |
| SCCC | 150 | 175 | Swedish | DRB1*0301-DQB1*0201 (HPV18-positive cases: OR = 3.8) | 35 |
| | | | | DRB1*0802-DQB1*0402 (all cases: OR = 10.0) | |
| | | | | DRB1*1001-DQB1*0501 (HPV18-positive cases: OR = 13.7) | |
| Cervical cancer | 126 | 165 | French | DRB1*1301, DRB1*1302 (OR = 0.3) | 36 |
| | | | | DRB1*1301/02-DQA1*0103-DQB1*0603 (OR = 0.25) | |
| CIN | 176 | 416 | British | DRB1*0401-DQB1*0301 (OR = 2.2) | 37 |
| | | | | DRB1*1101-DQB1*0301 (OR = 3.9) | |
| | | | | DRB1*0101-DQB1*0501 (OR = 0.5) | |
| CIN | 74 | 164 | Swedish | DQB1*0602 (all cases: OR = 2.2; HPV16-seropositive cases: OR = 5.7) | 38 |
| | | | | DRB1*15 (all cases: OR = 2.2; HPV16-seropositive cases: OR = 5.8) | |
| | | | | DRB1*15-DQA1*0102-DQB1*0602 (all cases: OR =2.2; HPV16-seropositive cases: OR = 5.8) | |
| | | | | DQA1*0501-DQB1*0301 (HPV16-seronegative cases: OR = 3.0) | |
| | | | | DR13-DQA1*0103-DQB1*0603 (OR = 0.1) | |
| CIN | 92 | 225 | Norwegian | DQA1*0102-DQB1*0602 (HPV-positive cases: OR = 3.2; HPV16-positive cases: OR = 10.1) | 39 |
| | | | | DQA1*0102-DQB1*0604 (HPV16-positive cases: OR = 0.1) | |
| CIN | 118 | 2440 | Dutch | B*44 (disease progression: OR = 9.0) | 40 |
| | | | | DRB1*07 (HPV 16 infection: OR = 5.9) | |
| CIN/SCCC | 142 | 138 | Spanish | Positive associations with HLA-A2, DR2, DQB1*0301 and DQB1*0402 | 41 |
| | | | | Negative association with DQB1*0603 | |
| CIN | 509 | 202 | American | DQB1*0302 homozygous or DQB1*0302 and B*07 (HPV16-positive cases: OR = 4.5 for LSIL and OR = 9.0 for HSIL) | 42 |
| | | | | DRB1*1501-DQB1*0602 (HPV16-positive cases: OR = 0.21 for HSIL) | |
| | | | | DRB1*13 (HPV16-positive cases: OR = 0.78 for LSIL and OR = 0.63 for HSIL) | |

found, even for different ethnic groups. Positive associations between HLA-DQB1*03 and SCCC were described in Caucasian, Black and Oriental populations (24,32,33). Haplotype DRB1*15-DQB1*0602, and its individual alleles were found to be positively associated with SCCC in several studies conducted on Caucasian, Hispanic and Black populations (29,31,38), although negative association with this haplotype was also reported (42). Furthermore, negative associations frequently involved the DRB1*13 alleles (31,36). Some alleles and haplotypes were found to be positively and negatively associated with SCCC depending on the population studied. Our group, in collaboration with Dr. Petzl-Erler, Federal University of Paraná, is investigating the HLA class II allele distribution in women with HPV infection and SCCC in Brazilian populations.

An interesting result reported by Ellis et al. (43) indicated a possible explanation for HLA associations with HPV infection and SCCC. The authors identified in a large proportion of HLA-B7 patients an HPV16 variant which has a point mutation in the E6 protein that alters an HLA-B7 binding epitope. This modification could affect the proper antigenic recognition by cytotoxic T lymphocytes (CTLs). The effect of these altered peptide ligands in impairing CTL function has been recently demonstrated (44).

An HPV16 variant that presents a base change at nucleotide 350 (T→G:Leu→Val), as compared to the prototype, was associated with persistent HPV infections (16). However, no correlations were observed between HLA class I and class II genes and HPV variants when the E6 and E7 sequences were analyzed (40). In another study, HPV16 and HPV18 E2 variants that co-segregate with the variant at position 350 were detected more frequently in DRB1*0401-DQB1*0301 and DRB1*1101-DQB1*0301 carriers (45).

Several reasons may be responsible for the conflicting results about the association between MHC genes and HPV-associated cervical disease. Other genes, closely linked to HLA genes, may be involved in the genetic susceptibility to papillomavirus infection and SCCC development. Different linkage disequilibrium patterns among populations may be responsible in part for the conflicting associations reported. Several non-HLA genes located in the MHC region also participate in the immune response and are related to disease susceptibility. An increased risk for death or severe neurological disease due to cerebral malaria was associated with the TNF2 allele (46), a variant of the TNF-α gene promoter region, located in the MHC class III region. A susceptibility gene for alveolar lung tumors in the mouse was mapped to the H-2 complex class III region (47).

Besides associations for SCCC and HPV infection, genetic susceptibility to two Epstein-Barr virus-associated tumors, namely nasopharyngeal carcinoma (48) and Hodgkin disease (49), was linked to the HLA class I and class II regions, respectively. Recently, an increased frequency of the DRB1*1501 and DQB1*0602 alleles was found in human T-cell lymphotropic virus type I (HTLV-I) carriers (50). These viruses are associated with adult T-cell leukemia and lymphoma. In cutaneous melanoma, an increased risk was reported for HLA-DQB1*0301 carriers (51). It is likely that HLA genes influence the development of virus-associated malignant diseases since these genes play a role in the regulation of the immune response against these viruses.

## Immunological response against HPV

In spontaneously regressing plane warts, the cellular infiltrate is composed mainly of T cells and mononuclear phagocytes (52). Furthermore, E6- and E7-specific CTLs were detected in the peripheral blood of patients with high grade lesions (53) and infiltrating HPV-associated tumoral tissues (54). It was

also demonstrated that the HPV E7 protein is a tumor-specific antigen important in animal models of tumor rejection (55). These results indicate that the cellular immune response is very important in the clearance of HPV infections. Furthermore, patients infected with human immunodeficiency virus (HIV) have a higher prevalence of HPV infection and malignant anogenital lesions. In HIV-1-positive women, Vernon et al. (56) showed that the more immunocompromised is the patient, the more likely she is to carry persistent HPV infections.

An evaluation of the immune response in the context of HPV infection and disease progression was performed by lymphoproliferative assays. De Gruijl et al. (57) found a stronger T helper cell proliferative response against HPV16 E7 peptides in patients with persistent HPV infection. On the other hand, Kadish et al. (58) observed that an efficient lymphoproliferative response specific for HPV16 E6 and E7 peptides was correlated with clearance of HPV infection and CIN regression. Other HPV proteins such as E1, E2 and L1 are also capable to elicit lymphocyte proliferation (59,60). In animal models, a positive lymphoproliferative response to cottontail rabbit papillomavirus L1 and L2 protein was detected in animals with regressing papilloma (61).

The evaluation of cytokine patterns in HPV-associated diseases has revealed that alterations in the cytokine balance are related to disease outcome. Depending on the set of cytokines secreted, T helper cells are divided into Th1 cells, which produce IL-2, IFN-$\gamma$ and TNF-ß, and Th2 cells, which produce IL-4, IL-5, IL-10 and IL-13 (62). While Th1 cytokines stimulate the cellular immune response, Th2 cytokines repress it. A Th1 response was correlated with wart regression (63), and less severe HPV-associated disease (64,65). Low levels of intratumoral IFN-$\gamma$ were related to a poor prognosis for SCCC (66). It was also demonstrated that in patients with HPV-associated lesions that are responsive to treatment with IFN-$\gamma$ the levels of Th1 cytokines and cellular recruitment were higher in responders than in nonresponders (67).

Several factors regulate the balance between Th1 and Th2 responses, such as cytokines produced by immunocompetent cells, antigen dose, costimulatory molecules and recruited APC (68). Although experimental evidence indicates that MHC molecules could participate in the regulation of Th1 and Th2 balance (69), the role of these molecules in this regulation remains unclear.

## p53 polymorphism and susceptibility to SCCC

A p53 polymorphism in codon 72 has been described, which encodes either arginine or proline residues. Interestingly, the frequency of the arginine allele increases proportionally to the latitude, while the proline allele shows an inverse effect, i.e., it is more frequent in Black populations, and the arginine allele predominates among Caucasians (70).

Associations with this polymorphism in human cancers has been reported. Buller et al. (71) reported significant differences in the distribution of these p53 alleles between ovarian cancer patients and controls. Storey et al. (72) observed that the p53 arginine variant is more susceptible to HPV E6-mediated degradation than the proline variant. Furthermore, these authors have shown that individuals homozygous for the arginine allele had a 7 times higher chance to bear an HPV-associated SCCC than heterozygous proline/arginine women.

However, similar analyses performed in other populations did not confirm the association between such polymorphism of the p53 gene and the risk to develop HPV-associated lesions (73,74). Our group is currently investigating this p53 polymorphism in a sample of Brazilian patients with HPV-positive SCCC and in healthy women.

In conclusion, several reports indicate that genetic background is important to define higher or lower susceptibility to HPV infection and to SCCC, particularly polymorphisms of the MHC and p53 genes. The mechanisms by which these polymorphisms may influence the course of HPV infections and cervical lesions are under investigation. Such knowledge may contribute to defining better preventive and therapeutic approaches to control the burden of cervical cancer.

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