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GENETIC POLYMORPHISM and CERVICAL CARCINOMA

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Abstract: Cervical cancer (CC) is the world's second most commonly diagnosed cancer in women and one of the most common causes of death among women in developing countries. Cervical cancer is a complicated disease caused by the interaction of gene mutations and the environment. Human papillomavirus (HPV) infection is linked to cervical cancer, according to epidemiological and laboratory studies. HPV infection is responsible for more than 90% of cervical cancer cases, with types 16 and 18 being the most common one. Cervical cancer develops slowly and is caused by the human papillomavirus (HPV). It typically affects women in their mid-50s age. Although the changes may be visible between the ages of 20 and 30, this is due to the slow progression. Genetic variation is commonly represented by single nucleotide polymorphisms (SNPs). The existence of single nucleotide polymorphisms (SNPs) has been linked to the development of cervical cancer in numerous studies**.** Single nucleotide polymorphisms (SNPs) linked to cervical cancer has been identified through studies of genome-wide and candidate gene associations. However, some studies have yielded contradictory results over the same SNP. We studied previously published case–control studies involving the SNPs linked to cervical cancer to carried out better understanding. Cervical carcinogenesis is a multifactorial process in which genetic and environmental risk factors interact and contribute to malignant transformation. To verify the findings of this study and further evaluate the effect of gene-gene and gene-environment interactions in determining CC risk.

Index Terms: **Cervical carcinoma, risk factors, genetic polymorphism, SNPs, genetic variants.**

INTRODUCTION

Cervical cancer (CC) is the world's second most commonly diagnosed cancer in women and one of the most common causes of death among women in developing countries. Cervical cancer is a complicated disease caused by the interaction of gene mutations and the environment. Human papillomavirus (HPV) infection is linked to cervical cancer, according to epidemiological and laboratory studies. HPV infection is responsible for more than 90% of cervical cancer cases, with types 16 and 18 being the most common one [1],[2].

The uterine cervix is the uterine neck. It is a strong, muscular tube-like structure that opens slightly into the vagina. It is made up of glands that produce a thick liquid known as cervical mucus. This keeps harmful foreign objects out of the uterus. Cervical cancer, on the other hand, is the abnormal cell growth in the cervix. It is the most common type of cancer in women.

Cervical cancer develops slowly and is caused by the human papillomavirus (HPV). It typically affects women in their mid-50s age. Although the changes may be visible between the ages of 20 and 30, this is due to the slow progression. The HPV vaccine is available for HPV prevention.

CAUSE/RISK FACTORS OF CERVICAL CANCER

Cervical cancer is caused by the proliferation of abnormal cells in the cervix. This is primarily associated with Human papillomavirus infection.

HPV: HPV is a sexually transmitted virus that is the leading cause of cervical cancer.

Having multiple sexual partners: Sexual contact increases the likelihood of contracting an HPV. Women who have multiple sexual partners are more likely to develop cervical cancer.

Birth control pill use: Long-term use of birth control pills raises the risk of cervical cancer.

Sexually transmitted diseases include: Cervical cancer is increased by STDs such as gonorrhoea and chlamydia.

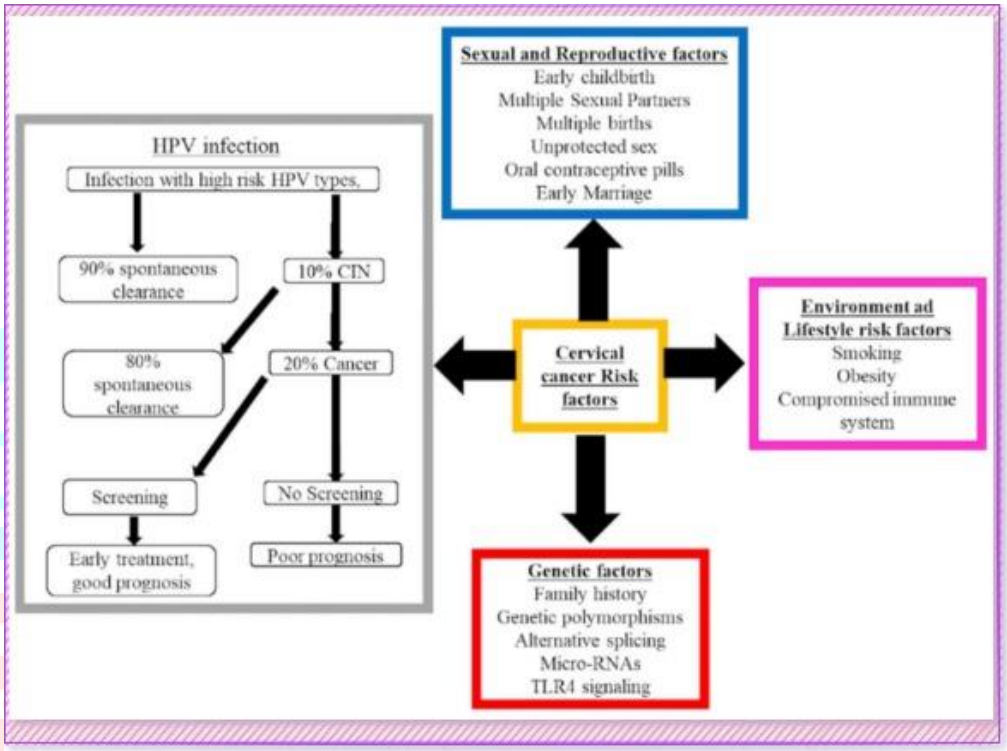

Fig 1: Risk factors of cervical cancer

SYMPTOMS OF CERVICAL CANCER

Cancer in its early stages is always asymptomatic. However, as the disease progresses, symptoms emerge.

The following are the most common symptoms:

- Bleeding between menstrual periods
- Bleeding just after a sexual intercourse
- Vaginal discharge that is abnormal
- Pelvic Pain/genital Suffering
- Postmenopausal women's bleeding
- Discomfort during a sex act

TREATMENT

The most appropriate type of treatment is determined primarily by the size of the tumour and the extent of the cancer's spread. If the tumour is discovered at an early stage, a minor surgical procedure (conization) can be performed. If the tumour has already spread to the surrounding tissue, doctors typically advise clearing the whole womb (a hysterectomy). During this procedure, the lymph nodes in a large area surrounding the womb are also removed. Radiotherapy is another option that could be considered. If the tumour cannot be removed surgically, radiotherapy is still an option. It can be combined with chemotherapy in some patients.

The early stage is usually treated with surgery to remove the uterus (hysterectomy). Early-stage cervical cancer can be cured and prevented from recurring with a hysterectomy. However, removing the uterus makes pregnancy impossible.

Simple hysterectomy: The cervix and uterus, and even the cancer, are removed. A simple hysterectomy is usually only an option in very early-stage cervical cancer.

Radical hysterectomy: With cancer, the cervix, uterus, a portion of the vagina, and lymph nodes in the area are removed.

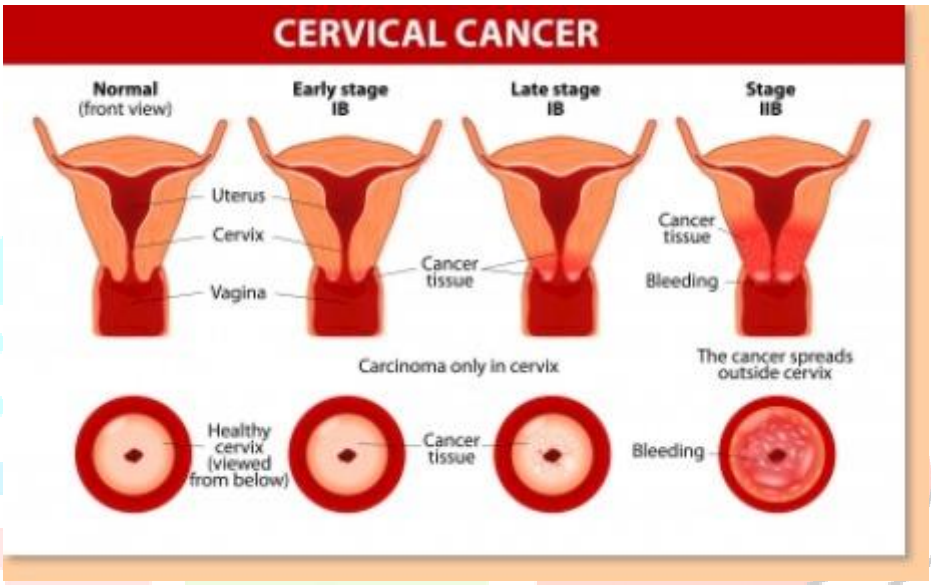

Fig 1: stages of cervical cancer

GENETIC POLYMORPHISM AND ASSOCIATION TO CERVICAL CANCER

Genetic variation is commonly represented by single nucleotide polymorphisms (SNPs). The existence of single nucleotide polymorphisms (SNPs) has been linked to the development of cervical cancer in numerous studies**.** Single nucleotide polymorphisms (SNPs) linked to cervical cancer has been identified through studies of genome-wide and candidate gene associations. However, some studies have yielded contradictory results over the same SNP. We studied previously published case–control studies involving the SNPs linked to cervical cancer to carried out better understanding.

GLUTATHIONE S- TRANFERASES

The Glutathione-S-transferase (GST) family genes encode enzymes that appear important in cytotoxic cellular defence. GSTs protect cells from the harmful effects of oxidative stress by cross-linking glutathione to endogenous lipid peroxidation products and inhibiting organic hydro-peroxides via selenium-independent glutathione peroxidase activity [4]. GSTM1 and GSTT1 gene deletions may contribute to cervical dysplasia through modulation of polycyclic hydrocarbon activation and detoxification and other compounds that affect oxidative stress and also the formation of DNA adduct [5]. Previous studies with GST and cervical neoplasms have found that the frequency of GSTM1 or GSTT1 in women with SIL is not significantly different compared with standard cervical control group. [5], [6], [7]. The null genotype of GSTT1 in high grade squamous intraepithelial lesion cases was more common than cases and controls in low grade squamous intraepithelial lesion, which used exfoliated cervical cell samples from a Japanese population. Furthermore, among the high risk HPV group, patients with high grade squamous intraepithelial lesion had a higher rate of null GSTT1 genotype than those with low grade squamous intraepithelial lesion. The fact that GSTT1 does not operate against the substratum for GST models 1-chloro 2,4-dinitrobenzene and does not bind to Shexyl-glutathione affinity matrices [8] differs from other GST classes. Mutations in the GSTT1 gene have been associated with a higher

incidence of myelodysplastic syndromes [9], astrocytoma, and meningioma [10]. In a previous study, 104 cell lines of genotypes derived from various human malignant tumours were examined for GSTM1 and GSTT1, and it was found that GSTT1 null genotype was showed in cervical tumour cells [3]. It would be interesting to study whether it happens before or late in the development of malignant phenotype cells that differentiate in the polymorphic frequency of a Null GSTT 1 genotype between squamous intraepithelial lesions and invasive cervical cancer.

HPV 16

The most common aetiological agent of cervical cancer are high-risk human papilloma virus [11], HPV16 being the world's most prevalent type in women with or without cervical abnormalities/cancer[12]. The factors that cause a significant subset of HPV16 infections to evolve to carcinoma are still unknown, but some research has indicated that HPV16 genetic variation could play a major role [13]-[18].

Previously, HPV16 variants were categorized into four main phylogeny based on common phylogenetic patterns of single-nucleotide polymorphisms (1) European and Asian, including European, Asian, African, Asian American/North American sub-lineages [19]-[21].

T350G, found in the E6 oncogene, causes an amino acid alteration from leucine to valine (L83V)., is a common polymorphism within the EUR lineage. As a result, the EUR lineage can be divided into samples usually contains 350T (EUR-350T) or 350G (EUR-350G). The results of a study have demonstrated a persistence of HPV16 variations in a host of ancestral races and progress to cervical intra-epithelial neoplasm grade 3 (CIN3). This polymorphism was associated with persistence and probability of progression to cervical lesions precancerous in EUR variant lineages (it also exists in non-EUR lineages). even if this was not observed in higher racial additive Latin American populations [22],[23],[18].

In all regions, the EUR lines represented a significant proportion of HPV16 isolates, (except Sub-Saharan Africa). The results showed significant heterogeneity by region worldwide for the test of the risk of cervical cancer associated with the common polymorphism EUR-350T/G; cervical cancer risk was associated substantially, in East Asia and Europe/Central Asia, with EUR-350T versions, compared with EUR-350G.

On the other hand, In South and Central America, the case is different. Although puzzling, there are indications of this regional heterogeneity in past country-specific research; EUR-350T variants in cervical diseases were heavily represented in contrast to EUR-350G in Netherlands [24] and China studies [25], even though there were no difference in other smaller European series [26]-[29]. In another study, the cancer of EUR-350T versus EUR-350G could also depend on numbers of Migrants in Europe. Moreover, in comparison to EUR-350G in Denmark [18], EUR-350T infections were likely to continue and transition to CIN3In the past, there was a comparable high correlation of EUR-350G with cervical cancer in Argentinean study in relation to the directly opposed results in South and Central America, and a Brazilian study has recently found that EUR-350G has a higher capacity for transforming human keratinocytes compared to EUR-350T (in vitro).

CCR2 and CCR5

The CCR5 human chemokine receptor is the major receptor for the CC chemokine ligands CCL3/MIP-1·, CCL4/MIP-1, (macrophage inflammatory protein, -1·, -1,) and CCL5/RANTES [31]. Using a panel of monoclonal antibodies against human CCR5. Some studies found that CCR5 is expressed by a subset of lymphocytes and macrophages in blood, non-inflamed tissues, primary and secondary lymphoid organs [32]. CCR5-32 is a truncated inactive receptor (a 32 base pair deletion in the CCR5 gene) that does not exist on the cell membrane. Homozygosity for the CCR5-32 gene predicts longer renal allograft survival [33], a lower risk of asthma [34], a milder form of rheumatoid arthritis [30], and an earlier onset of myocardial infarction [35]. CCR5-32 heterozygotes also have lower levels of the protein. Furthermore, CCR2 and CCR5 function as HIV-1 co-receptors. CCR5-32 homozygotes are highly resistant to macrophage-tropic strains of HIV-1 infection [36], and CCR5-32 is associated with steadier cancer progression to AIDS [37],[38]. The chemokine CCR2 receptor interacts primarily with the human CC family ligand CCL2 (formerly called MCP-1 monocyte chemoattractant protein), CCL7/MCP-3, CCL8/MCP2, CCL13/MCP-4 were all found on monocytes, functionalized T cells, natural killer cells, dendritic cells, and basophils.

LINC00673

Several studies have shown that tumour angiogenesis in cervical cancer is influenced by a variety of factors, including the regulation of numerous long noncoding RNAs (IncRNAs). The role of long noncoding RNA LINC00673 in the development and prognosis of many tumours, including pancreatic cancer, gastric cancer, non-small cell lung cancer, and tongue squamous cell carcinoma, has been extensively studied[39],[40],[41],[42]. Significant efforts have recently been made to investigate the effect of genetic variations in the IncRNA genes on tumour susceptibility. LINC00673 and its polymorphism rs11655237 had not previously been reported in the context of cervical cancer. Functional single-nucleotide polymorphism (SNP)-based study strategies have recently become popular in genetic association studies. Given the importance of LINC00673 in carcinogenesis, the LINC00673 rs11655237 variant may influence cervical cancer susceptibility. The risks of T cervical cancer were significantly higher in transporters of the A allele and genotype AA/AG of the rs11655237 polymorphism than in transporters of the G allele and genotype GG SNP rs11655237, a noncoding transcript variant in IncRNA LINC00673, demonstrated important DNase hypersensitivity in multiple cancer cell lines and binds transcription factors such as P300, FOXA1 and FOXA2. To elucidate the mechanisms by which the rs11655237 genotype inclined to cervical cancer. A clinical outcomes investigated the association of the rs11655237 genotype with LINC00673 expression.

***P*53 CODON 72 POLYMORPHISM**

*P*53 is a tumour suppressor gene that is involved in various mechanisms including apoptosis, transcriptional control, and cell cycle regulation and control [43], [44]. Many human tumours, particularly smoke-induced lung cancer, include mutations and deletions of the p53 gene, which results in loss of functional tumour suppression and de-regulation of the cell cycle [45]. A polymorphism in codon 72 of the p53 gene causes arginine (Arg) to be substituted for proline (Pro) in the gene product. The homozygous (Arg) genotype had an enhanced sensitivity to E6 degradation from oncogenic HPV of p53 protein [46].

Table 1: SNP genes associated with cervical cancer

GENE	SNP	GENOTYPE	P VALUE
MDM2	rs229744	T/G	0.0004
CYPA1 T6235C	rs4646903	C/T	0.005
CYP1A1 A4889G	rs1048943	G/A	<0.00001
IL-12B	rs3212227	A/C	0.0001
IL-12A	rs568408	G/A	0.006
P21 CODON31	rs1801270	C/A	0.87
XRCC3 CODON241	rs861539	C/T	0.7
IL-4R	rs1801275	A/G	0.09
IL-10C592A	rs1800872	C/A	0.007
CCND1	rs603965	G/A	0.14

CONCLUSION

Cervical carcinogenesis is a multifactorial process in which genetic and environmental risk factors interact and contribute to malignant transformation. However, wide genetic epidemiology research in the field of cancer diseases have proposed that polymorphic traits alone have lower capacity to modify individual prognosis. Several decades of intensive research have yielded massive amounts of information on the genetic susceptibility of Cervical cancer, but research evidence on CC susceptibility related to SNPs have been unclear. More studies with large sample sizes, detailed data regarding established risk factors for CC, and high quality are warranted to verify the findings of this study and further evaluate the effect of gene-gene and gene-environment interactions in determining CC risk.

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