SMGroup

Genetic Polymorphisms and Risk of Cervical Cancer

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INTRODUCTION

Cervical Cancer (CC) is the second most common cancer in women worldwide [1]. It has been established that High Risk Human PapillomaVirus (HR-HPV) is a major etiologic agent for CC development. However, the persistent infection by HR-HPV itself is not sufficient for CC development, only a small fraction of women infected with HR-HPV will eventually develop cervical cancer [2,3]. Nevertheless, despite the extremely high rate of infection by HR-HPV, the rate of cervical cancer, even in the prescreening area, has been less than one tenth that of exposure [4,5]. Thus, other factors are important for cervical lesion development and progression such as a use of hormonal contraceptives, multiparty, smoking, and some nutritional factors [6-8]. It is generally accepted that CC is a complex disease resulting from the interaction between environmental factors and genetic background [9].

The immune response raised against HPV determines whether the virus will be cleared or will persist and eventually result in CC [10].Since the main mechanism of defense against tumor depends on T cell response, polymorphisms in gene coding for T cell response molecules may

potentially affect the cancer-directed immune response [11,12]. Activation-Induced Cell Death (AICD) refers to the induction of apoptosis of previously activated T cells. Accumulating evidence also demonstrates that AICD is one of the important mechanisms responsible for the increased apoptosis rate among Tumor Infiltration Lymphocytes (TILs), which may protect transformed cells from elimination by antitumor immune responses and, therefore, contribute to carcinogenesis and cervical cancer progression [13,14].

Cytokines are molecules that are important in the defense of organisms against viral infections. They are produced by macrophages, monocytes, and lymphocytes, and act in an indirect way by determining a pattern of immune response or directly by inhibiting viral replication [15,16]. Polymorphisms in cytokines genes may be associated with differential levels of gene transcription, leading to individual variations that potentially affect cytokine production [17,18]. These polymorphisms may be important determinants for disease risk, severity or protection against conditions in which the immune system plays a significant role, such as malignancies [19]. Several recent investigations have focused on the association between cytokine gene polymorphisms and the development of cervical cancer [15,19-21].

One of the environmental factors, such as cigarette smoking, have been inconsistently linked to cervical disease. Cigarette smoke and increase the production of Radical Oxygen Species (ROS) in cells, resulting in oxidative lesions in DNA. The ROS may inflict oxidative DNA damage indirectly, by inactivation of enzymes that are involved in DNA repair, or directly, by generating DNA strand breaks and base damage that can lead to mutations in tumor suppressorgenes or oncogenes [22,23]. Common polymorphisms in DNA repair genes may alter protein function and an individual's capacity to repair damaged DNA; and may contribute to inter-individual variation of DNA repair capacity leading to genetic instability and cervical carcinogenesis [24].

Since many carcinogens (e.g. cigarette smoking) require metabolic activation before binding to DNA, multiple studies indicated the gene-environment interactions in relation to CC are linked to genes involved in phase 1 and phase 2 enzymes that are involved in the metabolism of carcinogens [25]. Previous studies have shown that polymorphisms in genes encoding carcinogen metabolizing enzymes that alter their expression and function may increase or decrease carcinogen activation and/or deactivation [25] and individuals with an elevated metabolic capacity to activate specific carcinogens may be at an increased risk of cancer [26].

Association between micronutrient depletion, particularly folate deficiency, and cervical lesions it has been studied. In this context, some investigations have been focused on the role of folate in cervical carcinogenesis [27,28]. Folate is essential for the synthesis of nucleotides, its deficit inducing double-strand breaks and increased cancer risk. Low levels of folate correlate with alterations in cell replication, DNA excision and repair and DNA methylation [29]. The apparent role of folate in carcinogenesis in cervical tissue has stimulated investigations of polymorphisms in the Folate Metabolizing Enzymes (e.g. MTHFR) and polymorphisms in folate

metabolizing enzymes genes are associated with the alteration of enzymatic activity and increase the susceptibility to cervical cancer development [28].

Abnormal cell proliferation is an important step in cancer. Cyclins are a family of proteins that control cell progression through the cell cycle by activating Cyclin-Dependent Kinase (CDK) enzymes [30]. Cyclins are proteins that have a critical function in the cell cycle progression during cell division [31]. Over-Expression of Cyclins (e.g. CCND1) induce tumor cells to pass the checkpoints of the cell cycle. Several studies have identified polymorphisms in Cyclins gene that causing an aberrant expression from protein and that are associated with cell proliferation and cervical carcinogenesis [32-34].

This chapter shows how all the above factors play an important role in cervical cancer development and as the individuals have different risk of developing cancer according to these factors in different populations. The challenge remains to optimize the treatments according to gene affected by polymorphisms and population groups.

POLYMORPHISMS IN GENES INVOLVED IN IMMUNE RESPONSE

The immune system is continually being exposed to foreign antigens and self-antigens. An intricate system is in place to induce the immune system that involves both T-cell receptor engagement and costimulatory signaling [35-37]. Antigens are presented by major histo-compatibility class I or II on an antigen-presenting cell to the T-cell receptor complex, which initiates the signal within the T cell. Infection with HR-HPV is an important factor in the development of cervical cancer. The persistent HPV infection induces an inflammatory response, and cytokines play an important role in this process [38].

Immune responses mediated by T cells, especially cytotoxic T lymphocytes, are important in controlling both HPV infection and HPV-associated cancers [39]. Full T cell activation requires engagement of the T cell receptor to the antigen bound major his to compatibility complex (MHC) on the antigen-presenting cell [40]. Costimulatory molecules work to amplify or counteract signals provided by the T-cell receptor complex [36,37,41] Typically, CD28 binds to B7-1/B7-2 on the T cell, leading to activation.

Data from immunosuppressive women have demonstrated the important role of host immunity in cervical carcinogenesis [42]. Polymorphism in involved in immune response genes can influence in the response to HPV infection, possibly modifying risk of cervical cancer.

Polymorphisms in CTLA-4 Gene

The CTLA-4, also known as CD152, gene is located on the region of human chromosome 2q33 and encodes the immune regulatory molecule that competes with CD28 and inhibits T-cell proliferation and signaling. The ligands for CTLA-4 are the same as for CD28 but with higher affinity. It is proved to be a key negative regulator of T-cell activity [35-37]. CTLA-4 is member

of the CD28 super family and is not constitutively expressed on T cells but is induced after CD28 binding and activation [36,43]. CTLA-4 engagement on activated T cells inhibits IL-2 transcription as well as progression through the cell cycle. Thus, its signaling has a direct effect on the T-cell proliferation beyond blocking signaling through CD28. CTLA-4 has been shown to play a role in human disease. According to genetic mapping, the CTLA-4 gene is a locus of susceptibility to disease and several important polymorphic sites have been reported in the entire region [37,44].

The most frequently studied polymorphisms are a C > T transition in the -318 position of the promoter sequence, an A > G transition in exon 1 at position +49, a dinucleotide (AT) n repeat in the 3' untranslated region, and, more recently, an A/G transition in the 3' untranslated region at +6230A > G (rs3087243) [43,45]. Several lines of evidence have shown that SNPs in the CTLA-4 gene exert differential effects on T cell response to viral infection [46-49]. Previous studies have revealed significant association of polymorphisms in the CTLA-4 gene at +49 A > G and susceptibility to multiple types of cancer, such as breast cancer, lung cancer, esophageal cancer, gastric cancer, colorectal cancer, renal cell cancer, oral cancer, and cervical cancer [44].

A study in Taiwanese women revealed no significant difference in the +49 A > G polymorphism, whereas the -318 C > T variant was significantly associated with HPV-16-associated cervical squamous cell carcinoma [45]. This finding was confirmed in a Polish population, re-emphasizing the importance of the -318 polymorphism and susceptibility to cervical cancer [48]. Another study from Iran also supported this observation and, in addition, reported the protective role of the A allele and AA genotype at position -1661 in the promoter region [49]. A study from Sweden highlighted the association of CTLA-4 -319(C/C)/ IFNG+874(A/A) with cervical cancer [50]; however, a study on the CTLA-4 polymorphism in a Chinese population reported the association of the +49 A/G polymorphism (AA vs.GG) with increased risk for hepatocellular carcinoma and cervical cancer [51]. The result of a meta-analysis of 22 eligible case-control studies also suggested association of the CTLA-4 +49 A > G polymorphism genotype (GA + AA) with an increased risk of cervical cancer, especially in Caucasians, Chinese, and other Asians [50].

A limited but promising association between the CTLA-4 polymorphism and the risk of cervical cancer demands data verification in other populations. Gokhale et.al, 2013 in a case-control study, the A/A genotype frequency (30.76% vs.17.6%, P = 0.01) as well as the allelic frequency for A (52.8% vs. 43.5%, P = 0.04) was significantly higher in cases compared to controls. No significant association was seen in the CTLA-4-318 C > T polymorphism. In forward stepwise binary logistic regression analysis considering age and parity as potential confounders, significant association was demonstrated between +49 A/A and cervical cancer [10]. This will help in the management of cervical cancer in HPV infected women, specifically where HPV vaccines are not affordable, suggesting use of CTLA-4+49A > G (rs231775) and CTLA-4-318 C > T as a common cervical cancer susceptibility marker.

Polymorphisms in FAS/FASL Genes

Activation-induced cell death (AICD) refers to the induction of apoptosis of previously activated T cells. AICD is a Fas ligand–dependent process [52]. Fas is a membrane protein that belongs to the tumor necrosis factor receptor superfamily [53]. The interaction between Fas and its receptor Fas ligand (FasL) induces the death signals, leading to cell apoptosis [54]. The down-regulation of Fas expression and/or up-regulation of FasL expression it has been detected in human tumors [55] included cervical cancer [56].

Single nucleotide polymorphisms (SNPs) in the promoter regions of FASL and FAS have been linked to the differential expression of these two genes. The FAS-1377G > A polymorphism (G or A at position -1377 bp) and the FAS-670A > G polymorphism (A or G at position -670 bp) disrupt Sp1 and STAT1 transcription factor binding sites respectively, and thus diminish promoter activity and decrease FAS gene expression [57,58]. The FASL-844T > C polymorphism (C or T at position -844bp) creates a binding site for a transcription factor, CAAT/enhancer-binding protein beta, resulting in a higher expression from FASL [59]. In addition, studies have shown an association of theFAS-1377G > A, FAS-670A > Gand FASL-844T > C polymorphisms in the Fas/FasL gene with susceptibility to cervical cancer.

Recently, was reported that SNPsFAS-1377G > A, FAS-670A > Gand FASL-844T > C are associated with the risk development of CC in a Korean [60], Japanese [61,62], Chinese [14,63,64] and African [65] population, also was observed that the FASL-844T > C polymorphism does not have a major impact on the susceptibility to cervical cancer in Korean [60] and African [65] population. However, all available results are not always consistent with one another, partially because of the small sample size, different ethnic background sand little effect of the polymorphisms on cancer risk (Table 1).

Table 1: Polymorphisms in FAS and FASL gene and their association with risk cervical cancer.

Genotypes	Population	OR	Number patients	References
-1377G > A polymorphism in FAS gene				
G/G	Korean	1.00	155	
G/A		0.76		Kang et. al. 2008
A/A		2.57		
G/G	African	1.00		
G/A		1.14	91	Chattersee et. al. 2009
A/A		1.37		
G/G + G/A	Chinese	1.00	318	Lai et. al. 2005
A/A		1.49		
-670A > G polymorphism in FAS gene				
A/A		1.00		

A/G	Japanese	1.08	83	Ueda et. al. 2006
G/G		2.56		
A/A		1.00		
A/G	Chinese	1.30	276	Lai et. al. 2003
G/G		2.20		
A/A	Japanese	1.00		
A/G + A/A		6.00	40	Uade et. al. 2005
-844T>C polymorphism in FASL gene				
T/T		1.00		
T/C	Chinese	1.68	314	Sun et. al. 2005
C/C		3.05		
T/T		1.00		
T/C	Chinese	1.01	318	Lai et. al. 2005
C/C		1.23		
T/T		1.00		
T/C	Korean	1.23	155	Kang et. al. 2008
C/C		1.10		
T/T		1.00		
T/C	African	0.98	91	Chattersee et. al. 2009
C/C		1.03		

Polymorphisms in TNF Gene

Tumor Necrosis Factor Alpha (TNF-α), is a pro-inflammatory cytokine, TNF-α plays a critical role in the pathogenesis of infectious, inflammatory, autoimmune, and malignant diseases [38,66]. TNF-α has been shown to be involved in the carcinogenesis through induction of proliferation, invasion, and metastasis [66]. Recently, it was found that the level of TNF-α in women with Cervical Intraepithelial Neoplasia (CIN) was much higher than in healthy individuals [67]. Hence, TNF-α expression levels could contribute to the pathogenesis and promoting of cervical cancer. It was recently shown that the transcription of this cytokine is highly affected by polymorphism in the promoter region of the TNF-α gene, SNPs that affect the expression of TNF-α are TNF-α -238G > A, TNF-α -308G > A, TNF-α -375C > T, TNF-α -857C > T and TNF-α -863C > A [68].

Numerous studies have studied the association of the polymorphisms in promoter region of the TNF-α gene and cervical cancer but there date are inconsistencies. Some studies reported no association between the TNF-α -238G > A, TNF-α -308G > A, TNF-α -863C > A polymorphisms and risk of cervical cancer [69,70]. However, others reports have shown that TNF-α -308G > A and TNF-α -857C > polymorphisms are significantly associated with the risk of cervical cancer [71-74]. It suggests that SNPs in the TNF-α promoter may represent anrisk to development of cervical cancer in women (Table 2).

Table 2: Polymorphisms in TNF gene and their association with risk cervical cancer.

Genotypes	Population	OR	Number patients	References
TNF*α*-308G > A polymorphism				
G/G	Portuguese	1.00	195	
A/G		1.81		Duarte et. al. 2005
A/A		2.54		
G/G	Indian	1.00	120	Kohaar et. al. 2007
A/G+A/A		2.80		
G/G	Indian	1.00	150	Singh et. al. 2009
A/G+A/A		2.24		
G/G	Romania	1.00		
A/G+A/A		1.60	78	Rotal et. al. 2014
TNF*α* -857C > T polymorphism				
C/C	Chinese	1.00	239	Zuo et. al. 2011
C/T		2.36		
T/T		1.76		

Polymorphisms in Cytokine Genes

Cytokines are molecules important in the defense of organisms against viral infections. They are produced by macrophages, monocytes, and lymphocytes. The these molecules act in an indirect way by determining a pattern of immune response or directly by inhibiting viral replication [75]. Polymorphism incytokine genes can influence immune response to HPV infection and possibly in the risk of cervical cancer.

Polymorphisms in IL-10 gene

Interleukin-10 (IL-10) is a T_{H2} anti-inflammatory cytokine that participates in the regulation of the immune response at several levels with important effects on B cells [76]. Several SNPs have been detected within the IL-10 gene sequence, especially within the promoter regions, including IL-10-392C > A, IL-10-1082A > G, IL-10-819C > T and IL-10-592A > C. These polymorphisms may be associated with differential levels of gene transcription, since some alleles can produce low, medium and high amounts of IL-10 [17].

IL-10-1082A > G polymorphism is correlated with a significantrisk of cervical cancerin Brazilian [19] and Japanese [77], while polymorphismsIL-10-819C > T and IL-10-592A > C also are associated with risk of cervical cancer in Indian [73] and Mexican [78] population, respectively (Table 3).On the other hand, the IL-10-1082A > G polymorphism it has been found not associated with risk of CC in African [79] and Dutch populations [80] The discrepancy may be explained by ethnic differences in IL-10 gene polymorphism.

Table 3: Polymorphisms in IL-10 and IL-4R*α* gene and their association with risk cervical cancer.

Genotypes	Population	OR	Number patients	References
-592C > A polymorphism in IL-10 gene				
C/C	Mexican	1.00	166	
C/A		2.00		Torres-Poveda et. al. 2012
A/A		2.07		
-819C > T polymorphism in IL-10 gene				
C/C	Indian	1.00	150	Singh et. al. 2009
C/T + T/T		1.52		
-1082A > G polymorphism in IL-10 gene				
A/A	Japanese	1.00	104	Matsumoto et. al. 2010
A/G + G/G		3.90		
A/A	Brazilian	1.00	82	Chagas et. al. 2013
A/G		1.05		
G/G		1.60		
-389A > C polymorphism in IL-4Rαgene				
A/A	Swedish	1.00	1285	Ivansson et. al. 2007
A/C		1.20		
C/C		1.90		

Polymorphisms in IL-4 gene

Interleukin 4 (IL-4) is a cytokine of great importance for regulation of the immune response. IL-4 induces differentiation of T-cells to the T2-type and causes a switch to IgE-production inB-cells.IL4 exerts its effects through IL4-α receptors (IL-4Rα), and which formed complex with IL-4 receptor [81], The IL-4R*α* gene is highly polymorphic and several SNPs have been associated with different diseases including, cancer [82,83]. -389A > C polymorphism, is a type of 'gain-of-function' mutation, which results in substitution of isoleucine for valine (I75V) in the extracellular domain of IL-4R*α* subunit. Since IL-4R is likely to affect the balance of $T_H1/2$ cells, it may affect the establishment of an HPV infection [84]. If the -389A > C polymorphism alters T_{H1}/T_{H2} balance, it may influence susceptibility to persistent HPV-infection and cancer, assuming that a T_H1 response is essential for HPV clearance. If the -389A > C polymorphism is linked to a T T_H2-biased response, which suggest an increased susceptibility to cervical cancer (Table 3), which it is supported by Ivansson et. al. 2007 [84].

POLYMORPHISMS IN GENES INVOLVED IN METABOLISM

Apart from the HR-HPV, there are several etiological co-factors such as cigarette smoking, drinking and long duration of oral contraceptive use [6,8]. Environmental factors such as lifestyle,

exposure to tobacco-derived carcinogens have been confirmed to be related to the development of cervical cancer [85]. Evidence for increased tobacco-associated DNA damage has been demonstrated in the cervical epithelium of smokers [86]. In a study, HPV-infected women exposed to kitchen smoke from using wood for 35 years had a risk high for developing cervical cancer [87]. Tobacco contains carcinogens like polycyclic aromatic hydrocarbons,aldehydes, benzoα-pyrene, ethyleneoxide, 4-aminobiphenyl, and nitrosamines, which are metabolically throughphases I and II enzymes [88].

Activation or detoxification of chemical carcinogens in tobacco smoke by metabolic enzymes (phase I and phase II respectively) has received a great deal of attention, as possible genetic factors for a variety of cancers [85,89,90]. Polymorphisms in the genes encoding the metabolic enzymes result in their altered expressions which lead to increased or decreased activation/detoxification of chemical carcinogens from tobacco smoke [91].

Polymorphisms in CYP1A1 Gene

The Carcinogens generally require activation to electrophilic reactive forms to produce DNA adducts, individuals with increased metabolic activity are at higher risk of cancer development [92].

CYP1A1 is involved in xenobiotic metabolism, classified as phase I cytochrome P-450 enzyme that converts environmental procarcinogens to reactive intermediates with carcinogenic effects. It is one of the major enzymes responsible for this conversion, and plays an important role in the metabolic activation of aromatic hydrocarbons found in tobacco smoke [93,94]. CYP1A1 has been examined extensively for its capacity to activate compounds with carcinogenic properties in experimental animals and humans [94-96]. Some polymorphisms of this enzyme have been found to be a risk factor for cancer [93]. Taskiran C. et., al. [93] propose the CYP1A1^{*3} A2455G (rs1048943) polymorphism in codon 462 of exon 7 (Ile/Val) as a risk factor for CIN, squamous cell cancer, and adeno cancer (Table 4). In contrast, Roszak A. et. al. [97] demonstrated that the CYP1A1 Ile/Val polymorphism was not associated with an increased risk of cervical cancer (Table 4). However, the adjusted OR for parity with the Ile/Val vs. Ile/Ile genotype was 1.739 (95 % CI 1.006–3.009, p = 0.0472). In a Meta-analysis of the association between CYP1A1 Ile462Val polymorphism and cervical cancer risk, it was associated with increased risk of cervical cancer in Caucasians and Asians population (Table 4) [95]. Similarly, SergentanisT.N. et.,al. [25], showed a strong association of the Ile462Val variant with cervical cancer in Caucasian population in an exploratory study through a Meta-analysis (Table 4).

Table 4: Polymorphism in CYP1A1 associated with lesions and cervical cancer.

Genotypes	Population	OR	Number Patients	Reference
CYP1A1*3 Ile462Val (rs1048943) polymorphism in Adenocancer				
Ile/Ile	Turkey	1.00	14	Taskiran et. al. 2014
Ile/Val		11.29		
Val/Val		-		
CYP1A1*3 Ile462Val (rs1048943) Polymorphism In Squamous Cell Cancer				
Ile/Ile	Turkey	1.00	71	Taskiran et. al. 2014
Ile/Val		5.76		
Val/Val		3.03		
CYP1A1*3 Ile462Val (rs1048943) cervical cancer				
Ile/Ile	Poland	1.00	456	Roszak et. al. 2014
Ile/Val		1.58		
Val/Val		-		
Val vs. Ile	Meta-analysis	1.43	2,423	Yang et. al. 2012
ValVal vs IleIle		2.43		
ValVal+ValIle vs IleIle		1.59		
ValVal vs IleIle+ValIle		1.81		
Ile/Val vs Ile/Ile	meta-analysis	2.36	350	Sergentanis et. al. 2012
Val/Val vs Ile/Ile		2.73		
Val/Val+Ile/Val vs Ile/Ile		2.28		
Val/Val vs IleIle+IleVal		1.76		
Ile/Val vs Ile/Ile	Caucasian	2.88	275	Sergentanis et. al. 2012
Val/Val vs Ile/Ile		2.96		
Val/Val+Ile/Val vs Ile/Ile		2.74		
Val/Val vs IleIle+IleVal		1.87		
CYP1A1 T3801C MspI (rs4646903) Polymorphisms in Cervical Squamous Intraepithelial Lesion				
m1/m1	Hawaii	1.00	131	Goodman et. al. 2001
m1/m2		1.20		
m2/m2		3.40		
CYP1A1 T3801C MspI (rs4646903) polymorphism in cervical cancer				
C vs. T	Meta-analysis	1.38	1,912	Xia et. al. 2013
CC vs. TT		2.06		
CC/CT. vs. TT		1.45		
CC vs. TT/CT		1.56		
TC vs. TT	Meta-analysis	1.50	722	Sergentanis et. al. 2012
CC vs. TT		2.66		
CC + TC vs. TT		1.61		
CC vs. TT + TC		2.09		

TC vs. TT	Caucasian	1.42	190	Sergentanis et. al. 2012
CC vs. TT		3.75		
CC + TC vs. TT		1.46		
CC vs. TT + TC		3.21		
CYP1A1 T6235C MspI polymorphism in cervical cancer				
Ile/Ile	Japanese			Sugawara et. al. 2003
Ile/Val				
Val/Val		1.18	75	

The CYP1A1 T3801C MspI (rs4646903) polymorphism is characterized by the T to C mutation at nucleotide 3801 in the 3'-noncoding region leading to aMspI restriction site of the CYP1A1 gene. This mutation can alter the level of gene expression or messenger RNA stability, resulting in a highly inducible activity of the enzyme [94]. CYP1A1 T3801C polymorphism is related with cervical squamous intraepithelial lesions (SIL). Women who were homozygous, but not heterozygous, for the CYP1A1 MspI variant allele were at significantly increased risk of cervical SIL (odds ratio (OR) = 3.4; 95% confidence interval (CI) = 1.1–10.7) compared to women who were homozygous for the wild-type allele (Table 4) [98]. Xia L et. al., by means of Meta-analysis with ten studies on cervical cancer suggested a significant association between the CYP1A1 T3801C polymorphism and cervical cancer risk (Table 4) [99]. Other Meta-analysis showed also the T3801C variant as associated with cervical cancer. However, the authors did not find association of the variant in Caucasian and Asian population (Table 4) [25].

Other variants have been studied in the CYP1A1 gene, but these have not shown association with cervical cancer risk. In Israeli women the variants 264T > C and 4889 G > A in CYP1A1 gene were not associated with cervical cancer risk [100]. Likewise, the T6235C transition in the non-coding 3'-flanking region, and the A4889G transition in exon 7, no significant association was found between these CYP1A1 polymorphisms and cervical cancer in Japanese population [101].

These researches suggested that a genetic polymorphism in the CYP1A1 gene may increase the risk of biopsy-confirmed cervical SIL and cervical cancer although the precise mechanism(s) for this relation is currently unclear. Interestingly, T3801C MspI and Ile462Val polymorphisms are the more associated with risk for cervical cancer in Caucasian and Asian population. Furthermore, certain variant genotypes of the CYP1A1 gene may cause enhanced enzymatic activity appear to play a role in susceptibility to adduct formation in DNA and presumably cervical cancer risk [102].

Polymorphisms in GST Gene

The Glutathione S-transferases (GSTs) are family of enzymes which are involved in the detoxification of chemicals found in the environment and naturally synthesized metabolites, and they play an important role in protecting tissue from oxidative damage [103]. In humans, GST family consists of cytosolic, mitochondrial, and microsomal proteins (now termed MAPEG, membrane associated proteins involved in eicosanoid and glutathione metabolism) [104].

The cytosolic family has been assigned to distinct classes: GSTA (alpha), GSTT1 (theta), GSTM1 (mu), and GSTP1 (pi), and GST (kappa) and GST (sigma) variants [105]. GSTs belonging to mu, theta, and pi classes (GSTM1, GSTT1 and GSTP1) play important roles in detoxification of metabolites of carcinogens in tobacco smoke [106]. In recent years, many studies were performed to detect the association between genetic polymorphisms of GSTs and cancer risk, especially for three loci in GSTM1, GSTT1, and GSTP1.Polymorphismsinvolving homozygous deletions of GSTT1, GSTM1 and GSTP1 genes are frequent in the populations [105]. Deletion of the GSTM1 and GSTT1 genes results in a 'null' genotype characterized by a general deficit in enzymatic activity, which seems to denote impaired ability to detoxify carcinogens, a state conferring an increased cancer risk [107]. Accordingly, an A–G transition at nucleotide 313 of the GSTP1 gene is linked to a change in enzymatic activity [108].

A significant relationship is observed between the risk of developing cancer and metabolism enzyme gene polymorphism. The relation between GST gene polymorphism and cervical cancer has been investigated in various studies (Table 5), which demonstrated that the risk of cervical cancer increases in women with GSTT1, GSTM1 or GSTP1 gene polymorphism [105,109-113].

Table 5: Polymorphisms in GSTM1, GSTT1, and GSTM3 genes and their association with risk cervical cancer.

Genotypes	Population	OR	Number patients	References
Polymorphism in GSTM1 gene				
Non-null	Indian	1.00	142	Sharma et. al. 2004
Null		2.50		
Non-null	Chinese	1.00	125	Huang et. al. 2006
Null		2.50		
Non-null	Indian	1.00	312	Joseph et. al. 2006
Null		2.40		
Non-null	Chinese	1.00	110	Singh et. al. 2008
Null		2.50		
Non-null	Turkish	1.00	98	Kiran et. al. 2010
Null		7.00		
Non-null	Indian	1.00	150	Abbas et. al. 2013
Null		4.00		
Polymorphism in GSTT1 gene				
Non-null	Indian	1.00	142	Sharma et. al. 2004
Null		1.70		
Non-null	Indian	1.00	312	Joseph et. al. 2006
Null		1.84		
Non-null	Chinese	1.00	110	Singh et. al. 2008
Null		1.52		

Non-null	Turkish	1.00	98	Kiran et. al. 2010
Null		10.2		
Polymorphism in GSTP1 gene				
A/A		1.00		
A/G + G/G	Turkish	6.40	98	Kiran et. al. 2010
A/A		1.00		
A/G	Indian	2.24	150	Abbas et. al. 2013
G/G		2.40		

Likewise it was found association of the GST polymorphisms with histological subtypes, squamous cell carcinoma and adeno carcinoma. Abb as et. al. showed that GSTM1 null genotype was significantly associated with adeno carcinoma and the risk of developing cervical cancer. GSTP1 genotypes did not show significant association with adeno carcinoma but individuals A/G and G/G genotypes were associated with the risk of developing adenocarcinoma of the cervix [114].The association between gene variants with smoking status has also studied. The association of null genotypes of GSTM1 (-/-), GSTP1 (G/G), GSTT1 (-/-) and in passive smokers showed significant association with an increased risk developing cervical cancer [114].

These studies show that that risk of cervical cancer significantly increases in passive smokers with GSTM1 null, GSTT1 null, GSTP1 (G/G) and GSTM3 (A/A) genotypes. However, larger sample sizes are required to confirm the possible interactions between different GST polymorphisms and passive smoking in cervical cancer cases.

POLYMORPHISMS IN GENES INVOLVED IN DNA REPAIR.

Previous studies have identified tobacco-specific carcinogens in the cervical mucus of smokers [115], and demonstrated smoking-related DNA damage in the cervical epithelium [86]. On the other hand, DNA-repair systems are essential for the maintenance of integrity of the genetic material and dysfunction in this repair systems have a critical roles in cancer development [116]. Among the DNA-repair systems, Base-Excision Repair (BER) pathway and Double-Strand Break (DSB) repair pathway constitute a primary defense against lesions generated by ionizing radiation and strong alky lating agents as well as lesions formed by DNA damaging agents such as smoke [117].

Polymorphisms in XRCC1 Gene

XRCC1 is a molecule that interacts with PARP-1[poly (ADP-ribose) polymerase-1], DNA polymerase b and DNA ligase III [118], plays a role in DNA single-strand break repair. XRCC1 has two BRCA1 carboxyl-terminal (BRCT) domains, denoted BRCTI and BRCT II, which are located centrally and at the C terminus of this polypeptide, respectively [119]. Single-nucleotide polymorphisms have been found at the C terminus of the BRCT I domain in the XRCC1 gene. The Arg399Gln variant is the most reported, Gln allele was thought to reduce DNA repair activity and

hence lead to increased DNA damage. However, this genetic polymorphism has been reported to both increase and reduce cancer susceptibility depending on the type and site of the cancer [120].

A study conducted in Japanese population showed in joint association of the XRCC1 Arg399Gln polymorphism and smoking status with cervical cancer that the XRCC1 Arg399Gln polymorphism is a genetic-susceptibility factor for the development of cervical cancer [121], (Table 6). Studies in Chinese, Thailand and Saudi Arabia population have also considered the Arg399Gln variant as a susceptibility factor for cervical cancer [122-125] (Table 6). Interestingly, the 280C > T and 118A > G variants have only been evaluated in Chinese population showing an association with cervical cancer [124] (Table 6). In addition to the previous variants Huang et. al. 2007 evaluated in Chinese population the 194C > T polymorphism funding an association with cervical cancer, similarly to Settheetham-Ishida et. al. 2011 in Thailand population (Table 6).

Table 6: Polymorphisms in XRCC1 and ERCC1 gene and their association with risk cervical cancer.

Genotypes	Population	OR	Number patients	References
194C > T polymorphism in XRCC1 gene				
C/C	Chinese	1.00	539	Huang et. al. 2007
C/T		1.13		
T/T		2.09		
C/C	Thailand	1.00	111	Settheetham-Ishida et. al. 2011
C/T		1.21		
T/T		6.73		
280C > T polymorphism in XRCC1 gene				
C/C	Chinese	1.00	80	Zhang et. al. 2012
C/T		0.68		
T/T		2.02		
399G > A polymorphism in XRCC1 gene				
G/G	Japanese	1.00	131	Niwa et. al. 2005
G/A		1.95		
A/A		2.98		
G/G	Chinese	1.00	539	Huang et. al. 2007
G/A		1.58		
A/A		2.32		
G/G	Thailand	1.00	111	Settheetham-Ishida et. al. 2011
G/A		1.45		
A/A				
G/G	Chinese	1.00	80	Zhang et. al. 2012
G/A		1.36		
A/A		1.53		

G/G		1.00		
G/A	Saudi Arabia	0.96	218	Alsbeih et. al. 2013
A/A		15.88		
118A > G polymorphism in XRCC1gene				
A/A		1.00		
A/G	Chinese	1.50	80	Zhang et. al. 2012
G/G		2.06		

OTHERS POLYMORPHISMS ASSOCIATED WITH RISK TO CERVICAL CANCER.

Polymorphisms in CCND1 Gene

CyclinD1 (CCND1) plays an important role in the transition of the cell cycle from the G1 phase to the S phaseduring cell division, and it has been suggested that acts as an active switch that regulates cell cycle progression [126]. Cyclin D1 can also act as a transcriptional protein leading to the stimulation of specific transcription factors, which could be important in cancer [127]. It has been reported that CCND1 mRNA is alternatively splicedto produce two transcripts (a and b), which are present simultaneouslyin a variety of normal tissues and cancer cells [128].

Over 100 single nucleotide polymorphisms have been identified in the cyclin D1 locus. Of the polymorphisms identified, the CCND1 870G > A polymorphism has received the most investigation. The polymorphism frequency in the Caucasion population, but large variances between racial and ethnic groups have been reported [128]. This polymorphism inexon 4 of CCND1 gene does not lead to an amino acid change, but it is associated with a splice site variation coding for two mRNA transcripts [129]. The alternatively spliced transcript encodes proteins lacking the destruction box, leading to an increased half-life of cyclin D1 protein [130].

Several studies have reporteda significant association between the CCND1 CCND 1870G > A polymorphism and the development of cervical cancer [83,127,131-134]. It has been observed that women carrying the CCND1 870A > A genotype have increased risk for the development of cervical (Table 7),The absence of an association between the CCND1G870A polymorphism and cervical cancer has been demonstrated in a Korean population [34]. Theauthors mention that these discrepanciesin the findings of the effect of the CCND1 870G > A polymorphismon the incidence of cervical cancer in various ethnicities may result from differences in the racial heterogeneity of the examined groups. Likewise can be also be due to each population's exposure to various environmental components, which, along with the CCND1 870G > A polymorphism, may alter the risk of cervical cancer incidence in the investigated ethnicities [133].

Table 7: Polymorphisms in CCND1gene and their association with risk cervical cancer.

Genotypes	Population	OR	Number patients	References
870G > A polymorphism in CCND1 gene				
G/G	Korean	1.00	222	
G/A		1.17		Jeon et. al. 2005
A/A		1.36		
G/G	Portugal	1.00	103	
G/A		1.03		Catarino et. al. 2005
A/A		3.45		
G/G	Indian	1.00	150	
G/A		0.80		Satinder et. al. 2008
A/A		3.70		
G/G	Swedish	1.00	196	
G/A		1.07		Castro et. al. 2009
A/A		1.56		
G/G	Poland	1.00	129	Warchol et. al. 2011
G/A + A/A		1.81		
G/G	Kazakhstan	0.61	207	
G/A		0.63		Djansugurova 2013
A/A		2.85		

Polymorphisms in MDM2 Gene

The human homolog of mouse double minute 2 (mdm2) protein is the main negative regulator of the p53 function, has been suggested to be mutated in a number of cancers [135]. Recently, a functional SNP in the MDM2 intronic promoter (named MDM2 309T > G) was identified, with a T to Gchange, this increases the affinity of the Sp1 transcription factor and result in increased MDM2 mRNA and protein synthesis. As a consequence, the abrogation of p53 tumor suppressor activity was enhanced, resulting in a decreased response to DNA-damaging agents and acceleration in tumorigenesis [136]. Indeed, emerging studies have shown that the MDM2 309T > Gis associated with the risk of different cancers including lung, breast, hepatocellular, gastric, and so on [137-140].

In Brazilian, Asian and Chinese population was found that the MDM2 309G/G genotype from MDM2 309T > G polymorphism was associated with a significantly increased risk of cervical cancer develop [141-143]. Likewise, Amaralet. al. found a statistically significant result of the MDM2 309T > G polymorphism with the progression oflow grade squamous intraepithelial lesions(LSIL) to high grade squamous intraepithelial lesions (HSIL), and was observed that the MDM2 309T > G polymorphism is associated with cervical carcinogenesis especially in the high-risk HPV group [142]. On the other hand, Meissner et. al. compared cervical carcinoma patients

with healthy patients and observed that theMDM2 309T > G polymorphism may not be a risk factor for the development of cervical carcinogenesis in northeastern Brazil population [144]. The divergence between the results of these studies might be caused by racial, ethnic or samples differences in the populations studied.

Polymorphisms in DNMT3B Gene

Although HR-HPV and several others environmental factors are the major cause of cervical cancer, only a fraction develop cervical cancer during their lifetime, suggesting that genetic and epigenetic factors are of importance in determining individuals' susceptibility to cancer [145].

DNA methylation is a major epigenetic mechanism that regulates chromosomal stability and gene expression [146], DNA methylation is mediated by a family of DNA Methyltransferases (DNMTs), of which three active forms(DNMT1, DNMT3A and DNMT3B) have been identified inmammalian cells [147]. An overall increase in the transcriptional activity of the two maintenance DNA methyl transferases, DNMT1 and DNMT3B, has been shown to occur in cervical cancer [148].

The DNMT3B gene, contains a C → T transition polymorphism (DNMT3B46359C > T polymorphism) in the promoter region, -149 base pairs from the transcription start site, which confers an increase in promoter activity [149]. There is evidence that the DNMT3B 46359C > T polymorphism might be associated with cancer in where carriers of the T allele, particularly heterozygotes, had a significant increase in risk of cancer [149,150]. Hernández-Sotelo et. al. found in Mexican population a statistically significant result of that this SNP is associated with cervical carcinogenesis especially in the heterozygotes group to DNMT3B 46359C > T polymorphism. On the other hand also found that the TT genotype of the DNMT3B 46359C > T polymorphism was associated with a significantly decreased risk of HSIL and LSIL [150].

FUTURE DIRECTIONS

The knowledge to date of the molecular mechanisms involved in the risk of cervical cancer, contributed by the scientific community leads to the question, what can we do?

The answer is not simple.

First of all, it needs to be studied further to dissect the complex molecular mechanisms regulating or contributing to disease; what is currently known may still be insufficient given the intricate network of molecules involved in cervical cancer. Second, the current knowledge can show what an individual may be missing or what has been gained that favors disease; this has facilitated the development of drugs to restore the missing pieces or eliminate de novo molecules produced during the disease that are responsible for the condition. Third, replacement molecular medicine is a promising alternative to rectify genetic mistakes, but its ethical and molecular implications require further consideration; however, it is still seen as a safe and viable alternative in the future.

This text mainly discusses the factors intrinsically involved within individuals and little about the interaction of viral on coproteins of high-risk HPV and the individual genome; the latter was not the main focus. However, it is very interesting to know how a few nucleotide changes in the gene that codes for E6 oncoprotein of HPV-16 interacts with the human transcriptome modifying its expression; there is not much information regarding this to date and would be very interesting to know its progress. This will remain to be discussed in the future.

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