



# Immune and Genetic Susceptibility in the Development of Cervical Cancer

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### Abstract

Cervical cancer is the second most frequent cancer in women worldwide. Although 99.7% of cases are attributed to a previous infection by Human papillomavirus, a small percentage of the infected women progress to cervical cancer, suggesting the existence of different risk factors involved in the development and progression of this pathology. Genetic variability related to the host immune system could play an important role in the defense response to Human papillomavirus and therefore to the probability of developing cervical cancer. Worldwide, several international studies have reported that some genetic variations in immune system, such as polymorphisms in genes HLA, CTLA-4, MTHFR, Tp53 and receptors of natural killer cells are associated with susceptibility to cervical cancer, although these variations can also play a protective role depending on the study population. The role of the genetic factors of the host cell is an important factor in the progression of the cervical cancer.

### Keywords

Immune response, Polymorphisms, Uterine cervical neoplasms, Human papillomavirus

### Introduction

Cervical cancer (CC) is the second most frequent cancer in women worldwide with more than 529,000 new diagnosed cases and 275,000 deaths every year [1]. More than 80% of deaths by CC are recorded in developing countries [2]. Epidemiologists have established an etiological association between CC and Human papillomavirus (HPV) [3], as 99.7% of cases of CC are attributed to a previous infection by HPV [4]. Despite many women are infected with HPV, only a small percentage develops the neoplasia [5]. Therefore, it must be considered several different risk factors involved in the development and progression of this tumor, and the genetic variability of the host cell being proposed as one of most influential [6]. Mutations and polymorphisms may cause a genetic imbalance in the woman, making her more or less susceptible to the development and progression of the disease. The aim of this review is to present

the genetic susceptibility factors, mainly about the immune system, for the development of CC.

### Immune Function-Related Genetic Variations

Genetic variability related to the host immune system could play an important role in the defense response to HPV and therefore to the probability of developing CC [7]. Thus, different polymorphisms and mutations in natural killer (NK) cell receptors, coding regions of the human leukocyte antigen (HLA) and T-lymphocyte antigens have been the object of various studies.

#### Polymorphisms in natural killer (NK) cell receptors

Four of surface receptors that control the NK cell activity are involved in the development and persistence of CC: NKp46 and NKp30, natural cytotoxicity receptors, and NKG2D, an activating receptor that is one of the five allelic variants of the heterodimer CD94:NKG2 [8,9]. Low regulation of these receptors has been demonstrated at the same time as decreased cytotoxic activity of NK cells in Mexican patients positive for HPV16 and with cervical carcinoma. However, the exact mechanism that triggers these imbalances remains known [8].

The NKG2D Thr72Ala (rs2255336) polymorphism has been linked to the loss of function of NK cells and T cells in different types of cancer [10-12]. The presence of this polymorphism has also been reported in Polish women with CC and women positive for HPV. The study suggested that women carriers of the NKG2D 72Thr genetic variant may exhibit a certain protection against the progression of the tumor towards advanced stages [9].

#### Polymorphisms of the HLA region

As the allelic variants of HLA are highly polymorphic, they are one of the most frequently studied elements in the search for genetic factors that influence HPV infection and the risk of developing CC [13,14]. Therefore, polymorphisms in genes in HLA-class I (HLA-A, HLA-B, HLA-C, HLA-G) and HLA-class II (HLA-DP, HLA-DQ and HLA-DR) have been widely researched.

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**HLA-A polymorphisms:** In Chinese women positive for high-risk HPVs and with differing degrees of cervical carcinoma, a relation was observed between HLA-A polymorphisms and the danger of developing cancer. Generally, without regard to the infectious stage of the HPV, there is a reduced risk of developing invasive cervical cancer (ICC) in patients carrying the A\* 0207/0215N and A\* 2402 alleles, which may confer a possible protective effect against the neoplasia [15]. However, a subsequent study showed that the A\* 2402 allele is associated with the possibility of contracting CC in Japanese women [16].

A\* 0206 is another allele studied for its involvement in CC. Several studies have concluded that Chinese and Japanese women infected with HPV and carriers of A\* 0206 could be less likely to develop a tumor [15,16].

**HLA-B polymorphisms:** In Costa Rican women positive for HPV and with differing degrees of cervical neoplasia, the B\* 07 and DQB1\* 0302 polymorphisms increased the likelihood of suffering high-grade squamous intraepithelial lesions (HSIL) and low-grade squamous intraepithelial lesions (LSIL) 8.2 and 5.3 times, respectively [17]. The role of the B\* 07 allele as a risk factor for cancer was also demonstrated in Chinese women from eight families with a history of cervical neoplasias. The authors of that study proposed the B\* 07 polymorphism as a potential molecular biomarker for a screening test for that carcinoma [18].

More recently, a study that evaluated the frequency of the B\* 51:01:02 and B\* 51:01:01 polymorphisms in patients in China with squamous cell carcinoma (SCC) of the cervix and positive for HPV suggested such allelic variants as factors of susceptibility and resistance to CC respectively [19].

**HLA-C polymorphisms:** Both killer cell immunoglobulin-like receptors (KIR) and their ligands have been related to the development of CC. In American women with ICC, an association of the HLA-C locus with the risk of developing the neoplasia has been suggested, possibly due to the action of certain NK cell ligands, specifically KIR ligands, after verifying the presence of the HLA-Cw ligand in women with ICC and particularly those infected with HPV16 and HPV18 [20].

In Korean women, a relation between KIR ligands and HPV-related cervical neoplasia has been reported. In patients with CC and positive for HPV16 and HPV18, the HLA-C\* 0303 and HLA-C\* 01 alleles which also act as KIR ligands could be an indicator of susceptibility to and protection against CC, respectively [21].

**HLA-DP polymorphisms:** The HLA-DP rs3077 and HLA-DP rs9277535 polymorphisms have been proposed as susceptibility markers for CCU as it has been shown that they increase the possibility of contracting the neoplasia in Chinese women. The results of that study also suggested that SNPs may play a role not only in CC but also in the persistence of HPV infection [22]. However, a study conducted on another female population of the same nationality indicated that there is no evidence to relate HLA-DP polymorphisms to susceptibility to CC [23].

**HLA-DQ and HLA-DR polymorphisms:** One of the first complete studies on the HLA region was carried out on 1,006 Dutch patients with differentiated cervical neoplasias. The 221 and 184 alleles were analyzed for their proximity to the region containing the HLA-DQ and HLA-DR genes. A significant decrease in the frequency of the 221 allele and a strong association of the 184 allele in patients with SCC suggest G51125 and MICA as genetic markers for susceptibility to CC [14]. From that report, the HLA-DQ and HLA-DR regions, particularly the HLA-DRB1 and HLA-DQB1 alleles, have been widely studied for their involvement in the development of CC.

The DRB1\* 04 and DQB1\* 0302 alleles have been positively related to Argentinian women with intraepithelial neoplasias (IEN) III and SCC and positive for HPV, whereas the DRB1\* 13 and DQB1\* 02 alleles have been related negatively to this subgroup. The researchers proposed the first two alleles as risk factors and the latter two as

resistance factors against the malignant progression of the tumor [24]. The role of the DRB1\* 04 allele was also demonstrated in Chinese women with a family history of CC who presented a greater frequency of the allele than a control group [25].

A study conducted with two groups of Chinese women, younger and older than 35 years, revealed that the women in the first group, diagnosed with SCC and positive for HPV16, showed a greater frequency of the DQB1\* 0301 allele (29.6%) than the women in the second group (12.9%). The DRB1\* 04 and DRB1\* 09 alleles most commonly appeared in women under 35 diagnosed with SCC and negative for HPV16 (14.1%, 26.6%) compared to their counterparts (5.9%; 10.5%). The DRB1\* 07 allele was only detected in the second group of women (SCC and positive for HPV16). However, the allelic frequency of DQB1\* 0501 was lower in women in the first group with SCC positive (7.4%) or negative for HPV16 (6.3%) in contrast to those in the second group (25.8%, 20.4%). The authors suggested that the allelic variants of DRB1 and DQB1 differed in both study groups and that this difference could be attributed to the infectious stage of HPV16 [26].

The effect of the genetic variation of the HLA-DRB1 and HLA-DQB1 alleles has also been studied in Tunisian women with ICC and SCC. DRB1\* 15 and DQB1\* 06 were associated with 2.7 and 3.5 times more risk of developing ICC, respectively. The DRB1\* 13-DQB1\* 03 haplotype showed a similar effect: an increase of 3.5 times in patients with ICC, whereas the DRB1\* 13-DQB1\* 06 haplotype was related to a weak (0.3 times) protective effect [27].

**HLA-G polymorphisms:** The influence of various polymorphisms in the 3' UTR region of the G antigen of major histocompatibility complex I (HLA-G 3'UTR) has been linked to CC. In Canadian women positive for HPV, the risk factor for developing ICC was significantly enhanced in cases with homozygous genotypes for G\* 01:01:02, G\* 01:06 and G\* 3'UTR 14-bp In/In, whereas the cases with heterozygosity for the wild allele (G\* 01:01:01) were significantly associated with a reduced risk of an invasive carcinoma [28].

In Brazilian patients, smokers and positive for HPV, the G\* 3'UTR 14-bp Del/Del and G\* 3'UTR 14-bp In/In polymorphisms were linked to less and greater danger of developing ICC, respectively. G\* 3'UTR 14-bp In/In was also related to an increased likelihood of suffering from HSILs. Likewise, the G\* 3'UTR 14-bp In/Del genotype was more frequently found in women with a family history of CC and HSILs. That study also reported the ( ) In/G and ( ) Del/G haplotypes, which are associated with increased and decreased risk of HSIL and ICC, respectively [29].

The ( ) Del/G haplotype has also been linked to a lower probability of developing ICC in Italian patients with differing histological degrees of CC and positive for HPV. The authors also proposed the ( ) Del/C haplotype as a link to increased likelihood of developing ICC [30].

Very recently, the +3142C/C polymorphism was associated with an increase in the risk factor for SCC in Taiwanese women and, in addition, its frequency is high in the subgroup of women positive for HPV16 [31].

## Polymorphisms of CTLA-4

The CTLA-4 gene, located on chromosome 2 at band q33, plays an important role in the deregulation of T-lymphocyte effector cells [32,33]. There is evidence of multiple polymorphisms in CTLA-4 associated with susceptibility to autoimmune diseases [34,35] and multiple single nucleotide polymorphisms (SNPs) in the coding region of CTLA-4 related to susceptibility to human tumors (renal cancer, breast cancer, melanoma, gastric cancer) [36,37]. It has been shown that in Chinese women positive for HPV, the CTLA-4 -318 C/T and CTLA-4 CT60 G/A SNPs affect the development of CC [32]. Although there is no clarity with respect to how the CTLA-4 polymorphisms trigger the neoplasia, its causes include the loss of homeostasis of the immune system [32], activation of the cytokine pathway [32] and the overexpression of CTLA-4; the latter may trigger inhibition of the immune activity of T cells in the presence of certain alleles [38].

## Genetic Variations Involved in DNA Synthesis

### Polymorphisms associated with the enzyme methylene tetrahydrofolate reductase (MTHFR)

Polymorphisms in the coding gene of MTHFR are linked to the risk of CC [39]. This homodimeric enzyme catalyzes the conversion of 5,10 methylenetetrahydrofolate to 5-methyltetrahydrofolate and directs the homeostasis between DNA synthesis and methylation [40]. The polymorphism most commonly associated with MTHFR is the transition from C to T at nucleotide 677 (677T), located on chromosome1p36 [41-43]. The MTHFR 677C > T (rs1801133) polymorphism changes amino acid 222, an alanine, to a valine and thereby decreases the activity of the enzyme, which is considered an influential factor in carcinogenesis [42]. Individuals with TT mutation in MTHFR have only 30% of the enzymatic activity that individuals with the wild-type genotype possess (CC), whereas the heterozygous (CT) have 65% of the normal enzymatic activity [41].

The incidence of MTHFR polymorphisms in women with CC contrasts: C77T has been considered a risk factor in Asian, European and American women [43,44], whereas in Indian women it has been related to a protective effect [45]. By contrast, a meta-analysis that involved Greek, Korean, Chinese, Indian and Dutch women did not demonstrate any association between the polymorphism and this tumor [41].

### Polymorphisms in the Tp53 gene

One of the most common mutations in all types of human cancers occurs in the tumor suppressor gene Tp53, which is located on chromosome17p13 [46]. The rs1042522 G > C SNP, also known as Arg72Pro, consists of the variation from G to C in exon 4 of Tp53, which is deactivated by the action of the early oncogene HPV E6. The presence of these polymorphisms could increase the affinity of viral E6 for Tp53, which would facilitate its degradation by means of ubiquitination [47]. Several studies have evaluated the role of Arg72Pro in Tp53 and the stages of initiation, progression and development of CC. Tp53 participates in the initiation of squamous intraepithelial lesions (SIL), in the progression of SIL to CC and in the risk of ICC in the presence of HPV. It has been reported that in populations like India, China, Japan and Korea the Arg72Pro polymorphism increases the risk of developing cancer, particularly in the Indian population [47,48].

## Discussion

The HPV infection is necessary but insufficient to trigger CC, which suggests the existence of various risk factors involved in its development and progression. One of most influential is the genetic variability of the host, which could make the individual more or less susceptible to developing the neoplasia. As in most cases the infection is eliminated thanks to innate immunity, the role of the immune system being key in the progression or regression of the disease [7].

The polymorphisms and genetic variants in HLA, CTLA-4, MTHFR, Tp53 and NK cells present differences depending on the study population [16,23,41,45] (Table 1). Therefore, it may be said that there is no consensus regarding the susceptibility to or protective effect against CC associated with the alleles considered in this review. Wang et al. hypothesized that multiple alleles associated with the risk of CC are required for this tumor to be able to develop; nevertheless, the presence of only one protective allele would be sufficient to protect against cancer [17]. On the other hand, there have been many more studies on Asian populations compared to the world population as there are differences in the evaluated parameters, such as age of the patients, type of HPV, state of the infection, carcinogenic stage and lifestyles. In this sense it would be interesting to consider future studies that, maintaining the same parameters, include a large number of demographic variables and a high density of genetic markers to determine the largest number of genetic variations possible.

Most of the genetic variations analyzed in this review appear in women positive for HPV and with some histological grade of CC; these variations could influence not only the genetic susceptibility to CC, but also the persistence of HPV infection.

Studying the genetic variations could be very useful when choosing an effective vaccine for CC because it is still not known how the vaccination affects the natural immunity and what the genetic consequences might be in vaccinated women [49], especially in women who present some of the polymorphisms mentioned.

To date, there have been no conclusive studies about how genetic susceptibility is mechanically related to the HPV infection and its

**Table 1:** Summary of genes associated with genetic susceptibility to cervical cancer in different populations.

Gene	Location	Genetic variation	Study population	Reference
CTLA-4	2q33	-318 C/T	Chinese women	[32]
		CT60 G/A	Chinese women	[32]
		A'0206	Chinese women	[15]
		A'0207/0215N	Chinese women	[15]
HLA-A	6p21.3	A'2402	Chinese women	[15]
			Japanese women	[16]
HLA-B	6p21.3	B'07	Costa Rican women	[17]
		B'51:01:01	Chinese women	[19]
		B'51:01:02	Chinese women	[19]
HLA-C	6p21.3	C'01	Korean women	[21]
		C'0303	Korean women	[21]
		C'w group 1	American women	[20]
HLA-DP	6p21.3	rs3077	Chinese women	[22]
		rs9277535	Chinese women	[22]
HLA-DQ y HLA-DR	6p21.3	DQB1'02	Argentinian women	[24]
		DQB1'0301	Chinese women	[26]
		DQB1'0302	Argentinian women	[24]
		DQB1'0501	Chinese women	[26]
		DQB1'06	Tunisian women	[27]
		DRB1'04	Argentinian women	[24]
			Chinese women	[25]
			Chinese women	[26]
		DRB1'07	Chinese women	[26]
		DRB1'09	Chinese women	[26]
		DRB1'13	Argentinian women	[24]
DRB1'13-DQB1'03	Tunisian women	[27]		
DRB1'13-DQB1'06	Tunisian women	[27]		
DRB1'15	Tunisian women	[27]		
HLA-G	6p21.3	G'01:01:01	Canadian women	[28]
		G'01:01:02	Canadian women	[28]
		G'01:06	Canadian women	[28]
		G'3'UTR 14-bp Del/Del	Brazilian women	[29]
		G'3'UTR 14-bp In/In	Canadian women	[28]
			Brazilian women	[29]
		G'3'UTR 14-bp In/Del	Brazilian women	[29]
		(')Del/C	Italian women	[30]
		(')Del/G	Brazilian women	[29]
			Italian women	[30]
(')In/G	Brazilian women	[29]		
+3142C/C	Taiwanese women	[31]		
MTHFR	1p36	MTHFR 677C > T (rs1801133)	Indian women	[45]
			Greek, Korean, Chinese, Indian and Dutch women.	[41]
			Greek, Korean, Chinese, Indian, Polish, American and Dutch women.	[43]
			Chinese women	[44]
NKG2D	12p13.2-p12.3	NKG2D Thr72Ala	Polish women	[9]
		NKG2D 72Thr	Polish women	[9]
Tp53	17p13	Arg72Pro (rs1042522)	Chinese, Korean, Japanese and Indian women.	[48]
			Caucasian and East Asian women.	[47]

progression to CC; therefore, a combination of cytological tests for HPV and immunity tests is needed, as well as a clinical follow-up of the affected patients to determine with certainty the role genetic factors play in the progression of CC.

Although the HPV infection is recognized as the main cause of CC, not all women infected by this microorganism develop preneoplastic or neoplastic lesions of the cervix. What is more, susceptibility to CC is conditional on the capacity of the immune response people have to the HPV infection and/or to its elimination from the body once it has already infected the host. The immune system response to this infection will depend largely on the genetic variability of each individual, given by various polymorphisms in HLA and NK cell receptors. In addition, protein polymorphisms such as Tp53 can increase the affinity of HPV oncogenes, thereby promoting an increase in the apoptosis inhibition rate in the infected cells.

For this reason, despite the implementation of the vaccine against some HPV genotypes in various countries, it will be necessary to assess the polymorphisms present in each population in order to establish the risk of developing CC as well as detection of the virus.

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