Review Article

A comprehensive review on host genetic susceptibility to human papillomavirus infection and progression to cervical cancer

Koushik Chattopadhyay
Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, Republic of South Africa

Cervical cancer is the second most common cancer in women worldwide. This is caused by oncogenic types of human papillomavirus (HPV) infection. Although large numbers of young sexually active women get HPV-infected, only a small fraction develop cervical cancer. This points to different co-factors for regression of HPV infection or progression to cervical cancer. Host genetic factors play an important role in the outcome of such complex or multifactor diseases such as cervical cancer and are also known to regulate the rate of disease progression. The aim of this review is to compile the advances in the field of host genetics of cervical cancer. MEDLINE database was searched using the terms, 'HPV', 'cervical', 'CIN', 'polymorphism(s)', 'cervical' + *the name of the gene* and 'HPV' + *the name of the gene*. This review focuses on the major host genes reported to affect the progression to cervical cancer in HPV infected individuals.

Key words: Cervical cancer, genetics, HPV, polymorphism, progression

Introduction

Cervical cancer is the second most common cancer in women world-wide with an annual 493,243 cases and 273,505 deaths.[1] The incidence of cervical cancer is higher in developing countries and less in developed countries with an effective cervical screening program. About 80% of the cases occur in developing countries. In some of the places, cervical cancer is the most common cancer in women. Latin America, the Caribbean, sub-Saharan Africa and South and South-East Asia have the highest incidence rate.[2,3] The main cause of cervical cancer is infection by human papillomavirus (HPV).

During their life-time many women become infected with HPV, but interestingly only a small fraction of them develop cervical cancer and the rest regress to a normal healthy state. This suggests the role of additional risk factors playing an important role in the outcome of the infection. These risk factors include host and viral genetic factors along with environmental and life style factors.

Host genetic risk factors to HPV infection and cervical cancer: The genetic link to cervical cancer development is strongly supported by epidemiological studies. A hereditary component of cervical tumors was detected in comparisons of twins[4] and in a mother-daughter family study. The possibility of host genetic predisposition is strengthened by the observation that biological first degree relatives of the women who have developed a cervical tumor experience a two-fold risk of developing cervical tumor compared to non-biological relatives of women with cervical tumor.[5] The heritability of cervical tumors has been determined as 27%.[6]

Materials and Methods

A review of peer-reviewed literature in the MEDLINE database was conducted. Major host genes that have

Access this article online	
Quick Response Code:	Website: www.ijhg.com
	DOI: 10.4103/0971-6866.92087

Address for correspondence: Dr. Koushik Chattopadhyay, Flat no. 12, Roseric, 67 Lena Arhens Road, Bulwer, Durban – 4001, Republic of South Africa. E-mail: chattopadhyayk@india.com.

been considered to play either a susceptible or protective role in the development of cervical intraepithelial neoplasia (CIN) or cervical cancer from HPV infection have been discussed. The following medical subject headings (MESH) and text words were used to search the MEDLINE database, 'HPV', 'cervical', 'CIN', and 'polymorphism(s)'. Separate searches were carried out for each individual candidate host gene using the search terms, 'cervical, *the name of the gene*', 'HPV, *the name of the gene*'. Studies on human subjects and published in any languages were considered. The studies that compared allele or genotype frequencies of candidate host genes in cervical cancer patients or patients in any grade of CIN with non-cancerous healthy individuals or among the different groups of cases were eligible for this review.[7,8]

Human leukocyte antigen genes (HLA): ***HLA*** comprises a family of genes within the major histocompatibility complex (MHC) localized on Chromosome 6 (6p). *HLA* genes are divided into 2 major classes; Class I genes (most notably *HLA* A, B and C genes) and Class II genes (most notably DR, DQ and DP genes). *HLA* Class I molecules (HLA Class I gene product) are expressed in all nucleated cells and present foreign antigens to CD8+ Cytotoxic T lymphocytes (CTLs) (acquired immune response). CD8+ T cells have the ability to kill the foreign antigen presented to them by the *HLA* Class I molecules. *HLA* Class II molecules (*HLA* Class II gene products) are typically expressed in cells of the immune system, such as dendritic cells, macrophages, B-lymphocytes and are known to be important in presenting antigenic peptides to CD4+ helper T-lymphocytes. Class I and Class II *HLA* genes are highly polymorphic, a necessity for evolutionary survival as it provides resistance to potential pathogens by binding and presenting a wide variety of antigenic peptides. Presence of *HLA* molecules that bind HPV antigens with high affinity might confer a protective effect on the progression of cervical cancer; on the other hand presence of *HLA* molecules that do not recognize and bind a wide variety of HPV antigens might be associated with the susceptibility of the disease.

HLA A, B and C genes have been investigated by several groups in different population in relation to cervical cancer. Contrasting results have been found. *HLA* A2, A*01, A*24, A*1104, B7, B15, B63 and Cw*0202 loci have been reported to be associated with increased risk of developing cervical cancer.[9-19] On the other hand, a protective effect has been found for *HLA* A*0207/0215N or A*2402.[18]

HLA DQ and *DR* genes have been extensively studied by many groups in different population across the globe. DQA1*01, *03, DQB1*02, *03, *04, *06 and DQw1, DQw3 alleles have been associated with increased risk of developing the disease.[10,11,14,20-47] A protective association has also been found with DQA1*0501 and DQB1*0201, *0103, *0301/*0501, *04, *05, *050201, *06 alleles.[27,33,34,44,45,48-51] DRB1 *4, *5, *11, *13, *15, *16 were found to be susceptible loci.[12,14,15,30,31,36,38-40,42,43,51-57] and DR *1, *2, *4, *6, *12, *13, *14, *15 were found to be protective loci.[10-12,15,43,48,51,58] Only a few studies investigated the DO and DP genes and reported a positive association with severity of the disease with both the DOB1*03 and DPB1 genes.[40,59,60]

The interactions of DQ-DR haplotypes and their effect on cervical cancer showed interesting results. An increased association with the disease was found for DRB1-DQB1 (04-03, 15-06, 16-05, 08-04) and DQA1-DQB1 (01-06, 05-03).[30-32,40,54,61-65] A protective effect was also found for DQA1-DQB1 (02-02), DRB1-DRB1 (1301-02) and DRB1-DQB1 (15-06).[10,25,46,52,60,61,65]

Tp53: *Tp53* gene localized on chromosome 17q 13.1 encodes protein 53 (p53) and is a tumor suppressor gene that regulates the cell cycle. In case of DNA damage, *Tp53* is up regulated and causes G1 arrest of the cell allowing the genetic damage to be repaired. HPV 16 and 18 encodes two major oncoproteins, E6 and E7. These two proteins interfere with the cellular tumor suppressor proteins. *Tp53* gene is commonly known to have a polymorphism in codon 72 with two alleles encoding either arginine (Arg/Arg) or praline (pro/pro). This polymorphism was first investigated by *Storey et. al.* in cervical cancer patients. They reported a seven times higher risk of developing HPV-associated cervical carcinogenesis in individuals with Arg homozygosity than with heterozygous genotype. Several groups investigated the *Tp53* codon 72 polymorphism in cervical cancer susceptibility in different ethnic groups with contradictory

results. Many studies on various ethnic groups found *Tp53* codon 72 Arg as a risk allele for HPV infection and progression to cervical cancer comparing case-control individuals.[66-84] *Tp53* codon 72 Arg was found to be associated with adenocarcinoma but not with squamous cell carcinoma (SCC) and conferring susceptible effect to GSTT1 null individuals. A large number of case-control studies in different ethnic groups failed to show an association of Arg allele with HPV infection and progression to cervical cancer.[78,85-117]

Tp53 codon 72 Arg allele was also found to have decreased association to cervical abnormalities and HPV infection. On the other hand, the *Tp53* Pro/Pro genotype was reported to have a higher risk in developing cervical cancer.

Tumor necrosis factor (TNF) genes: *TNF* genes are situated centromeric to the HLA-B genes and telomeric to the C2 genes.[47] TNF is a cytokine and is produced mainly by activated macrophages. *TNF* genes produce two immunologically important proteins, TNF-α and TNF-β. These proteins play a crucial role in the inflammatory response and immune activities toward tumor cells.[118] TNF acts through the TNF Receptors (TNF-R1 and R2) and is a part of the complex pathway of triggering apoptosis. The binding of TNF to TNF-R1 initiates the pathway that leads to caspase activation via the adapter proteins (TRADD, FADD) committing the cell to apoptosis. This binding is also involved in activation of transcription factors involved in cell survival and inflammatory responses.[119] TNF also interacts with tumor cells to trigger cytolysis. Cancer patients have been found with increased levels of TNF- α.[120,121] Several polymorphic sites have been reported in *TNF* locus including five microsatellites of TNFa-e.[122] *TNFa* is closely linked to *TNF*- β gene and contains 14 different alleles (a1-a14) with an AC/GT dinucelotide repeat. Several groups investigated the role of various polymorphic sites of *TNF* gene in association to cervical cancer in different ethnic populations. A positive association was found with cervical cancer and the presence of *TNFa-8, TNF-α -572, -857, -863* and also with *TNF G-308A*.[123-125] *G-308A* did not show any association in South African population.[126]

MHC class I polypeptide-related sequence A (MICA): The MICA gene is located on chromosome 6, centromeric to *HLA-B* and telomeric to *TNF* and encodes the highly polymorphic MHC (HLA) class I chain-related gene A. The MICA is expressed by keratinocytes and epithelial cells on the cell surface and interacts with T cells and has an important role in immune response and direct induction of mucosal immunity.[125,127] The protein functions as a stress-induced antigen broadly recognized by intestinal epithelial gamma delta T cells. MICA is also involved in presentation of foreign antigens to the immune system.[128] Exon 5 of *MICA* gene contains a microsatellite locus with 5 alleles, in strong linkage disequilibrium with *HLA-B* alleles.[129] Different polymorphic sites of MICA were investigated in Swedish and Asian population but none were found to have an association with cervical cancer.

WAF1/p21: The *WAF1/p21* gene is located on chromosome 6p21.2 and is a Tp53 mediator. Any changes in this gene may affect the regulation of cell growth and result in excessive proliferation of cancer cells. A serine to arginine change has been well documented followed by a C to A transversion at the third base of codon 31.[130,131] Different groups studied this polymorphism with mixed results. Ser/Ser genotype was found to be the susceptible genotype for adenocarcinoma in high risk HPV but not for SCC.[72] Ser/Arg genotype was associated with susceptibility to cervical cancer.[132] Some studies failed to find any association between this polymorphism and cervical cancer.[133,134]

Interleukin-10 (IL-10): *IL-10* gene is localized on chromosome 1. IL-10 is a TH2 type cytokine produces a suppressive effect on cell mediated immunity (CMI).[135-137] Increased expression of IL-10 is reported in SCC[138] and increased serum levels of IL-10 in cervical cancer.[139] One of the polymorphisms that is associated with low, medium or high production of IL-10 situates in the promoter region of the gene at position-1082.[140] Several studies investigated this polymorphism with conflicting results. -1082 A/G was found to be the risk genotype for cervical cancer.[141] However, -1082G allele was shown to have an inverse association with HPV persistency.[142] A few studies failed to find any association of this polymorphism with cervical cancer.[143-146]

Methylenetetrahydrofolate reductase (MTHFR):

MTHFR gene is situated on chromosome 1p36.3.[147] MTHFR enzyme regulates the metabolism of folate and methionine, which are critical for DNA methylation and synthesis. C to T transition at nucleotide position 677 of the *MTHFR* gene results in alanine to valine. Compared to homozygous wild type (Ala/Ala) both heterozygous (Ala/Val) and homozygous (Val/Val) variants reduce MTHFR enzyme activity in individuals with a low folate status.[148,149] Hence this polymorphism might cause an abnormal DNA methylation and DNA synthesis which can lead to an increased risk of developing cancer. This polymorphism is less frequent in blacks than in Caucasians.[150] Different groups investigated the effect of this polymorphism in different case-control populations with conflicting results. Some found the polymorphism as a risk factor to develop cervical cancer[151-154] while others did not.[155-157] A reduced risk of developing CIN II/III for the mutant-type carriers compared to the wild type carriers of this polymorphism was also reported.[152]

Interferon-gamma (IFN-γ): *IFN-* γ gene is mapped on chromosome 6. IFN- γ is crucial in defending against viruses and in the induction of immune mediated inflammatory responses.[158] T to A change at the +874 position from translation start site in the first intron of IFN-γ gene was reported to have a high IFN- γ production. A low (A/A), medium (A/T) and high (T/T) IFN-γ production is associated with +874 single nucleotide polymorphism (SNP).[159] This polymorphism did not show any association with cancer of the cervix.[146]

Chemokine receptor-2 (CCR2): *CCR2* gene is situated on chromosome 3p21. One of the earliest responses of human body to injury or infection is the release of chemokines that triggers penetration of local inflammatory and immune cells.[160] It has been postulated that HPV disrupts the interaction between epithelial cells and the immune system by deregulating the expression of chemokines which have been associated with bacterial or viral infections, autoimmune diseases, heart diseases and many others.[161] MCP-1 is a ligand for chemokine receptor CCR2 produced largely by tumor cells. MCP-1 is responsible for recruiting macrophages to tumors in bladder, cervix, ovary, lung and breast. Though macrophages display tumor cytotoxicity, tumor-associated macrophages (TAMs) mainly have protumor functions[162] and help in tumor angiogenesis. More expression of MCP-1 recruits more macrophages and speeds up the process of tumor progression. When the epithelial cells are infected by HPV, it reduces the MCP-1 expression from low-grade squamous intraepithelial lesions (LSIL) to high-grade squamous intraepithelial lesions (HSIL)[163] and the levels of MCP-1 expression increases again from HSIL to invasive cervical cancer (ICC). Tumor cells have been reported with high levels of MCP-1 expression.[164] Macrophages, which are recruited by MCP-1 chemokine, express CCR2 on their cell surface.

CCR2 has two isoforms – CCR2A and CCR2B originated from the CCR2 gene by alternative splicing. A single nucleotide polymorphism (SNP) of G to A at position 190 of CCR2 gene changes amino acid valine (GTC) to isoleucine (ATC) at codon 64 (*CCR2-V64I*). This conservative amino acid change takes place in the first transmembrane domain of CCR2A and CCR2B. This change makes CCR2A more stable and increases its half-life but does not any way affect the stability of CCR2B isoform. The increased stability of CCR2A might accumulate a large amount of this isoform on the macrophage cell surface which also interferes with the CCR2B function. This misleads the cells and the macrophage recruitment drops during the development of the tumor which hampers the tumor angiogenesis and eventually gives a protective effect to the tumor progression. This polymorphism (*CCR2-V64I*) has been extensively studied and several reports show a protective role of the polymorphism with AIDS,[165-168] multiple sclerosis[169] and breast cancer.[170] This polymorphism was studied in Portuguese, Swedish and South African black and mixed-ancestry population. Comparing squamous intraepithelial lesions (SIL) with ICC showed a protective effect of the A allele for developing ICC from SIL.[171] The A allele was also found to be a risk allele for developing HSIL[172] and cervical cancer[173] compared to healthy controls. Contrasting to that, a decreased risk of developing cervical cancer was reported in the presence of the A allele.[174] Some groups failed to find an association of this polymorphism with cervical cancer,[175] pre-cancerous lesions or HPV infection.[173]

Fas and Fas ligand (FasL): *Fas* gene is situated on

chromosome 10q24.1. The role of corrupted apoptosis has long been well documented for development of tumorigenesis. Tumorigenesis is achieved not only by increased cell proliferation but also by a decreased apoptotic rate.[176] Defects in the mechanism of apoptosis genes have been identified as cancer causing agents. Apoptosis is dependent greatly by signals from cell surface death receptor Fas/CD95. Together with Fas ligand (FasL), it triggers programmed cell death.[177] The signal produced by the DNA binding of transcription factors SP1 (stimulatory protein 1) and STAT1 (signal transducer and activator of transcription 1) are associated with transcriptional activation and expression of Fas gene. Fas -1377 bp and -670 bp are situated within SP1 and STAT1 binding sites respectively. It has been shown that a change of A at -1377 of Fas promoter considerably reduces SP1 binding compared to -1377G resulting in a decrease of Fas gene expression.[178,179] Gamma interferon activation signal (GAS) is a binding element responsible for DNA binding of STAT1. -670bp is located within GAS binding site. A change of G at -670 of Fas promoter region partially or completely abolishes the GAS element, hence significantly reduces the Fas gene expression [180,181] which results in decreased activation induced cell death (AICD) and uncontrolled growth of the virus. It has also been shown that a higher basal expression of FasL is associated with the C allele at position 844 of *FasL* gene than with the T allele.[181] Reduced expression of FasL inhibits the apoptotic activity of the Fas-FasL pathway. Studies on these polymorphisms with cervical cancer ranging from Asian, European to Black and mixed-ancestry African have shown conflicting results. An association of Fas-670A allele and A/A genotype with higher risk of developing cervical cancer was reported.[182] Other studies on case-controls and affected sib-pairs (ASP) did not find any association of this polymorphism with cancer of the cervix.[183-185] Fas-1377 polymorphism was not found to be associated with disease severity.[185,186] FasL844C allele and C/C genotype was found to be susceptible to cervical cancer;[187] however, other groups refuted this result.[185,188]

CASP8: *CASP8* gene is localized on chromosome 2q33-34 and codes for caspase 8. This gene is also known as *FLICE* or *MCH5*. Two commonly known polymorphisms in the *CASP8* gene have been well studied, namely *CASP8* D302H and *CASP8* -652 6N ins/del.[189] Among these, only *CASP8* -652 6N ins/del (rs3834129) polymorphism is associated with susceptibility to cervical cancer.[190] A functional polymorphism of a six nucleotide deletion of AGTAAG at the position 652 of the promoter region of the *CASP8* gene (*CASP8* -652 6N ins/del) has been identified. This six nucleotide deletion destroys a binding element for transcriptional activator stimulatory protein-1 (SP1) which reduces capase-8 expression leading to decreased AICD in CTLs.[190]

The influence of *CASP8* -652 6N ins/del polymorphism on cervical cancer was investigated and a reduced risk of cervical cancer was reported with *CASP8* -652 6N del/del.[190]

Genes encoding detoxifying enzymes (CYP1A1, CYP2D6, GSTM1, GSTT1): Environmental risk factors have been speculated to play an important role in HPV infection and persistence by many researchers. Smoking is a well-known environmental risk factor[191] in progression to cervical cancer, suggesting a possible link with allelic changes at the genes encoding for detoxifying enzymes. CYP1A1 and CYP2D6 are phase 1 cytochrome P450 enzyme that catalyze the modification of various enzymes including carcinogenic enzymes and help the phase 2 enzymes, glutathione S-transferases (GST family), to convert to extractable compounds.

CYP1A1: Several polymorphisms have been described for *CYP1A1*, a T to C change (m2) in the 3' non-coding region of the gene leading to an MspI restriction site has been well studied. An increased risk of developing cervical cancer with C allele, C/C and T/C genotype of m2 polymorphism compared to wild type T/T genotype was observed.[70,192,193] No association of this polymorphism with disease severity was observed as well.[177] Other studies reported m1 polymorphism (G) and CYP1A1*3 as the risk alleles for cervical cancer.[194,195]

CYP2D6: CYP2D6 is classified in wild type homozygous extensive metabolizers (EM) carrying a mutation of G to A at intron 3/exon 4, heterozygous extensive metabolizers (HEM) carrying a base pair deletion in exon 5 and poor metabolizers (PM) with a total gene

deletion. This polymorphism has been studied in cancer with contradictory results.[195,196] It was shown that EM is a susceptible allele and genotype for high grade CIN in women who smoke, but the same is not true for progression to SCC.[196]

*GSTM1: GSTM1*genotype is a combination of *GSTM1*0*, *GSTM1**A and *GSTM1*B* alleles. *GSTM1*0* is also called GSTM1 null, which is a deletion of the gene and no expression of protein for homozygotes. Studies with this polymorphism showed a positive association with susceptibility to cervical cancer and high risk HPV infection and GSTM1 null genotype,[72,193,197,198] whereas other groups failed to find any association.[70,199-201]

GSTT1: GSTT1 gene plays a role in phase two detoxification of carcinogens present in tobacco smoke and also in pesticides like halo-methanes and methyl bromide.[195] Some studies with this polymorphism on cervical cancer patients found an association of this genotype with increasing risk of developing cervical cancer or HSIL;[70,202-204] on the other hand, some studies reported no association with cancer of the cervix.[193,195,198,202]

This review compiles the major host genetic risk factors that have been found associated and not-associated with HPV infection and progression to cancer of the cervix. Zoodsma *et al,* published a meta-analysis of *HLA* genes and other non-HLA candidate genes. They reviewed 35 publications for *HLA* genes and 32 publications for Tp53 gene. A review article by *Hildesheim et al*, on *HLA* genes considered 28 publications. Another meta-analysis of Tp53 gene reviewed 37 publications. All these reviews considered publications up till 2002. The present review is wider in every sense as it considers a greater number of publications. This is also an updated review of host genetic susceptibility to cervical cancer compared to the above-mentioned reviews. This review also includes more genes (such as Fas, FasL, CCR2-V64I and IFN-γ) than reviewed by Zoodsma *et al.*

In conclusion, this review shows a broad picture of host genetic determinants to HPV infection, different stages of neoplasia and progression to cervical cancer. It is not possible to pin-point one or two genes causing severity or conferring a protective effect to a complex disorder like cervical cancer, rather depends on different genes involved in different pathways in addition to the main causative agent. It is also evident that a complex disease like cervical cancer depends on different parameters and a critical interaction between different genes and also between gene and environment play a crucial role in that.

Acknowledgement

I would like to thank Prof. Anna-Lise Williamson (Institute of Infectious Disease and Molecular Medicine, Medical Virology, University of Cape Town) and Dr. Collet Dandara (Institute of Infectious Disease and Molecular Medicine, Human Genetics, University of Cape Town) for editing and reviewing the virology part and the genetics part of the review respectively. Funding was provided by University of Cape Town, Poliomyelitis Research Foundation (PRF) and National Research Foundation (NRF), South Africa.

References

1. Castellsague XS, de Aguado S, Louie D, Bruni KS, Munoz L, Diaz J, *et al*. HPV and cervical cancer in the world 2007 report. Vaccine 2007;26:S3.
2. Parkin DM. Global cancer statistics in the year 2000. Lancet Oncol 2001;2:533-43.
3. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000: The global picture. Eur J Cancer 2001;37 (Suppl 8):S4-66.
4. Galloway DA. Papillomavirus vaccines in clinical trials. Lancet Infect Dis 2003;3:469-75.
5. Magnusson PK, Sparen P, Gyllensten UB. Genetic link to cervical tumours. Nature 1999;400:29-30.
6. Hemminki K, Dong C, Vaittinen P. Familial risks in cervical cancer: Is there a hereditary component? Int J Cancer 1999;82:775-81.
7. Zhu M, Zhao S. Candidate gene identification approach: Progress and challenges. Int J Biol Sci 2007;3:420-7.
8. Tabor HK, Risch NJ, Myers RM. Candidate-gene approaches for studying complex genetic traits: Practical considerations. Nat Rev Genet 2002;3:391-7.
9. Duggan-Keen MF, Keating PJ, Stevens FR, Sinnott P, Snijders PJ, Walboomers JM, *et al*. Immunogenetic factors in HPV-associated cervical cancer: Influence on disease progression. Eur J Immunogenet 1996;23:275-84.
10. Hildesheim A, Schiffman M, Scott DR, Marti D, Kissner T, Sherman ME, *et al*. Human leukocyte antigen class I/II alleles and development of human papillomavirus-related cervical neoplasia: Results from a case-control study conducted in the United States. Cancer Epidemiol Biomarkers Prev 1998;7:1035-41.
11. Wang SS, Wheeler CM, Hildesheim A, Schiffman M, Herrero R, Bratti MC, *et al*. Human leukocyte antigen class I and II alleles and risk of cervical neoplasia: Results from a population-based study in Costa Rica. J Infect Dis 2001;184:1310-4.

12. Krul EJ, Schipper RF, Schreuder GM, Fleuren GJ, Kenter GG, Melief CJ. *HLA* and susceptibility to cervical neoplasia. Hum Immunol 1999;60:337-42.
13. Chan PK, Cheung JL, Cheung TH, Lin CK, Tam AO, Chan DP, *et al*. HLA-B alleles, high-risk HPV infection and risk for cervical neoplasia in southern Chinese women. Int J Cancer 2006;118:1430-5.
14. Montoya L, Saiz I, Rey G, Vela F, Clerici-Larradet N. Cervical carcinoma: Human papillomavirus infection and HLA-associated risk factors in the Spanish population. Eur J Immunogenet 1998;25:329-37.
15. Silva B, Vargas-Alarcon G, Zuniga-Ramos J, Rodriguez-Reyna TS, Hernandez-Martinez B, Osnaya N, Kofman S, Torres-Lobaton A, Granados J. Genetic features of Mexican women predisposing to cancer of the uterine cervix. Hum Pathol 1999;30:626-628.
16. Trimble CL, Piantadosi S, Gravitt P, Ronnett B, Pizer E, Elko A, *et al*. Spontaneous regression of high-grade cervical dysplasia: Effects of human papillomavirus type and *HLA* phenotype. Clin Cancer Res 2005;11:4717-23.
17. Carreon JD, Martin MP, Hildesheim A, Gao X, Schiffman M, Herrero R, *et al*. Human leukocyte antigen class I and II haplotypes and risk of cervical cancer. Tissue Antigens 2005;66:321-4.
18. Chan DP, Cheung TH, Tam AO, Cheung JL, Yim SF, Lo KW, *et al*. Risk association between human leukocyte antigen-A allele and high-risk human papillomavirus infection for cervical neoplasia in Chinese women. J Infect Dis 2005;192:1749-56.
19. Wang SS, Hildesheim A, Gao X, Schiffman M, Herrero R, Bratti MC, *et al*. Comprehensive analysis of human leukocyte antigen class I alleles and cervical neoplasia in 3 epidemiologic studies. J Infect Dis 2002;186:598-605.
20. Wank R, Thomssen C. High risk of squamous cell carcinoma of the cervix for women with HLA-DQw3. Nature 1991;352:723-5.
21. Helland A, Borresen AL, Kaern J, Ronningen KS, Thorsby E. *HLA* antigens and cervical carcinoma. Nature 1992;356:23.
22. Wank R, Schendel DJ, Thomssen C. *HLA* antigens and cervical carcinoma. Nature 1992;356:22-3.
23. David AL, Taylor GM, Gokhale D, Aplin JD, Seif MW, Tindall VR. HLA-DQB1*03 and cervical intraepithelial neoplasia type III. Lancet 1992;340:52.
24. Wank R, Meulen JT, Luande J, Eberhardt HC, Pawlita M. Cervical intraepithelial neoplasia, cervical carcinoma, and risk for patients with HLA-DQB1*0602,*301,*0303 alleles. Lancet 1993;341:1215.
25. Helland A, Borresen AL, Kristensen G, Ronningen KS. DQA1 and DQB1 genes in patients with squamous cell carcinoma of the cervix: Relationship to human papillomavirus infection and prognosis. Cancer Epidemiol Biomarkers Prev 1994;3:479-86.
26. Mehal WZ, Lo YM, Herrington CS, Evans MF, Papadopoulos MC, Odunis K, *et al*. Role of human papillomavirus in determining the *HLA* associated risk of cervical carcinogenesis. J Clin Pathol 1994;47:1077-81.
27. Gregoire L, Lawrence WD, Kukuruga D, Eisenbrey AB, Lancaster WD. Association between HLA-DQB1 alleles and risk for cervical cancer in African-American women. Int J Cancer 1994;57:504-7.
28. Odunsi K, Terry G, Ho L, Bell J, Cuzick J, Ganesan TS. Association between *HLA* DQB1 * 03 and cervical intra-epithelial neoplasia. Mol Med 1995;1:161-71.
29. Nawa A, Nishiyama Y, Kobayashi T, Wakahara Y, Okamoto T, Kikkawa F, *et al*. Association of human leukocyte antigen-B1*03 with cervical cancer in Japanese women aged 35 years and younger. Cancer 1995;75: 518-21.
30. Apple RJ, Becker TM, Wheeler CM, Erlich HA. Comparison of human leukocyte antigen DR-DQ disease associations found with cervical dysplasia and invasive cervical carcinoma. J Natl Cancer Inst 1995;87:427-36.
31. Odunsi K, Terry G, Ho L, Bell J, Cuzick J, Ganesan TS. Susceptibility to human papillomavirus-associated cervical intra-epithelial neoplasia is determined by specific *HLA* DR-DQ alleles. Int J Cancer 1996;67:595-602.
32. Sanjeevi CB, Hjelmstrom P, Hallmans G, Wiklund F, Lenner P, Angstrom T, *et al*. Different HLA-DR-DQ haplotypes are associated with cervical intraepithelial neoplasia among human papillomavirus type-16 seropositive and seronegative Swedish women. Int J Cancer 1996;68: 409-14.
33. Ferrera A, Olivo A, Alaez C, Melchers WJ, Gorodezky C. *HLA* DOA1 and DOB1 loci in Honduran women with cervical dysplasia and invasive cervical carcinoma and their relationship to human papillomavirus infection. Hum Biol 1999;71:367-79.
34. Cuzick J, Terry G, Ho L, Monaghan J, Lopes A, Clarkson P, *et al*. Association between high-risk HPV types, *HLA* DRB1* and DQB1* alleles and cervical cancer in British women. Br J Cancer 2000;82:1348-52.
35. Neuman RJ, Huettner PC, Li L, Mardis ER, Duffy BF, Wilson RK, *et al*. Association between DQB1 and cervical cancer in patients with human papillomavirus and family controls. Obstet Gynecol 2000;95:134-40.
36. Beskow AH, Josefsson AM, Gyllensten UB. *HLA* class II alleles associated with infection by HPV16 in cervical cancer *in situ*. Int J Cancer 2001;93:817-22.
37. Dehaghani AS, Amirzargar A, Farjadian S, Ghaderi A. HLA-DQBl alleles and susceptibility to cervical squamous cell carcinoma in Southern Iranian patients. Pathol Oncol Res 2002;8:58-61.
38. Ghaderi M, Wallin KL, Wiklund F, Zake LN, Hallmans G, Lenner P, *et al*. Risk of invasive cervical cancer associated with polymorphic *HLA* DR/DQ haplotypes. Int J Cancer 2002;100:698-701.
39. Matsumoto K, Yasugi T, Nakagawa S, Okubo M, Hirata R, Maeda H, *et al*. Human papillomavirus type 16 E6 variants and *HLA* class II alleles among Japanese women with cervical cancer. Int J Cancer 2003;106:919-22.
40. Engelmark M, Beskow A, Magnusson J, Erlich H, Gyllensten U. Affected sib-pair analysis of the contribution of *HLA* class I and class II loci to development of cervical cancer. Hum Mol Genet 2004;13:1951-8.
41. Dao DD, Sierra-Torres CH, Robazetti SC, de Gomez MN, Konig R, Lema C, *et al*. HLA-DQB1 and cervical cancer in Venezuelan women. Gynecol Oncol 2005;96:349-54.
42. Zoodsma M, Nolte IM, Schipper M, Oosterom E, van der Steege G, de Vries EG, *et al*. Analysis of the entire *HLA* region in susceptibility for cervical cancer: A comprehensive study. J Med Genet 2005;42:e49.
43. Schiff MA, Apple RJ, Lin P, Nelson JL, Wheeler CM, Becker TM. *HLA* alleles and risk of cervical intraepithelial

neoplasia among Southwestern American Indian women. Hum Immunol 2005;66:1050-6.
44. Wu Y, Chen Y, Li L, Cao Y, Liu Z, Liu B, *et al*. Polymorphic amino acids at codons 9 and 37 of HLA-DQB1 alleles may confer susceptibility to cervical cancer among Chinese women. Int J Cancer 2006;118:3006-11.
45. Lema C, Fuessel-Haws AL, Lewis LR, Rady PL, Lee P, Turbat-Herrera EA, *et al*. Association between HLA-DQB1 and cervical dysplasia in Vietnamese women. Int J Gynecol Cancer 2006;16:1269-77.
46. Wu Y, Liu B, Lin W, Xu Y, Li L, Zhang Y, *et al*. HPV16 E6 variants and *HLA* class II polymorphism among Chinese women with cervical cancer. J Med Virol 2007;79:439-46.
47. Bhattacharya P, Sengupta S. Predisposition to HPV16/18-related cervical cancer because of proline homozygosity at codon 72 of p53 among Indian women is influenced by HLA-B*07 and homozygosity of HLA-DQB1*03. Tissue Antigens 2007;70:283-93.
48. Beskow AH, Moberg M, Gyllensten UB. *HLA* class II allele control of HPV load in carcinoma *in situ* of the cervix uteri. Int J Cancer 2005;117:510-4.
49. Chan PK, Cheung JL, Cheung TH, Lin CK, Siu SS, Yu MM, *et al*. HLA-DQB1 polymorphisms and risk for cervical cancer: A case-control study in a southern Chinese population. Gynecol Oncol 2007;105:736-41.
50. Peng S, Trimble C, Wu L, Pardoll D, Roden R, Hung CF, *et al*. HLA-DQB1*02-restricted HPV-16 E7 peptide-specific CD4+ T-cell immune responses correlate with regression of HPV-16-associated high-grade squamous intraepithelial lesions. Clin Cancer Res 2007;13:2479-87.
51. Climent C, Nazario CM, Umpierre S, Quintero M, Gorbea S. Major histocompatibility complex class II polymorphisms and risk of cervical cancer in Puerto Rican women. P R Health Sci J 2007;26:97-101.
52. Sastre-Garau X, Loste MN, Vincent-Salomon A, Favre M, Mouret E, de la Rochefordiere A, *et al*. Decreased frequency of HLA-DRB1 13 alleles in Frenchwomen with HPV-positive carcinoma of the cervix. Int J Cancer 1996;69:159-64.
53. Gostout BS, Podratz KC, McGovern RM, Persing DH. Cervical cancer in older women: A molecular analysis of human papillomavirus types, *HLA* types, and p53 mutations. Am J Obstet Gynecol 1998;179:56-61.
54. Maciag PC, Schlecht NF, Souza PS, Franco EL, Villa LL, Petzl-Erler ML. Major histocompatibility complex class II polymorphisms and risk of cervical cancer and human papillomavirus infection in Brazilian women. Cancer Epidemiol Biomarkers Prev 2000;9:1183-91.
55. Cervantes J, Lema C, Valentina Hurtado L, Andrade R, Hurtado Gomez L, Torrico L, *et al*. HLA-DRB1*1602 allele is positively associated with HPV cervical infection in Bolivian Andean women. Hum Immunol 2003;64:890-5.
56. Sastre-Garau X, Cartier I, Jourdan-Da Silva N, De Cremoux P, Lepage V, Charron D. Regression of low-grade cervical intraepithelial neoplasia in patients with HLA-DRB1*13 genotype. Obstet Gynecol 2004;104:751-5.
57. Mahmud SM, Robinson K, Richardson H, Tellier PP, Ferenczy AS, Roger M, *et al*. *HLA* polymorphisms and cervical human Papillomavirus infection in a cohort of Montreal University students. J Infect Dis 2007;196:82-90.
58. Chan PK, Cheung TH, Lin CK, Siu SS, Yim SF, Lo KW, *et al*. Association between HLA-DRB1 polymorphism, high-risk HPV infection and cervical neoplasia in southern Chinese. J Med Virol 2007;79:970-6.
59. Vandenvelde C, De Foor M, van Beers D. HLA-DOB1*03 and cervical intraepithelial neoplasia grades I-III. Lancet 1993;341:442.
60. Wu Y, Liu B, Lin W, Xu Y, Li L, Zhang Y, *et al*. Human leukocyte antigen class II alleles and risk of cervical cancer in China. Hum Immunol 2007;68:192-200.
61. Apple RJ, Erlich HA, Klitz W, Manos MM, Becker TM, Wheeler CM. *HLA* DR-DQ associations with cervical carcinoma show papillomavirus-type specificity. Nat Genet 1994;6:157-62.
62. Allen M, Kalantari M, Ylitalo N, Pettersson B, Hagmar B, Scheibenpflug L, *et al*. *HLA* DQ-DR haplotype and susceptibility to cervical carcinoma: Indications of increased risk for development of cervical carcinoma in individuals infected with HPV 18. Tissue Antigens 1996;48:32-7.
63. Helland A, Olsen AO, Gjoen K, Akselsen HE, Sauer T, Magnus P, *et al*. An increased risk of cervical intra-epithelial neoplasia grade II-III among human papillomavirus positive patients with the HLA-DQA1*0102-DQB1*0602 haplotype: A population-based case-control study of Norwegian women. Int J Cancer 1998;76:19-24.
64. Zehbe I, Tachezy R, Mytilineos J, Voglino G, Mikyskova I, Delius H, *et al*. Human papillomavirus 16 E6 polymorphisms in cervical lesions from different European populations and their correlation with human leukocyte antigen class II haplotypes. Int J Cancer 2001;94:711-6.
65. De Araujo Souza PS, Villa LL. Genetic susceptibility to infection with human papillomavirus and development of cervical cancer in women in Brazil. Mutat Res 2003;544:375-83.
66. Yang YC, Chang CL, Chen ML. Effect of p53 polymorphism on the susceptibility of cervical cancer. Gynecol Obstet Invest 2001;51:197-201.
67. Storey A, Thomas M, Kalita A, Harwood C, Gardiol D, Mantovani F, *et al*. Role of a p53 polymorphism in the development of human papillomavirus-associated cancer. Nature 1998;393:229-34.
68. Andersson S, Rylander E, Strand A, Sallstrom J, Wilander E. The significance of p53 codon 72 polymorphism for the development of cervical adenocarcinomas. Br J Cancer 2001;85:1153-6.
69. Zehbe I, Voglino G, Wilander E, Genta F, Tommasino M. Codon 72 polymorphism of p53 and its association with cervical cancer. Lancet 1999;354:218-9.
70. Kim JW, Lee CG, Park YG, Kim KS, Kim IK, Sohn YW, *et al*. Combined analysis of germline polymorphisms of p53, GSTM1, GSTT1, CYP1A1, and CYP2E1: Relation to the incidence rate of cervical carcinoma. Cancer 2000;88:2082-91.
71. Jee SH, Lee JE, Park JS. Polymorphism of codon 72 of p53 and environmental factors in the development of cervical cancer. Int J Gynaecol Obstet 2003;80:69-70.
72. Lee SA, Kim JW, Roh JW, Choi JY, Lee KM, Yoo KY, *et al*. Genetic polymorphisms of GSTM1, p21, p53 and HPV infection with cervical cancer in Korean women. Gynecol Oncol 2004;93:14-8.
73. Makni H, Franco EL, Kaiano J, Villa LL, Labrecque S,

Dudley R, *et al*. P53 polymorphism in codon 72 and risk of human papillomavirus-induced cervical cancer: Effect of inter-laboratory variation. Int J Cancer 2000;87:528-33.
74. Dos Santos Oliveira Ldo H, Fernandez Ade P, Xavier BL, Machado Rodrigues Ede V, Cavalcanti SM. Analysis of the p53 gene and papillomavirus detection in smears from cervical lesions. Sao Paulo Med J 2002;120:20-2.
75. Van Duin M, Snijders PJ, Vossen MT, Klaassen E, Voorhorst F, Verheijen RH, *et al*. Analysis of human papillomavirus type 16 E6 variants in relation to p53 codon 72 polymorphism genotypes in cervical carcinogenesis. J Gen Virol 2000;81:317-25.
76. Dokianakis DN, Spandidos DA. P53 codon 72 polymorphism as a risk factor in the development of HPV-associated cervical cancer. Mol Cell Biol Res Commun 2000;3:111-4.
77. Klug SJ, Wilmotte R, Santos C, Almonte M, Herrero R, Guerrero I, *et al*. TP53 polymorphism, HPV infection, and risk of cervical cancer. Cancer Epidemiol Biomarkers Prev 2001;10:1009-12.
78. Pegoraro RJ, Rom L, Lanning PA, Moodley M, Naiker S, Moodley J. P53 codon 72 polymorphism and human papillomavirus type in relation to cervical cancer in South African women. Int J Gynecol Cancer 2002;12:383-8.
79. Saranath D, Khan Z, Tandle AT, Dedhia P, Sharma B, Contractor R, *et al*. HPV16/18 prevalence in cervical lesions/cancers and p53 genotypes in cervical cancer patients from India. Gynecol Oncol 2002;86:157-62.
80. Nagpal JK, Sahni S, Das BR. P53 codon 72 polymorphism and susceptibility to development of human papilloma virus-associated cervical cancer in Indian women. Eur J Clin Invest 2002;32:943-8.
81. Mitra S, Misra C, Singh RK, Panda CK, Roychoudhury S. Association of specific genotype and haplotype of p53 gene with cervical cancer in India. J Clin Pathol 2005;58:26-31.
82. Arbel-Alon S, Menczer J, Feldman N, Glezerman M, Yeremin L, Friedman E. Codon 72 polymorphism of p53 in Israeli Jewish cervical cancer patients and healthy women. Int J Gynecol Cancer 2002;12:741-4.
83. Qie M, Zhang Y, Wu J. Study on the relationship between cervical cancer and p53 codon 72 polymorphism. Hua Xi Yi Ke Da Xue Xue Bao 2002;33:274-5.
84. Ojeda JM, Ampuero S, Rojas P, Prado R, Allende JE, Barton SA, *et al*. p53 codon 72 polymorphism and risk of cervical cancer. Biol Res 2003;36:279-83.
85. Wong YF, Chung TK, Cheung TH, Nobori T, Hampton GM, Wang VW, *et al*. p53 polymorphism and human papillomavirus infection in Hong Kong women with cervical cancer. Gynecol Obstet Invest 2000;50:60-3.
86. Minaguchi T, Kanamori Y, Matsushima M, Yoshikawa H, Taketani Y, Nakamura Y. No evidence of correlation between polymorphism at codon 72 of p53 and risk of cervical cancer in Japanese patients with human papillomavirus 16/18 infection. Cancer Res 1998;58: 4585-6.
87. Nishikawa A, Fujimoto T, Akutagawa N, Iwasaki M, Takeuchi M, Fujinaga K, *et al*. p53 Polymorphism (codon-72) has no correlation with the development and the clinical features of cervical cancer. Int J Gynecol Cancer 2000;10:402-7.
88. Josefsson AM, Magnusson PK, Ylitalo N, Quarforth-Tubbin P, Ponten J, Adami HO, *et al*. p53 polymorphism and risk of cervical cancer. Nature 1998;396:531;author reply 532.
89. Gustafsson AC, Guo Z, Hu X, Ahmadian A, Brodin B, Nilsson A, *et al*. HPV-related cancer susceptibility and p53 codon 72 polymorphism. Acta Derm Venereol 2001;81:125-9.
90. Malcolm EK, Baber GB, Boyd JC, Stoler MH. Polymorphism at codon 72 of p53 is not associated with cervical cancer risk. Mod Pathol 2000;13:373-8.
91. Madeleine MM, Shera K, Schwartz SM, Daling JR, Galloway DA, Wipf GC, *et al*. The p53 Arg72Pro polymorphism, human papillomavirus, and invasive squamous cell cervical cancer. Cancer Epidemiol Biomarkers Prev 2000;9:225-7.
92. Inserra P, Abrahamsen M, Papenfuss M, Giuliano AR. Ethnic variation of the P53 codon 72 polymorphism, HPV persistence, and cervical cancer risk. Int J STD AIDS 2003;14:800-4.
93. Rosenthal AN, Ryan A, Al-Jehani RM, Storey A, Harwood CA, Jacobs IJ. p53 codon 72 polymorphism and risk of cervical cancer in UK. Lancet 1998;352:871-2.
94. Lanham S, Campbell I, Watt P, Gornall R. p53 polymorphism and risk of cervical cancer. Lancet 1998;352:1631.
95. Giannoudis A, Graham DA, Southern SA, Herrington CS. p53 codon 72 ARG/PRO polymorphism is not related to HPV type or lesion grade in low- and high-grade squamous intra-epithelial lesions and invasive squamous carcinoma of the cervix. Int J Cancer 1999;83:66-9.
96. Brady CS, Duggan-Keen MF, Davidson JA, Varley JM, Stern PL. Human papillomavirus type 16 E6 variants in cervical carcinoma: Relationship to host genetic factors and clinical parameters. J Gen Virol 1999;80:3233-40.
97. Hayes VM, Hofstra RM, Buys CH, Hollema H, van der Zee AG. Homozygous arginine-72 in wild type p53 and risk of cervical cancer. Lancet 1998;352:1756.
98. Govan VA, Loubser S, Saleh D, Hoffman M, Williamson AL. No relationship observed between human p53 codon-72 genotype and HPV-associated cervical cancer in a population group with a low arginine-72 allele frequency. Int J Immunogenet 2007;34:213-7.
99. Helland A, Borresen-Dale AL. p53 polymorphism and cervical cancer. Lancet 1999;354:1561-2.
100. Ngan HY, Liu VW, Liu SS. Risk of cervical cancer is not increased in Chinese carrying homozygous arginine at codon 72 of p53. Br J Cancer 1999;80:1828-9.
101. Hou MM, Xi MR, Cao ZY, Yang KX, Sun ZL. P53 codon 72 polymorphism in cervical cancers and its correlation with HPV16,18E6. Sichuan Da Xue Xue Bao Yi Xue Ban 2006;37:404-7.
102. Min-min H, Ming-rong X, Ze-yi C, Kai-xuan Y, Zhi-lin S. Analysis of p53 codon 72 polymorphism and its association with human papillomavirus 16 and 18 E6 in Chinese cervical lesions. Int J Gynecol Cancer 2006;16:2004-8.
103. Yamashita T, Yaginuma Y, Saitoh Y, Kawai K, Kurakane T, Hayashi H, *et al*. Codon 72 polymorphism of p53 as a risk factor for patients with human papillomavirus-associated squamous intraepithelial lesions and invasive cancer of the uterine cervix. Carcinogenesis 1999;20:1733-6.
104. Niwa Y, Hamajima N, Atsuta Y, Yamamoto K, Tamakoshi A, Saito T, *et al*. Genetic polymorphisms of p73 G4C14-to-A4T14 at exon 2 and p53 Arg72Pro and the risk of cervical cancer in Japanese. Cancer Lett 2004;205:55-60.

105. Tachezy R, Mikyskova I, Salakova M, Van Ranst M. Correlation between human papillomavirus-associated cervical cancer and p53 codon 72 arginine/proline polymorphism. Hum Genet 1999;105:564-6.
106. Baek WK, Cho JW, Suh SI, Suh MH, Shin DH, Cho CH, *et al*. p53 codon 72 polymorphism and risk of cervical carcinoma in Korean women. J Korean Med Sci 2000;15:65-7.
107. Kim JW, Roh JW, Park NH, Song YS, Kang SB, Lee HP. Polymorphism of TP53 codon 72 and the risk of cervical cancer among Korean women. Am J Obstet Gynecol 2001;184:55-8.
108. Tenti P, Vesentini N, Rondo Spaudo M, Zappatore R, Migliora P, Carnevali L, *et al*. p53 codon 72 polymorphism does not affect the risk of cervical cancer in patients from northern Italy. Cancer Epidemiol Biomarkers Prev 2000;9:435-8.
109. Cenci M, French D, Pisani T, Alderisio M, Lombardi AM, Marchese R, *et al*. p53 polymorphism at codon 72 is not a risk factor for cervical carcinogenesis in central Italy. Anticancer Res 2003;23:1385-7.
110. Comar M, Molin GD, Guaschino S, Campello C. p53 at codon 72 polymorphism, human papillomavirus infection and cervical lesions: A cross-sectional study from northeastern Italy. Eur J Obstet Gynecol Reprod Biol 2004;114:210-4.
111. Kucera E, Tong D, Reinthaller A, Leodolter S, Zeillinger R, Sliutz G. p53 polymorphism at codon 72--does it constitute a risk for squamous intraepithelial lesions and invasive cancer of the cervix in Central Europeans? Wien Klin Wochenschr 2000;112:817-20.
112. Pillai MR, Sreevidya S, Pollock BH, Jayaprakash PG, Herman B. Polymorphism at codon 72 of p53, human papillomavirus, and cervical cancer in South India. J Cancer Res Clin Oncol 2002;128:627-31.
113. Katiyar S, Thelma BK, Murthy NS, Hedau S, Jain N, Gopalkrishna V, *et al*. Polymorphism of the p53 codon 72 Arg/Pro and the risk of HPV type 16/18-associated cervical and oral cancer in India. Mol Cell Biochem 2003;252:117-24.
114. Abba MC, Villaverde LM, Gomez MA, Dulout FN, Laguens MR, Golijow CD. The p53 codon 72 genotypes in HPV infection and cervical disease. Eur J Obstet Gynecol Reprod Biol 2003;109:63-6.
115. Brenna SM, Silva ID, Zeferino LC, Pereira JS, Martinez EZ, Syrjanen KJ. Prognostic value of P53 codon 72 polymorphism in invasive cervical cancer in Brazil. Gynecol Oncol 2004;93:374-80.
116. Settheetham-Ishida W, Singto Y, Yuenyao P, Tassaneeyakul W, Kanjanavirojkul N, Ishida T. Contribution of epigenetic risk factors but not p53 codon 72 polymorphism to the development of cervical cancer in Northeastern Thailand. Cancer Lett 2004;210:205-11.
117. Settheetham-Ishida W, Kanjanavirojkul N, Kularbkaew C, Ishida T. Human papillomavirus genotypes and the p53 codon 72 polymorphism in cervical cancer of Northeastern Thailand. Microbiol Immunol 2005;49:417-21.
118. Li CY, Liu JH, Huang BJ. Correlation between P53 codon 72 polymorphism and tumorigenesis of cervical cancer. Ai Zheng 2004;23:1396-9.
119. Wilson NS, Dixit V, Ashkenazi A. Death receptor signal transducers: Nodes of coordination in immune signalling networks. Nat Immunol 2009;10:348-55.
120. Carroll MC, Katzman P, Alicot EM, Koller BH, Geraghty DE, Orr HT, *et al*. Linkage map of the human major histocompatibility complex including the tumor necrosis factor genes. Proc Natl Acad Sci USA 1987;84:8535-9.
121. Beutler B, Cerami A. The biology of cachectin/TNF: A primary mediator of the host response. Annu Rev Immunol 1989;7:625-55.
122. Ardizzoia A, Lissoni P, Brivio F, Tisi E, Perego MS, Grassi MG, *et al*. Tumor necrosis factor in solid tumors: Increased blood levels in the metastatic disease. J Biol Regul Homeost Agents 1992;6:103-7.
123. Ghaderi M, Nikitina L, Peacock CS, Hjelmstrom P, Hallmans G, Wiklund F, *et al*. Tumor necrosis factor a-11 and DR15-DQ6 (B*0602) haplotype increase the risk for cervical intraepithelial neoplasia in human papillomavirus 16 seropositive women in Northern Sweden. Cancer Epidemiol Biomarkers Prev 2000;9:1067-70.
124. Stanczuk GA, Sibanda EN, Tswana SA, Bergstrom S. Polymorphism at the -308-promoter position of the tumor necrosis factor-alpha (TNF-alpha) gene and cervical cancer. Int J Gynecol Cancer 2003;13:148-53.
125. Govan VA, Constant D, Hoffman M, Williamson AL. The allelic distribution of -308 Tumor Necrosis Factor-alpha gene polymorphism in South African women with cervical cancer and control women. BMC Cancer 2006;6:24.
126. Abrahamsson J, Carlsson B, Mellander L. Tumor necrosis factor-alpha in malignant disease. Am J Pediatr Hematol Oncol 1993;15:364-9.
127. Udalova IA, Nedospasov SA, Webb GC, Chaplin DD, Turetskaya RL. Highly informative typing of the human TNF locus using six adjacent polymorphic markers. Genomics 1993;16:180-6.
128. Zwirner NW, Fernandez-Vina MA, Stastny P. MICA, a new polymorphic HLA-related antigen, is expressed mainly by keratinocytes, endothelial cells, and monocytes. Immunogenetics 1998;47:139-48.
129. Groh V, Steinle A, Bauer S, Spies T. Recognition of stress-induced MHC molecules by intestinal epithelial gammadelta T cells. Science 1998;279:1737-40.
130. Ota M, Katsuyama Y, Mizuki N, Ando H, Furihata K, Ono S, *et al*. Trinucleotide repeat polymorphism within exon 5 of the MICA gene (MHC class I chain-related gene A): Allele frequency data in the nine population groups Japanese, Northern Han, Hui, Uygur, Kazakhstan, Iranian, Saudi Arabian, Greek and Italian. Tissue Antigens 1997;49:448-54.
131. Bahram S, Bresnahan M, Geraghty DE, Spies T. A second lineage of mammalian major histocompatibility complex class I genes. Proc Natl Acad Sci USA 1994;91:6259-63.
132. Santos AM, Sousa H, Pinto D, Portela C, Pereira D, Catarino R, *et al*. Linking TP53 codon 72 and P21 nt590 genotypes to the development of cervical and ovarian cancer. Eur J Cancer 2006;42:958-63.
133. Chedid M, Michieli P, Lengel C, Huppi K, Givol D. A single nucleotide substitution at codon 31 (Ser/Arg) defines a polymorphism in a highly conserved region of the p53-inducible gene WAF1/CIP1. Oncogene 1994;9:3021-4.
134. Sun Y, Hildesheim A, Li H, Li Y, Chen JY, Cheng YJ, *et al*. No point mutation but a codon 31ser-->arg polymorphism of the WAF-1/CIP-1/p21 tumor suppressor gene in nasopharyngeal carcinoma (NPC): The polymorphism

distinguishes Caucasians from Chinese. Cancer Epidemiol Biomarkers Prev 1995;4:261-7.
135. Roh J, Kim M, Kim J, Park N, Song Y, Kang S, *et al*. Polymorphisms in codon 31 of p21 and cervical cancer susceptibility in Korean women. Cancer Lett 2001;165: 59-62.
136. Harima Y, Sawada S, Nagata K, Sougawa M, Ostapenko V, Ohnishi T. Polymorphism of the WAF1 gene is related to susceptibility to cervical cancer in Japanese women. Int J Mol Med 2001;7:261-4.
137. Moore KW, O'Garra A, de Waal Malefyt R, Vieira P, Mosmann TR. Interleukin-10. Annu Rev Immunol 1993;11:165-90.
138. De Waal Malefyt R, Abrams J, Bennett B, Figdor CG, de Vries JE. Interleukin 10(IL-10) inhibits cytokine synthesis by human monocytes: An auto-regulatory role of IL-10 produced by monocytes. J Exp Med 1991;174:1209-20.
139. Chang CH, Furue M, Tamaki K. B7-1 expression of Langerhans cells is up-regulated by pro-inflammatory cytokines, and is down-regulated by interferon-gamma or by interleukin-10. Eur J Immunol 1995;25:394-8.
140. Clerici M, Merola M, Ferrario E, Trabattoni D, Villa ML, Stefanon B, *et al*. Cytokine production patterns in cervical intraepithelial neoplasia: Association with human papillomavirus infection. J Natl Cancer Inst 1997;89: 245-50.
141. Chopra V, Dinh TV, Hannigan EV. Circulating serum levels of cytokines and angiogenic factors in patients with cervical cancer. Cancer Invest 1998;16:152-9.
142. Szoke K, Szalmas A, Szladek G, Veress G, Gergely L, Toth FD, *et al*. IL-10 promoter nt -1082A/G polymorphism and human papillomavirus infection in cytologic abnormalities of the uterine cervix. J Interferon Cytokine Res 2004;24:245-51.
143. Turner DM, Williams DM, Sankaran D, Lazarus M, Sinnott PJ, Hutchinson IV. An investigation of polymorphism in the interleukin-10 gene promoter. Eur J Immunogenet 1997;24:1-8.
144. Stanczuk GA, Sibanda EN, Perrey C, Chirara M, Pravica V, Hutchinson IV, *et al*. Cancer of the uterine cervix may be significantly associated with a gene polymorphism coding for increased IL-10 production. Int J Cancer 2001;94:792-4.
145. Roh JW, Kim MH, Seo SS, Kim SH, Kim JW, Park NH, *et al*. Interleukin-10 promoter polymorphisms and cervical cancer risk in Korean women. Cancer Lett 2002;184: 57-63.
146. Govan VA, Carrara HR, Sachs JA, Hoffman M, Stanczuk GA, Williamson AL. Ethnic differences in allelic distribution of IFN-g in South African women but no link with cervical cancer. J Carcinog 2003;2:3.
147. Zoodsma M, Nolte IM, Schipper M, Oosterom E, van der Steege G, de Vries EG, *et al*. Interleukin-10 and Fas polymorphisms and susceptibility for (pre) neoplastic cervical disease. Int J Gynecol Cancer 2005; 15(Suppl 3):282-90.
148. Farzaneh F, Roberts S, Mandal D, Ollier B, Winters U, Kitchener HC, *et al*. The IL-10 -1082G polymorphism is associated with clearance of HPV infection. BJOG 2006;113:961-4.
149. Goyette P, Sumner JS, Milos R, Duncan AM, Rosenblatt DS, Matthews RG, *et al*. Human methylenetetrahydrofolate reductase: Isolation of cDNA mapping and mutation identification. Nat Genet 1994;7:551.
150. Harmon DL, Woodside JV, Yarnell JW, McMaster D, Young IS, McCrum EE, *et al*. The common 'thermolabile' variant of methylene tetrahydrofolate reductase is a major determinant of mild hyperhomocysteinaemia. QJM 1996;89:571-7.
151. Stevenson RE, Schwartz CE, Du YZ, Adams MJ Jr. Differences in methylenetetrahydrofolate reductase genotype frequencies, between Whites and Blacks. Am J Hum Genet 1997;60:229-30.
152. Gerhard DS, Nguyen LT, Zhang ZY, Borecki IB, Coleman BI, Rader JS. A relationship between methylenetetrahydrofolate reductase variants and the development of invasive cervical cancer. Gynecol Oncol 2003;90:560-5.
153. Piyathilake CJ, Macaluso M, Johanning GL, Whiteside M, Heimburger DC, Giuliano A. Methylenetetrahydrofolate reductase (MTHFR) polymorphism increases the risk of cervical intraepithelial neoplasia. Anticancer Res 2000;20:1751-7.
154. Goodman MT, McDuffie K, Hernandez B, Wilkens LR, Bertram CC, Killeen J, *et al*. Association of methylenetetrahydrofolate reductase polymorphism C677T and dietary folate with the risk of cervical dysplasia. Cancer Epidemiol Biomarkers Prev 2001;10:1275-80.
155. Sull JW, Jee SH, Yi S, Lee JE, Park JS, Kim S, *et al*. The effect of methylenetetrahydrofolate reductase polymorphism C677T on cervical cancer in Korean women. Gynecol Oncol 2004;95:557-63.
156. Zoodsma M, Nolte IM, Schipper M, Oosterom E, van der Steege G, de Vries EG, *et al*. Methylenetetrahydrofolate reductase (MTHFR) and susceptibility for (pre)neoplastic cervical disease. Hum Genet 2005;116:247-54.
157. Lambropoulos AF, Agorastos T, Foka ZJ, Chrisafi S, Constantinidis TC, Bontis J, *et al*. Methylenetetrahydrofolate reductase polymorphism C677T is not associated to the risk of cervical dysplasia. Cancer Lett 2003;191:187-91.
158. Henao OL, Piyathilake CJ, Waterbor JW, Funkhouser E, Johanning GL, Heimburger DC, *et al*. Women with polymorphisms of methylenetetrahydrofolate reductase (MTHFR) and methionine synthase (MS) are less likely to have cervical intraepithelial neoplasia (CIN) 2 or 3. Int J Cancer 2005;113:991-7.
159. Piyathilake CJ, Azrad M, Macaluso M, Johanning GL, Cornwell PE, Partridge EE, *et al*. Protective association of MTHFR polymorphism on cervical intraepithelial neoplasia is modified by riboflavin status. Nutrition 2007;23:229-35.
160. Billiau A, Heremans H, Vermeire K, Matthys P. Immunomodulatory properties of interferon-gamma: An update. Ann N Y Acad Sci 1998;856:22-32.
161. Pravica V, Perrey C, Stevens A, Lee JH, Hutchinson IV. A single nucleotide polymorphism in the first intron of the human IFN-gamma gene: Absolute correlation with a polymorphic CA microsatellite marker of high IFN-gamma production. Hum Immunol 2000;61:863-6.
162. Kleine-Lowinski K, Rheinwald JG, Fichorova RN, Anderson DJ, Basile J, Munger K, *et al*. Selective suppression of monocyte chemoattractant protein-1 expression by human papillomavirus E6 and E7 oncoproteins in human cervical epithelial and epidermal cells. Int J Cancer 2003;107: 407-15.

163. Gerard C, Rollins BJ. Chemokines and disease. Nat Immunol 2001;2:108-15.
164. Mantovani A, Bottazzi B, Colotta F, Sozzani S, Ruco L. The origin and function of tumor-associated macrophages. Immunol Today 1992;13:265-70.
165. Riethdorf L, Riethdorf S, Gutzlaff K, Prall F, Loning T. Differential expression of the monocyte chemoattractant protein-1 gene in human papillomavirus-16-infected squamous intraepithelial lesions and squamous cell carcinomas of the cervix uteri. Am J Pathol 1996;149: 1469-76.
166. Kleine-Lowinski K, Gillitzer R, Kuhne-Heid R, Rosl F. Monocyte-chemo-attractant-protein-1 (MCP-1)-gene expression in cervical intra-epithelial neoplasias and cervical carcinomas. Int J Cancer 1999;82:6-11.
167. Loannidis JP, Rosenberg PS, Goedert JJ, Ashton LJ, Benfield TL, Buchbinder SP, *et al*. Effects of CCR5-Delta32, CCR2-64I, and SDF-1 3'A alleles on HIV-1 disease progression: An international meta-analysis of individual-patient data. Ann Intern Med 2001;135:782-95.
168. Smith MW, Dean M, Carrington M, Winkler C, Huttley GA, Lomb DA, *et al*. Contrasting genetic influence of CCR2 and CCR5 variants on HIV-1 infection and disease progression. Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC), ALIVE Study. Science 1997;277:959-65.
169. Mulherin SA, O'Brien TR, Ioannidis JP, Goedert JJ, Buchbinder SP, Coutinho RA, *et al*. Effects of CCR5-Delta32 and CCR2-64I alleles on HIV-1 disease progression: The protection varies with duration of infection. AIDS 2003;17:377-87.
170. Doms RW, Peiper SC. Unwelcomed guests with master keys: How HIV uses chemokine receptors for cellular entry. Virology 1997;235:179-90.
171. Miyagishi R, Niino M, Fukazawa T, Yabe I, Kikuchi S, Tashiro K. C-C chemokine receptor 2 gene polymorphism in Japanese patients with multiple sclerosis. J Neuroimmunol 2003;145:135-8.
172. Zafiropoulos A, Crikas N, Passam AM, Spandidos DA. Significant involvement of CCR2-64I and CXCL12-3a in the development of sporadic breast cancer. J Med Genet 2004;41:e59.
173. Chatterjee K, Dandara C, Hoffman M, Williamson AL. CCR2-V64I polymorphism is associated with increased risk of cervical cancer but not with HPV infection or pre-cancerous lesions in African women. BMC Cancer 2010;10:278.
174. Coelho A, Matos A, Catarino R, Pinto D, Sousa H, Pereira D, *et al*. The influence of chemokine receptor CCR2 genotypes in the route to cervical carcinogenesis. Gynecol Obstet Invest 2007;64:208-12.
175. Coelho A, Matos A, Catarino R, Pinto D, Pereira D, Lopes C, *et al*. Protective role of the polymorphism CCR2-64I in the progression from squamous intraepithelial lesions to invasive cervical carcinoma. Gynecol Oncol 2005;96: 760-4.
176. Zheng B, Wiklund F, Gharizadeh B, Sadat M, Gambelunghe G, Hallmans G, *et al*. Genetic polymorphism of chemokine receptors CCR2 and CCR5 in Swedish cervical cancer patients. Anticancer Res 2006;26:3669-74.
177. Ivansson EL, Gustavsson IM, Magnusson JJ, Steiner LL, Magnusson PK, Erlich HA, *et al*. Variants of chemokine receptor 2 and interleukin 4 receptor, but not interleukin 10 or Fas ligand, increase risk of cervical cancer. Int J Cancer 2007;121:2451-7.
178. Zornig M, Hueber A, Baum W, Evan G. Apoptosis regulators and their role in tumorigenesis. Biochim Biophys Acta 2001;1551:F1-37.
179. Ando K, Hiroishi K, Kaneko T, Moriyama T, Muto Y, Kayagaki N, *et al*. Perforin, Fas/Fas ligand, and TNF-alpha pathways as specific and bystander killing mechanisms of hepatitis C virus-specific human CTL. J Immunol 1997;158:5283-91.
180. Huang QR, Morris D, Manolios N. Identification and characterization of polymorphisms in the promoter region of the human Apo-1/Fas (CD95) gene. Mol Immunol 1997;34:577-82.
181. Sibley K, Rollinson S, Allan JM, Smith AG, Law GR, Roddam PL, *et al*. Functional FAS promoter polymorphisms are associated with increased risk of acute myeloid leukemia. Cancer Res 2003;63:4327-30.
182. Kanemitsu S, Ihara K, Saifddin A, Otsuka T, Takeuchi T, Nagayama J, *et al*. A functional polymorphism in fas (CD95/APO-1) gene promoter associated with systemic lupus erythematosus. J Rheumatol 2002;29:1183-8.
183. Lai HC, Lin WY, Lin YW, Chang CC, Yu MH, Chen CC, *et al*. Genetic polymorphisms of FAS and FASL (CD95/CD95L) genes in cervical carcinogenesis: An analysis of haplotype and gene-gene interaction. Gynecol Oncol 2005;99:113-8.
184. Lai HC, Sytwu HK, Sun CA, Yu MH, Yu CP, Liu HS, *et al*. Single nucleotide polymorphism at Fas promoter is associated with cervical carcinogenesis. Int J Cancer 2003;103:221-5.
185. Chatterjee K, Engelmark M, Gyllensten U, Dandara C, van der Merwe L, Galal U, *et al*. Fas and FasL gene polymorphisms are not associated with cervical cancer but differ among Black and Mixed-ancestry South Africans. BMC Res Notes 2009;2:238.
186. Wu J, Metz C, Xu X, Abe R, Gibson AW, Edberg JC, *et al*. A novel polymorphic CAAT/enhancer-binding protein beta element in the FasL gene promoter alters Fas ligand expression: A candidate background gene in African American systemic lupus erythematosus patients. J Immunol 2003;170:132-8.
187. Dybikowska A, Sliwinski W, Emerich J, Podhajska AJ. Evaluation of Fas gene promoter polymorphism in cervical cancer patients. Int J Mol Med 2004;14:475-8.
188. Engelmark MT, Renkema KY, Gyllensten UB. No evidence of the involvement of the Fas -670 promoter polymorphism in cervical cancer *in situ*. Int J Cancer 2004;112:1084-5.
189. Sergentanis TN, Economopoulos KP. Association of two CASP8 polymorphisms with breast cancer risk: A meta-analysis. Breast Cancer Res Treat 2010;120:229-34.
190. Sun T, Gao Y, Tan W, Ma S, Shi Y, Yao J, *et al*. A six-nucleotide insertion-deletion polymorphism in the CASP8 promoter is associated with susceptibility to multiple cancers. Nat Genet 2007;39:605-13.
191. Sun T, Zhou Y, Li H, Han X, Shi Y, Wang L, *et al*. FASL -844C polymorphism is associated with increased activation-induced T cell death and risk of cervical cancer. J Exp Med 2005;202:967-74.

192. Plummer M, Herrero R, Franceschi S, Meijer CJ, Snijders P, Bosch FX, *et al*. Smoking and cervical cancer: Pooled analysis of the IARC multi-centric case--control study. Cancer Causes Control 2003;14:805-14.
193. Goodman MT, McDuffie K, Hernandez B, Bertram CC, Wilkens LR, Guo C, *et al*. CYP1A1, GSTM1, and GSTT1 polymorphisms and the risk of cervical squamous intraepithelial lesions in a multiethnic population. Gynecol Oncol 2001;81:263-9.
194. Juarez-Cedillo T, Vallejo M, Fragoso JM, Hernandez-Hernandez DM, Rodriguez-Perez JM, Sanchez-Garcia S, *et al*. The risk of developing cervical cancer in Mexican women is associated to CYP1A1 MspI polymorphism. Eur J Cancer 2007;43:1590-5.
195. Joseph T, Chacko P, Wesley R, Jayaprakash PG, James FV, Pillai MR. Germline genetic polymorphisms of CYP1A1, GSTM1 and GSTT1 genes in Indian cervical cancer: Associations with tumor progression, age and human papillomavirus infection. Gynecol Oncol 2006;101:411-7.
196. Taskiran C, Aktas D, Yigit-Celik N, Alikasifoglu M, Yuce K, Tuncbilek E, *et al*. CYP1A1 gene polymorphism as a risk factor for cervical intraepithelial neoplasia and invasive cervical cancer. Gynecol Oncol 2006;101:503-6.
197. Chen C, Madeleine MM, Weiss NS, Daling JR. Glutathione S-transferase M1 genotypes and the risk of squamous carcinoma of the cervix: A population-based case-control study. Am J Epidemiol 1999;150:568-72.
198. Sharma A, Sharma JK, Murthy NS, Mitra AB. Polymorphisms at GSTM1 and GSTT1 gene loci and susceptibility to cervical cancer in Indian population. Neoplasma 2004;51:12-6.
199. Idle JR, Armstrong M, Boddy AV, Boustead C, Cholerton S, Cooper J, *et al*. The pharmacogenetics of chemical carcinogenesis. Pharmacogenetics 1992;2:246-58.
200. Worrall SF, Corrigan M, High A, Starr D, Matthias C, Wolf CR, *et al*. Susceptibility and outcome in oral cancer: Preliminary data showing an association with polymorphism in cytochrome P450 CYP2D6. Pharmacogenetics 1998;8:433-9.
201. Warwick A, Sarhanis P, Redman C, Pemble S, Taylor JB, Ketterer B, *et al*. Theta class glutathione S-transferase GSTT1 genotypes and susceptibility to cervical neoplasia: Interactions with GSTM1, CYP2D6 and smoking. Carcinogenesis 1994;15:2841-5.
202. Sobti RC, Kaur S, Kaur P, Singh J, Gupta I, Jain V, *et al*. Interaction of passive smoking with GST (GSTM1, GSTT1, and GSTP1) genotypes in the risk of cervical cancer in India. Cancer Genet Cytogenet 2006;166:117-23.
203. Hayes JD, Pulford DJ. The glutathione S-transferase supergene family: Regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. Crit Rev Biochem Mol Biol 1995;30:445-600.
204. Ueda M, Hung YC, Terai Y, Saito J, Nunobiki O, Noda S, *et al*. Glutathione-S-transferase and p53 polymorphisms in cervical carcinogenesis. Gynecol Oncol 2005;96:736-40.

Cite this article as: Chattopadhyay K. A comprehensive review on host genetic susceptibility to human papillomavirus infection and progression to cervical cancer. Indian J Hum Genet 2011;17:132-44.

Source of Support: University of Cape Town, Poliomyelitis Research Foundation (PRF) and National Research Foundation (NRF), South Africa., **Conflict of Interest:** Nil