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
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-a.[122] TNFa is closely linked to TNF-β gene and contains 14 different alleles (a1-a14) with an AC/GT dinucleotide 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):
gene is associated macrophages (TAMs) mainly have protumor function. 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 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) 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. 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, multiple sclerosis and breast cancer. 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. The A allele was also found to be a risk allele for developing HSIL and cervical cancer compared to healthy controls. Contrasting to that, a decreased risk of developing cervical cancer was reported in the presence of the A allele. Some groups failed to find an association of this polymorphism with cervical cancer, pre-cancerous lesions or HPV infection.

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.\[^{[180,181]}\] This 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 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.\[^{[170,192,193]}\] 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.\textsuperscript{[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.\textsuperscript{[196]}

\textit{GSTM1}: GSTM1 genotype is a combination of \textit{GSTM1*0}, \textit{GSTM1*A} and \textit{GSTM1*B} alleles. \textit{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,\textsuperscript{[72,193,197,198]} whereas other groups failed to find any association.\textsuperscript{[70,199-201]}

\textit{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.\textsuperscript{[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;\textsuperscript{[70,202-204]} on the other hand, some studies reported no association with cancer of the cervix.\textsuperscript{[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 \textit{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 \textit{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-\(\gamma\)) than reviewed by Zoodsma \textit{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.

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