Impact of host molecular genetic variations and HIV/HPV co-infection on cervical cancer progression: A systematic review

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Review

Impact of Host Molecular Genetic Variations and HIV/HPV Co-infection on Cervical Cancer Progression: A Systematic review

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Abstract

Only a small subset of women who are co-infected with Human Immunodeficiency Virus sub-type I (HIV) and persistence oncogenic Human papillomavirus (HPV), progress rapidly to invasive cervical cancer by mechanisms that are currently poorly understood. The use of Highly Active Antiretroviral Therapy (HAART), with ensuing immune reconstitution of CD4 T-cells, does not appear to prevent rapidly progressing cervical carcinogenesis. Therefore, to better understand the cervical cancer pathogenesis in HIV/HPV co-infected women, this review focuses on identifying host molecular genetic variations and genetic alterations in cervical cancer progression that may play a role in disease progression. This is an important aspect for individualised genomic profiling and targeted molecular prevention in order to improve the management of the disease in this sub-population.

Key words: Host molecular genetics, cervical cancer, HIV/HPV co-infection, genomic profiling and molecular targeted prevention

1. Introduction

Every year, more than 530,000 women worldwide are diagnosed with invasive cancer of the uterine cervix and approximately 275,000 die from the disease (1, 2). More than 88% of these deaths occur in developing countries especially in sub Saharan Africa (3).

Oncogenic Human papillomavirus (HPV), is one of the primary causative agents for cervical cancer (4). However, Human Immunodeficiency Virus sub-type 1 (HIV) as a co-infection, may influence cervical disease progression and invasive cancer outcomes in HIV positive women (3, 5-8). HIV positive women are also more likely to have concurrent infections of single or multiple strains of oncogenic HPV, compared to HIV negative women (4, 6, 9-12). Furthermore, published data clearly shows that, persistent oncogenic HPV and HIV co-infections, contribute to rapidly progressing cervical carcinogenesis when compared to HIV negative women with a single, multiple, or no HPV infection (13-16). Although HIV/HPV co-infection is common in sub-Saharan Africa, only relatively few infected patients develop cervical disease and only about one third of 'in situ' cervical carcinomas progress to invasive cancer (9, 11). Surprisingly, the risk of developing invasive cervical cancer does not decrease following Highly Active Antiretroviral Therapy (HAART), which targets the HIV infection (9, 17-20).

On the contrary, a proportion of the patients with invasive cervical cancer have no detectable HIV/HPV viral co-infection (21, 22).

It has been argued that, despite underlying immunodeficiency and immune reconstitution, the existing cervical carcinogenesis process in HIV/HPV co-infected women is further influenced by host molecular genetic factors, which vary between individuals (18, 23, 24) (Figure 1). It has also been suggested that the rate of cervical disease progression and likely protection may depend on host immunogenetic variations (25-29).

Specifically, the argument is that, cervical cancer progression is controlled via the microsatellite instability pathway amongst HIV/HPV co-infected women and through the loss of heterozygosity (LOH) pathway amongst HPV-only infected women (18, 23, 30, 31). While many studies have documented the association between HIV infection and rapidly invasive cervical cancer development, none have shown a direct link between HIV/HPV co-infection and the degree of disease invasiveness and rate of progression (32-34).

These considerations have determined the focus of this review which is to assess the current knowledge of the influence of host molecular genetic variations, genetic alterations, and HIV/HPV co-infection on rapidly progressing cervical carcinogenesis. We have reviewed published cohort studies and further investigations. We have also examined the evidence for possible involvement of host molecular genetic alterations and immunogenetic variations in HIV/HPV co-infected cervical carcinogenesis. This review stems from research conducted into further knowledge on individualised genomic profiling and targeted molecular prevention in order to improve management of the disease in this subpopulation (8, 35).

2. Methods

We have conducted our methodology according to similar published studies (36, 37). A comprehensive, systematic literature search of peer-reviewed, published articles from the NCBI, PubMed, EBSCO, Medline, Elsevier Science, Springer Link and the Google Scholar bibliographic databases was carried out. We included all original research studies, short communications, critical reviews and meta-analyses, reports on genes susceptible for cervical cancer and immune response, and factors changing risk or offering likely protection of cervical cancer development, ever published prior to May, 31st 2018. Information on specific alleles and/or genes were noted and critically reviewed. The key words/phrases used for the search were 'host molecular genetics', 'cervical cancer susceptibility', 'HIV/HPV co-infection', 'HIV and cervical cancer', 'cancer genomic profiling and molecular targeted prevention', 'cervical cancer, mutations and viruses' and 'cervical cancer genetics'. We excluded all studies on epigenetics of cervical cancer as these were not deemed to be relevant to our study topic and focus. There were no specific analytical methods used for the examination of articles due to the nature of our study.

3. Results and Discussion

In this section we will discuss;

i) Cervical cancer pathogenesis, HAART and HIV/HPV co-infection.

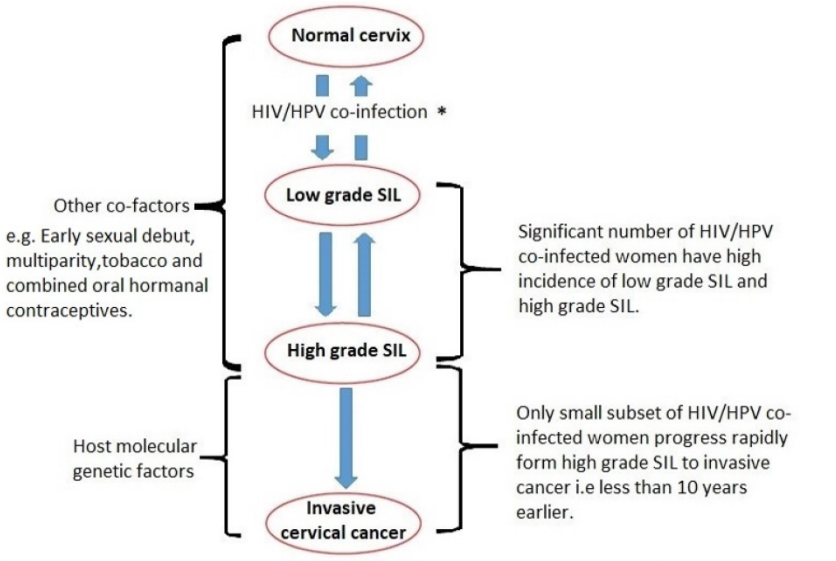

Figure 1: Cervical carcinogenesis process in HIV/HPV co-infected women. SIL is squamous intraepithelial lesion.

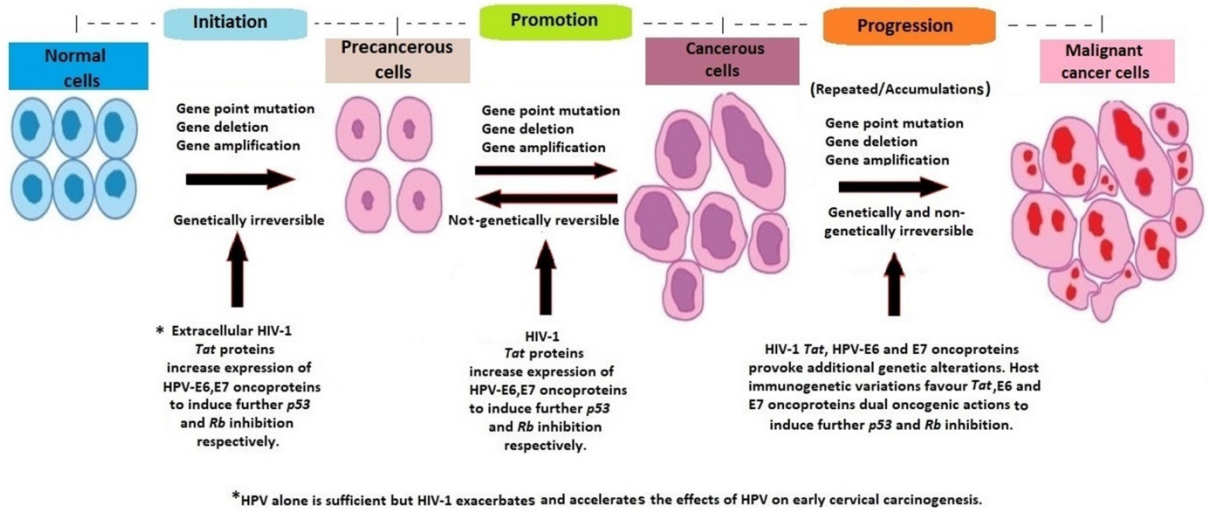

Figure 2: Host molecular genetic variations and alterations in HIV/HPV co-infected cervical carcinogenesis.

ii) Host HLA polymorphisms, genetic mutations and HIV/HPV co-infection in cervical cancer progression.

iii) Molecular genetic variations, genes, chromosomes, SNPs and HPV persistence in cervical disease progression and susceptibility.

iv) What is not known in host molecular genetics of cervical carcinoma?

i) Cervical cancer pathogenesis, HAART and HIV/HPV co-infection

The pathogenesis of cervical cancer involves three important steps; high risk HPV viral genome integration into host genome, the oncogenic effects of HPV oncoproteins E6, E7, and the accumulation of recurrent, unrepaired genetic alterations in host chromosomal DNA (38-41). Furthermore, there is an interaction between HPV and HIV co-infections, resulting in an increased risk of HPV-associated morbidity and cervical cancer mortality among HIV-positive women (34, 42). In a few cases, HIV/HPV-associated cervical cancerous cells, non-genetically regress spontaneously to pre-cancerous cells. Persistent accumulation of uncorrected mutations and additional pro-oncogenic effects of HIV-1 *Tat* and HPV E6, E7 oncoproteins, lead to the progression of cancerous cells to invasive malignant cancer cells, regardless of the use of HAART (11, 14, 34, 43, 44) (Figure 2).

The immunosuppressive effects of HIV infection are associated with the rapid progression of HPV-induced cervical pre-malignant lesions. This may influence the rapid onset of cervical disease and further effects on clinical outcome. However, the direct mechanism is not clear (45-47). Additionally, the effects of duration of HAART use in cervical carcinogenesis prevention are still unknown (48, 49).

In a study by De Jong et al (50), they suggested that absence of functional HPV16-specific CD4+ T-cell immune responses found in women with cervical cancer may explain further development of the cervical disease despite immune reconstitution following HAART initiation or in patients with competent CD4+ T-cell count. Additionally, it has been already reported that not all women who progress rapidly to invasive cervical cancer are HIV positive. This suggests that, there are many other possible host factors apart from immunosuppression or HIV/HPV co-infection that may play a role in rapidly progressing cervical carcinogenesis (39, 42, 51, 52).

HIV proteins can directly cause cancer growth by interfering with cellular functions (8, 42, 49, 53). For example, HIV *Tat* proteins directly interact with the host tumour suppressor genes *p53/pRb/p130/p107* and induce increased cell proliferation, which promote the effect of HPV oncoproteins E6 and E7 in the rapidly progressing cervical carcinogenesis (33, 42, 49, 53, 54). The increased rate of HPV-associated cervical disease in HIV positive women is aggravated by HIV/HPV molecular interactions because HIV *Tat* proteins can modulate HPV E2 gene expression, which in turn, influences HPV viral replication (55, 56). However, Hirbod *et al*. (57), Nkwanyana *et al*. (58) and Bebell *et al*. (59) have suggested that cervical mucosal inflammation in HIV infected women may be associated with low CD4 (+) cell counts during acute infection. Although this suggestion agrees with cancer microenvironment theories that chronic and persistent inflammation contributes to cancer development and can predispose to rapidly progressing cervical carcinogenesis, the effect has been observed only in a subset of HIV/HPV co-infected women (60-62). It has been shown that,

inflammatory mediators on the surface of the uterine cervical epithelial cells, can promote adhesion of HIV infected leukocytes. This in turn facilitates HIV *Tat* proteins uptake by cervical epithelial cells before their transformation into cancerous cells (54).

The oncogenic potential of high risk HPV may contribute to the accumulation of mutations in proto-oncogenes and tumor suppressor genes between G1 phase and S-phase of the cell cycle in the host (23, 63). This process is mostly mediated by the oncoproteins E6 and E7 which hijack host genomic DNA, then bind and inactivate the tumour suppressor genes, p53 and the retinoblastoma protein (pRb), respectively, to further inhibit apoptosis. This process is achieved through the Ubiquitin-mediated degradation pathway (13, 64-66).

It is clear therefore that, apart from immunosuppression, additional genetic and genomic alterations are necessary for pre-cancerous cells to sufficiently progress into malignant and invasive cancer cells, especially following HAART, which reconstitute the host immune competency (67).

ii) Host HLA polymorphisms, genetic mutations and HIV/HPV co-infection in cervical cancer disease progression

In some populations, carcinogenesis of squamous cell carcinoma is more susceptible to genetic variations and alterations than adenocarcinoma (68, 69). Since the immune system normally mobilizes to clear viral infections, the development of virus-associated cancers result from a failure of anti-viral immunity. Furthermore, in cervical carcinogenesis, host immune-competence gradually diminishes as cervical disease progresses to invasive cervical cancer (64).

The genes coding for the Human Leukocyte Antigen (HLA) system, which reside on the short arm of human chromosome 6, (except for the gene for β2-microglobulin) play a central role in immune recognition and the subsequent clearance of virally infected cells (70-75). Therefore, any variations or structural genomic changes within the HLA region, which influence immune evasion by viruses and cancer cells, may determine the lesions likely to progress to invasive cancer (43, 49, 71, 73, 76). In a study of HLA genes in cervical cancer patients compared to healthy controls, expression of HLA I genes, were downregulated, suggesting that host genetic variations of HLA class I genes also have a significant bearing on specifically HPV16-related cervical carcinogenesis (77). HPV16 E5 oncoprotein and downregulation of the surface HLA class I expression has already been reported (78). However, genetic predisposition and variability in the HLA genes, have shown considerable contradictory findings in different study populations (36, 79, 80). Variations in HLA II genes and cervical cancer susceptibility have been investigated in different geographical populations with inconsistent findings, highlighting the complexity of the viral/host/environmental ecosystem (69, 80-85). For example, predispositions of the HLA system and a positive cervical cancer association with the TNF genes for apoptosis was previously reported (86-88). Although in the South African population, *TNF G*-308 did not show any association with cervical cancer susceptibility (37, 89).

It has been widely reported that loss of heterozygosity (LOH) mutations and microsatellite instability (MSI) at multiple genomic loci including the HLA region, are the most common host genetic alterations seen in cervical cancer tissues (90, 91). This possibly indicates that the integrity of the HLA region is compromised during the process of carcinogenesis (92-94). LOH and MSI are caused by genetic alterations such as the physical deletion of a chromosomal region, a tumor suppressor gene, or chromosomal non-disjunction during mitotic recombination. It has been reported that the mechanisms of LOH/MSI may be remarkably chromosome-specific (73, 90, 93, 95, 96), with some chromosomes being completely lost while more than half of the losses are associated with the loss of only a part of the chromosome (90, 97). Essentially, the mechanism underlying HIV/HPV co-infection and cervical cancer development with regard to LOH/MSI or immunogenetic variations is still poorly understood (72). It has been hypothesised that, cervical cancer progression is influenced by the extent of LOH/MSI and HLA variations in immune response towards oncogenic HPV clearance and the combined pro-oncogenic effects of the HIV/HPV co-infection (96, 98-100).

Host genetic variations in the HLA genes that influence the primary immune response and the severity of LOH/MSI at the HLA genomic loci may, therefore, determine which lesions are at the highest risk for rapid progression to invasive cervical cancer in HIV/HPV co-infected women (36, 79).

iii) Molecular genetic variations, genes, chromosomes, SNPs and HPV persistence in cervical disease progression and susceptibility.

Currently, there are no consistent data on the association between any gene polymorphism in cervical cancer and disease outcome (101). In studies of different chromosomes, the changes involving loss of 2q, 3p, 4p, 4q, 5q, 6q, 11q, 13q, 17q and 18q regions and gain of 1q, 3q, 5p and 8q at various stages of

cervical cancer have shown possible association with either oncogenic HPV persistence or cervical cancer disease progression (63, 102) (Table 1). Presence of chromosomal aneuploidy, which increases genomic instability in rapidly progressing carcinogenesis was reported in both cervical pre-cancer and cervical invasive cancer (103-105). Furthermore, the presence of an isochromosome 5p associated with cervical cancer susceptibility has been reported in a number of different studies (106-108).

Table 1. Summary of host gene polymorphisms, SNPs and chromosomal locations found to be associated with either HPV persistence or cervical disease progression worldwide.

HOST GENES AND SNPs	CHROMOSOME	COHORT SIZE AND NATURE OF THE STUDY	POPULATION STUDIED	HPV 16 OR 18 GENOME INTERACTION WITH HOST GENES
A) Genes involved in HPV persistence				
CTLA-4,−318 C/T	2q33.2	Case-control, 144 cases vs 378 controls	Taiwan (147)	-
STING	5q31.2	Cross-sectional, 148 patients	Thailand	E2 downregulates *STING* (148)
HLA-DQB1	6p21.32		Sweden (82)	
		Case-control, 1306 cases vs 288 controls		E5, E7 downregulate expression of MHC molecules (149)
GTF2H4 rs2894054	6p21.33	Double case-control, 469cases, 390 women with persistent HR-HPV and 452 controls	Costa Rica (150)	-
MICA	6p21.33	GWAS, 1075 Cases and 4014 Controls	Sweden (96)	E5, E7 downregulate expression of MHC molecules (149)
SULF1, rs4737999	8q13.2-q13.3	Double case-control, 469cases, 390 women with persistent HR-HPV and 452 control	Costa Rica (150)	-
IFNA1	9p21.3	Cross-sectional, 148 patients	Thailand	E2, E6 downregulate *IFNA1* (148)
IL2RA, rs2476491	10p15.1	Double case-control, 141 cases, 38 HSIL and 176 controls	Portugal (151)	E6, E7 interferes with cytokines pathways (149, 152)
PRDX3, rs7082598	10q26.11	Cross-sectional, 68 patients	China	E6, E7 downregulate *PRDX3* (153)
C1RL, rs12227050	12p13.31	Double case-control, 469cases, 390 women with persistent HR-HPV and 452 control	Costa Rica (154)	-
OAS3, rs12302655	12q24.13	Double case-control, 469cases, 390 women with persistent HR-HPV and 452 control	Costa Rica (150)	-
DUT, rs3784621	15q21.1	Double case-control, 469cases, 390 women with persistent HR-HPV and 452 control	Costa Rica (150)	-
TP53(p53), rs1042522	17p13.1	Cross-sectional, 577 patients	USA (155)	E6 degrades p53 (156)
NLRP1, rs11651270 ***NLRP3***, rs10754558 and ***IL18***, rs1834481	17p13.2	Case-control, 246 cases vs 310 controls, 12 SNPs in seven genes	Brazil (157)	-
TYMS, rs2342700	18p11.32	Case-control, 65 cases vs 202 controls	Nigeria (158)	-
RPS19, rs2305809	19q13.2	Case-control, 65 cases vs 202 controls	Nigeria (158)	-
IRF3, rs7251	19q13.33	Double case-control, 469cases, 390 women with persistent HR-HPV and 452 control	Costa Rica (159)	E6 prevents *IFN*-α mRNA (160)
B) Genes involved in cervical disease progression				
EXO1, rs4149963	1q43	Double case-control, 469cases, 390 women with persistent HR- HPV and 452 controls	Costa Rica (159)	-
TIPARP, rs2665390	3q25.3	Case-control, 790 cases vs 717 controls	Algeria, Morocco, India, Thailand (161)	-
PIK3CA	3q26.32	Cross-sectional, 285 cases		E6, E7 increase APOBEC-mediated mutagenesis (163).
			Mexico, Guatemala, Venezuela (162)	
LAMP3	3q27.1		Japan (164)	-
		Double case-control, 47 cases, 15 tissues with CIN and 5 tissue controls		
RFC4	3q27.3	Case-control and Meta-analysis, 40 cases vs 20 controls	Brazil (165)	E1, E2 ORFs disruption interferes *RFC4* (166)
POLN, rs17132382	4p16.3	Double case-control, 416 cases, 356 women with persistent HR-HPV and 425 controls	Costa Rica (150)	E6 interacts with *POLN* (167)
MIR146A, rs2910164	5q33.3	Case-control, 447 cases vs 443 controls	China (168)	E6 under-express miRNAs(169)

HOST GENES AND SNPs	CHROMOSOME	COHORT SIZE AND NATURE OF THE STUDY	POPULATION STUDIED	HPV 16 OR 18 GENOME INTERACTION WITH HOST GENES
TNF	6p21.33	Descriptive, *in vitro*	USA (170)	E6 down-regulates *TNF* (171)
URG4	7p13	Cross-sectional, 167 cc patients	China (172)	-
MYC	8q24.2	Descriptive, Case series, 1 cc patient	USA	E7 fusion causes *MYC* overexpression (173)
CDKN2A (p16)	9p21.3	Cross-sectional, 139 cases	Japan (174)	E7 inactivates *Rb*1 (p16 overexpression) (174)
TAP	11q12.3	Descriptive, *in vitro*	China (175)	E7 down-regulates *TAP* (171)
IFNG , rs11177074	12q15	Double case-control, 416 cases, 356 women with persistent HR- HPV and 425 controls	Costa Rica (150)	E6 inhibit interferon related responses (171, 176).
MDM2	12q15	Descriptive, *in vitro*	Italy	E2 interacts *MDM2* ubiquitin ligase (177)
RB1	13q14.2	Descriptive, *in vitro*	USA (178)	E7 binds and degrades *pRb* (178, 179).
CYP1A1 m2, rs1048943	15q24.1	Case-control, 100 cases vs 100 controls	India (180)	-
TELO2, rs4786772	16p13.3	Double case-control, 416 cases, 356 women with persistent HR- HPV and 425 controls	Costa Rica (154)	-
FANCA, rs2239359	16q24.3	Double case-control, 469cases, 390 women with persistent HR- HPV and 452 controls	Costa Rica (159)	E6 promotes reprogramming of *FANCA* (181)
CYBA, rs7195830	16q24.3	Double case-control, 469cases, 390 women with persistent HR- HPV and 452 controls	Costa Rica (159)	-
EVER1/EVER2, rs9893818	17q25.3	Double case-control, 416 cases, 356 women with persistent HR- HPV and 425 controls	Costa Rica (150)	E7 binds zinc ions to prevent *EVER1/2* and E5 binds to EVER1/2 (78)
FGFR-TK1	17q25.3	Descriptive, Case series, 3 cc patients	USA and Brazil (182)	E6 induce expression of *FGF-BP* (182)

It has been observed that, HR-HPV-DNA potentially integrates into more than 117 unique sites into the host genome to influence cervical carcinogenesis (109, 110). Several other genomic regions with changes in the number of DNA copies (copy number-altered regions or CNAs), common in solid tumors, have been confirmed by comparative genomic hybridization (CGH), Florescent *'In situ'* Hybridization (FISH) and single nucleotide polymorphisms (SNPs), reflecting the important role of HPV infection and specific genomic alterations in cervical carcinogenesis (111).

Individuals with a *Tp53* gene polymorphism in codon 72 (Arginine homozygosity) have been reported to be at a seven times higher risk for HPV associated cervical cancer development than the heterozygous genotype (37, 112). However, a pooled data analysis on 49 studies worldwide published in 2009, found no association between cervical cancer and the *TP53* codon 72 polymorphism (113). The most frequently-mutated tumor suppressor gene in cervical cancer is believed to be *Cystatin E/M*, however, these results are not consistent in different study populations (114, 115).

Previous studies in cervical cancer molecular genetics using SNPs have shown that the accumulation of cellular genomic damage such as point mutations, gene amplifications, and LOH/MSI in both pre-cancerous and cancerous lesions occurs at rs13117307 at 4q12, rs8067378 at 17q12, rs4282438 and rs9277952 at 6p21.32 (89, 110). There were, however, no SNPs associated with cervical cancer risk in *p21* rs1801270, BRIP1 rs2048718, and rs11079454 polymorphisms (116). Furthermore, the recurrent cellular genetic alterations in cervical cancer were observed only in primary mutational signatures, 1B and 2(APOBEC) (117) (118). Women who are carriers of genes or alleles that may affect the expression of immune molecules capable of HPV infection recognition are at increased risk for developing cervical cancer. However, variations in *CD83*, a marker of dendritic cell maturation that may assist the T cell response to HPV infection, have shown little or no influence on cervical cancer (119, 120). Contrarily, Yu et al (121) in 2009, confirmed an association between *CD83* polymorphisms and cervical cancer susceptibility and suggested that polymorphisms in this gene and cervical disease association may depend on tumour histology.

Mutations in cyclin dependent kinase inhibitor, *WAF1* have shown a positive association with cervical cancer susceptibility, although some studies, based on different study populations report contradictory findings (37, 122, 123). Somatic genomic mutations, notably copy number variations, in the genes *PIK3CA, STK11, PTEN, TP53,* and *KRAS 4-7*, have been associated with cervical cancer development (35, 63). Mutations, and/or polymorphisms in transporters associated with antigen processing genes, *TAP-1* and *TAP-2* were not associated with development of cervical cancer (124, 125). Although, Zoodzma *et al* (69) reported an increased risk of cervical cancer in

individuals with allele 184 at the *MICA* locus (with a recessive effect), subsequent investigations have not been able to replicate this finding (126).

Certain heritable syndromes involving defects in the DNA damage repair system which present susceptibility to cervical cancer have been studied. For example, Fanconi anemia syndrome (genes include *FANCA, FANCC, FANCL*), is an inherited genetic disorder characterized by defects in DNA damage repair system. In addition, Mathew, (127) suggested an association between this syndrome and cervical cancer. However, in a subsequent study in a Swedish population, no association between Fanconi anemia and susceptibility to cervical cancer was shown (128). Enigmatically, however, in a study using *FANCA* gene deficient mice, Park et al (129) demonstrated susceptibility of HPV 16 E7-driven cervical cancer.

The *ERAP1-575* gene on chromosome 5, and the *TAP2-379*, and *TAP2-651* loci on chromosome 6, have been tested in Asian populations, and shown to be consistently associated with cervical cancer risk (130, 131). The rs799917 TT genotype in the *BRCA1* gene has been associated with a significantly decreased risk of cervical cancer (89, 132). Some variants in the chemokine receptor-2A (*CCR2A*), a transcribed isoform of *CD192*, situated on chromosome 3p21, have demonstrated a protective effect against invasive cervical cancer development from squamous intraepithelial lesions (SIL) in Swedish, Portuguese, and South African Black and Mixed-Ancestry populations. It has also been described as a risk allele for high grade squamous intraepithelial lesions and cervical cancer development in healthy individuals. In other studies, however, the G46295A variant in *CD192* was reported not to confer genetic susceptibility towards cervical cancer development (37, 133-135).

The activation of Caspase 8 (CASP8), represents an important initiating event in the death receptor-induced apoptosis gene. However, the deleted allele of the CASP8 polymorphism has been associated with decreased risk for cervical cancer in a Chinese population (136). Studies in African populations have not found any association between *CASP8* polymorphisms and cervical cancer susceptibility (65).

Although, we have discussed numerous interactions of several genes, chromosomes, SNPs and the HPV oncoproteins E6 and E7, the exact mechanisms of interactions with the HIV co-infection, and the mechanisms by which the combined pro-oncogenic effects of HIV *Tat* proteins and HPV oncoproteins E6 and E7, further provoke additional genetic alterations in some women to influence the rate of cervical cancer progression is not yet known (54, 137).

iv) What is not known in host molecular genetics of cervical carcinoma?

There is lack of available research addressing some specific questions that need to be asked:

a) Why do variations at the MHC II locus increase the risk of cervical cancer? Although this has not been studied before in an HIV/HPV co-infected population, it does appear that the main host genetic susceptibility factors for cervical cancer may be related to the immune recognition of HPV-infected or HPV transformed cervical epithelial cells (138).

b) Do variations in the HLA II genes, *DRB1*DQB1 influence HIV positive cervical carcinogenesis (139)?

c) Are host molecular genetic polymorphisms at certain genomic loci more likely to influence cervical carcinogenesis in HIV/HPV co-infected women (83)? The immunogenetics of cervical carcinomas from HIV positive women has not yet been studied (140, 141).

d) What are the effects of LOH/MSI at 6p in HIV/HPV co-infected cervical carcinomas (96)?

e) What are the effects of HAART on the incidence and severity of cervical cancer in HIV/HPV co-infected women with regard to molecular genetic variations?

f) How do the anti-apoptotic effects of Protease Inhibitors (PI), influence cervical carcinogenesis (44)?

g) Can the significant genomic loci, candidate tumour suppressor genes and the biological pathways of the genetic framework of susceptibility or heritability to cervical cancer which have been indicated by the reported genome-wide association studies be elucidated (84, 126, 142)?

h) Can further research confirm whether susceptibility loci in one population are specifically replicated in another e.g. HLA, 4q12, 17q12 (80, 116, 143, 144)?

i) Why is the apparent effect of the *P72R* polymorphism in *TP53* gene not consistent in different ethnicities (116)? This is despite the evidence that cervical cancer susceptibility loci in each ethnic group vary considerably.

j) Does HIV/HPV co-infection provoke additional host genetic alterations on chromosome 6p specifically at the HLA-II loci, DRBI and DQB1, to influence the rate of cervical disease development in HIV/HPV co-infected women (139)?

Overall, the evidence suggests that HPV persistent infection with oncogenic genotypes is a necessary, but not sufficient, risk factor for cervical carcinogenesis. We hypothesise that, HIV co-infection exacerbates and increases the rate of progression to

invasive cervical cancer by promoting additional genetic alterations and mutations in chromosomal regions carrying tumour suppressor genes, apoptosis-related genes, DNA damage-repair genes, and cell cycle- regulatory genes by the cumulative oncogenic effects of the combined viruses. It is, however, not yet clear why only a small subset of HIV/HPV co-infected women progress rapidly to the invasive disease and others do not.

4. Conclusions and recommendations

To the best of our knowledge, this is the first study to analyse the HIV/HPV co-infection and correlation with host molecular genetics in the development of cervical cancer. Although there is limited published data on the interaction of the HIV *Tat* proteins and HPV oncoproteins, E6 and E7, and host molecular genetic susceptibility to cervical cancer progression, this review compiles the reports on the major host molecular genetic risk factors that have been shown to be associated with both rapidly progressing cervical cancer progression and susceptibility.

Our review has considered the gaps in knowledge for cervical cancer progression in general, and in HIV/HPV co-infected women, particularly. We have provided an updated literature review, which includes large number of genes and possible mutations for host molecular genetic susceptibility to cervical cancer development. We have discussed the influence of HIV/HPV co-infection, HIV Tat protein, HPV oncoproteins E6 and E7and host tumour suppressor genes in the disease time course and compared various published studies. Proper focus on high-risk populations for cervical cancer disease (e.g. HIV-infected women) should decrease the number of advanced cases of invasive cervical cancer by identification of early molecular genetic changes. This can be achieved by assessing molecular genetic risk factors using predictive testing (PT) for cervical disease development in HIV/HPV co-infected women (145, 146). In addition, the implementation of new genetic profiling and cervical cancer-screening programs for all women infected with HIV is envisaged (146).

At this stage we cannot point to one or a few genes that may affect susceptibility, severity or increase rate of progression of cervical cancer in the presence of HIV and HPV co-infection as many genes are involved in different molecular pathways. Generally, the genetic variations or mutations that affect host genes for the immune response against oncogenic HPV clearance, tumour suppressor genes, apoptosis-related genes, DNA damage-repair genes and cell cycle- regulatory genes are responsible for cervical cancer susceptibility and rapidly progressing disease. There is also inter-population or multi-population differences and a range of confounding host and viral factors, including environmental effects such as host behaviour and demographics. This may be why different genes have been found to be associated, or not associated, with cervical cancer development in different study populations.

In a South African population, we are currently investigating the hypothesis that HIV/HPV co-infection provokes additional host genetic alterations on chromosome 6p specifically at the HLA-II loci, DRBI and DQB1, to influence the rate of cervical disease development in HIV/HPV co-infected women (139). The impact of this work is expected to advance our current understanding of the interaction between HIV and HPV co-infections and rapidly invasive cervical cancer progression with regard to host molecular genetic and immunogenetic variations. Findings from this study will enlighten the primary goals of genetically-targeted therapy, in the prevention of disease, and the individualization of cervical cancer treatment (89). This will enable genetic profiling and individualization in prevention and treatment of invasive cervical cancer in women living with HIV/AIDS. It will also assist in the development of immunogenetic markers to detect cervical cancer development in early stages through severity of LOH/MSI. This work, therefore, recognises the urgent need to move away from the "one size fits all" generalization in prevention and treatment of cervical cancer (89).

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Competing Interests

The authors have declared that no competing interest exists.

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