RESEARCH PAPER

Hla and Tp53 Polymorphism in Hpv Driven Cervical Carcinogenesis- A Review

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ABSTRACT
Cervical cancer remains a significant global health burden, primarily driven by persistent high-risk Human Papillomavirus (HPV) infection. However, the transition from infection to malignancy is heavily influenced by the host's genetic predisposition. A comprehensive literature search was conducted across PubMed, Scopus, and Web of Science which explores the synergistic role of TP53 (rs1042522) and HLA alleles (Class I, II, and G) in cervical carcinogenesis. The synthesis reveals a "dual-layered" vulnerability including immune evasion layer, where specific HLA polymorphisms (such as DRB1*15 and DQB1*0602) impair antigen presentation and allow HPV to bypass immune surveillance, and a tumor suppressor layer, where the TP53 Arg72 variant shows increased susceptibility to E6-mediated degradation, disarming the apoptotic response. Ultimately, the interaction between HLA-mediated immune failure and TP53-mediated suppressor loss creates a high-risk molecular environment, suggesting that integrating host genetic profiling into screening programs could significantly enhance personalized early detection and targeted intervention for high-risk populations.

Keywords: Human Papillomavirus, Cervical cancer, HPV E6/E7, TP53 mutation
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1. INTRODUCTION

One of the leading causes of death in women is cervical cancer. These cancers claim lives of more than 4,00,000 people in a year [1,2]. Among these cervical malignancies more than 90% are caused by Human Papillomavirus (HPV) and is one of the most prevalent sexually transmitted disease (STD) in the world and can lead to chronic infections in both men and women. While human body often clears HPV naturally, persistent high-risk HPV (hrHPV) infections can progress to various cancers, including penile, cervical, oropharyngeal cancers, and anal, significantly impacting public health [3,4]. Although it can infect both sexes women are more vulnerable with an estimate of 80% women may contract it by the age of 50 years [5]. The World Health Organization (WHO) now acknowledges HPV as the primary cause of a wide number and type of malignancies [6-8]. The oncogenes present in HPV are the major cause of inducing malignancies among infected individuals [9-11]. Although majority of HPV infections are clinically silent due to absence of obvious signs, a few lesions can progress to invasive cancers with observable symptoms [12].

Globally, the prevalence of HPV infection and related cancers shows considerable variation. Worldwide epidemiological data indicates regions exhibiting the highest prevalence rates (≥ 33.87%) include South America, Africa, and specific parts of Europe. On the other hand, Australia and other European regions demonstrate intermediate prevalence, ranging from 16.93% to 33.87%. However certain countries like North and South America report lower HPV infection rates, typically below 16.93%. These variations in HPV prevalence across the world highlights the importance of screening programs, safe sexual practices, vaccination coverage and socioeconomic determinants across various population [13].

HPV induced cervical cancer starts with mild cellular alternation in cervix that can later developed into cancer if

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immune system fails to counteract it. HPV infection's role in cervical cancer progression remains unnoticeable in women up to 15-20 years making it a pathogen of greater importance [14]. With the progression of cervical cancer women can experience several symptoms including vaginal abnormalities (bleeding can occur after menopause, between cycles, or after sex). The bleeding during periods can also be heavier and longer than usual, pain during sex, vaginal discharge (unusual vaginal discharge, the discharge can be watery or blood-mixed and foul smelling), advanced symptoms (difficulty urinating, back pain, abdominal pain, severe weight loss, swelling legs, or pelvic pain). Despite the unconfirmed role of hereditary factors in the development of invasive cervical cancer from High-Grade Squamous Intraepithelial Lesions (HSIL), familial clustering of cervical cancer has been consistently observed for over 60 years. This long-standing evidence highlights the need for further investigation into a potential genetic predisposition [15]. Strong supporting data come from the Swedish cancer registry, which has demonstrated a high familial relative risk of cervical cancer [16]. Specifically, these studies indicate that female siblings and offspring of affected individuals have a 1.5–2.3 relative risk of developing the disease [17]. This suggests that genetic components may contribute to an individual's susceptibility to cervical cancer.

In this review article we will be discussing on the Human Leukocyte Antigen (HLA) and Tumor Protein 53 (TP53) gene polymorphism in human helping HPV persistence inside host and its development to cervical cancer in women.

2. REVIEW METHODOLOGY

A comprehensive literature search was conducted across PubMed, SCOPUS and Web of Science to identify relevant studies published between 1990 to 2025. The search strategy utilized combination of words like Group 1 (TP53): "p53", "TP53", "TP-53", "p-53", "codon 72" , Group 2 (Variation): "polymorphism", "variability", "mutation", "gene", "SNP", "rs1042522", "rs17878362" , Group 3 (Pathology): "cervical cancer", "cervix", "cervical intraepithelial neoplasia", "CIN", "HPV", "carcinogenesis" and Group 4 (HLA): "HLA", "human leukocyte antigen", "Major Histocompatibility Complex (MHC)", "HLA class I", "HLA class II", "HLA-G". Studies only publish in English were included. Initially screening was performed using title and abstract followed by full text review.

3. HPV AND CERVICAL CANCER: UNDERSTANDING THE RELATION

Persistent HPV infection can subsequently develop into cervical cancer which can be ultimately life threatening. The risk of developing severe complications or development of cancer varies depending on the specific HPV strain. Among the over 180 distinct types of HPV, approximately 40 are sexually transmitted. These sexually transmitted strains target moist epithelial tissues, such as the mucosal membranes of the anogenital and oral regions, to establish infection. However, it is crucial that majority of HPV infections, particularly those acquired through non-sexual contact, manifest as cutaneous warts on the feet and hands [18]. In view of this the vast majority of HPV strains may be categorized as either low-risk or high-risk. The high-risk genotypes are linked to a considerable percentage of oropharyngeal cancers as well as a number of anogenital malignancies, such as those of the anus, cervix, vagina, vulva, and penis. High-risk HPV genotypes, especially 16 and 18, are linked to most HPV-related cancers. Their ability to express viral oncoproteins (E6 and E7) by disrupting host cell cycle regulation and tumor suppressor pathways, these contribute to their oncogenic potential (Fig.1). Other hrHPV includes type 33, 45, 31, 58 and 52 associated with cervical cancer [19,20]. However, low-risk HPV (lrHPV) are the main contributing factors behind benign epithelial proliferations such anogenital cutaneous warts. While these lesions can cause discomfort and are highly transmissible, progression to malignancy is very rare. HPV-related cervical cancers typically progress over 10 to 20 years, a timeline that can be accelerated in immunocompromised individuals. Subsequently with the progression of invasive cervical cancer, when not identified and managed, is a life-threatening outcome in 95% of cases [21,22]. The development of HPV infection to cervical cancer is a multidimensional process influenced by interplay of viral, host, and environmental determinants. Although prolonged exposure to hrHPV strains is crucial for development of CCs, the rate and likelihood of neoplastic transformation are modulated by several other cofactors, including host immune status, parity, age at first pregnancy, contraceptive use, and co-infection with other sexually transmitted infections.

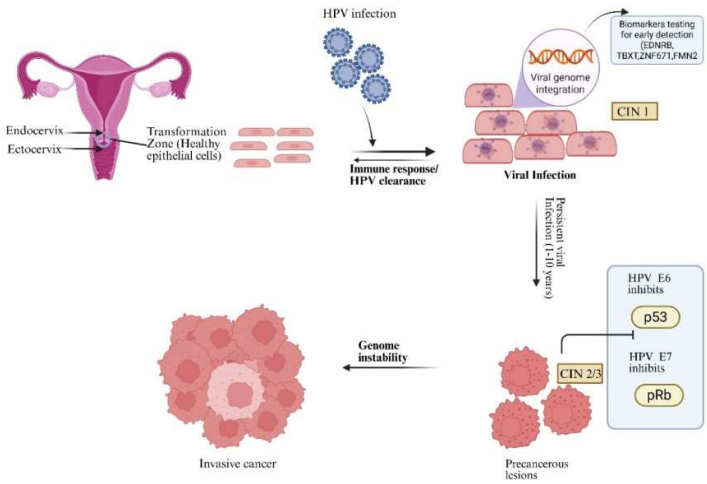

Fig.1. Stages of HPV related cervical cancer progression (Created in BioRender. Padhi, S. (2025) https://BioRender.com/xk6z1kw)

Fig.1 Illustrates the Schematic representation of the progression from Human Papillomavirus (HPV) infection to invasive cervical carcinoma. The process begins at the cervical transformation zone, where healthy epithelial cells are susceptible to HPV infection. While most infections are cleared by the host immune response, viral genome integration into the host cell DNA can lead to low-grade Cervical Intraepithelial Neoplasia (CIN 1), often detectable through specific biomarkers (e.g., EDNRB, TBXT, ZNF671, FMN2). Persistent viral infection over 1–10 years facilitates the transition to precancerous lesions (CIN 2/3), driven primarily by the high-risk viral oncoproteins E6 and E7, which inhibit the tumor suppressors p53 and pRb, respectively. This loss of cell cycle control induces profound genomic instability, eventually culminating in the development of invasive cancer.

4. HPV AND DISEASE PATHOGENESIS:

The cervix uteri, the most inferior portion of the uterus, comprises two distinct epithelial compartments the ectocervix and the endocervix. While the endocervix is lined with columnar glandular epithelium, the ectocervix is covered by stratified squamous epithelium.

These two tissue types converge at the squamocolumnar junction (SCJ), also known as the transformation zone. This specific anatomical area is highly susceptible to HPV infection and subsequent neoplastic transformation, making it the primary origin for cervical precancerous lesions. The majority of early HPV infections, especially those that result in low-grade squamous intraepithelial lesions (LSIL) or cervical intraepithelial neoplasia stage 1 (CIN1), resolve spontaneously within two years in approximately 90% of cases. Although re-infections are common, they rarely result in cancer. Genetic diversity is critical in resolving these infections and restricting progression to invasive disease, as only a small percentage of women with HPV ultimately develop invasive cervical cancer [23]. However, if an HPV infection persists and the host immune system fails to clear the virus over time, it can advance to higher-grade precancerous lesions. These include HSIL, which encompass cervical intraepithelial neoplasia stage 2 (CIN2) and stage 3 (CIN3), as well as carcinoma in situ. This progression is linked to several factors including the sustained presence of oncogenic HPV infection, particularly high-risk types; the viral load within the infected cells; the composition and local microenvironment of the cervical tissue at the site of viral integration; the potential for progressive cellular damage; and the impact of multiple reinfections with the same or different HPV types. The combine effect of all these factors can ultimately lead to progression of invasive malignancies if untreated [24].

5. HPV E6 AND E7 ONCOPROTEINS: DRIVERS OF CERVICAL CARCINOGENESIS

The growth and progression of cervical carcinoma mediated by HPV oncoproteins E6 and E7. E6 oncoproteins in cervical cells target and inactivate p53, a crucial tumor suppressor protein. This interaction subsequently leads to p53 degradation, compromising the cell's natural ability to suppress development. This enhances the risk of cancer, as the cellular mechanism to counteract HPV E6 leads to the elimination of this essential tumor-suppressive protein. Simultaneously, the HPV E7 protein promotes cancer risk by interfering with the function of another crucial tumor-suppressing protein, retinoblastoma protein (Rb), thereby deregulating cell cycle control [25] (Fig. 2).

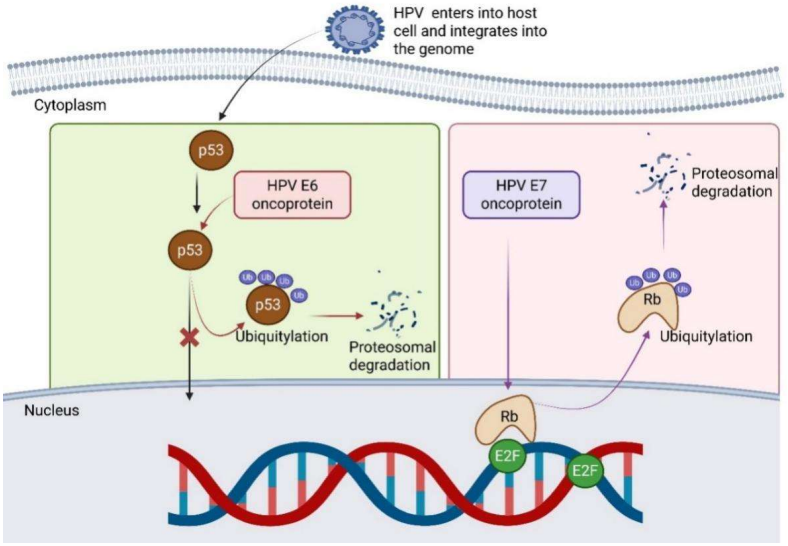

Fig. 2. HPV E6 and E7 mechanism of action for development of cervical cancer (Created in BioRender. Padhi, S. (2025) https://BioRender.com/zx7ycja)

Fig.2 showed the Molecular mechanisms of HPV-induced oncogenesis through E6 and E7 oncoprotein-mediated degradation of host tumor suppressors. Following viral entry and genomic integration, the HPV E6 oncoprotein targets the p53 tumor suppressor for ubiquitylation and subsequent proteasomal degradation, effectively bypassing p53-mediated DNA repair and apoptosis. Simultaneously, the HPV E7 oncoprotein binds to the Retinoblastoma protein (Rb), triggering its ubiquitylation and degradation; this releases the E2F transcription factor from the Rb-E2F complex, allowing it to translocate to the nucleus and initiate the transcription of S-phase genes. Together, these synergistic pathways disrupt critical cell cycle checkpoints, leading to unregulated cellular proliferation and the potential for malignant transformation.

6. HOST GENETIC VARIATIONS INFLUENCING CERVICAL CANCER

The variations in Deoxyribonucleic acid (DNA) coding and noncoding regions in humans, makes each of us distinct. These variations increase individual vulnerability to a variety of illness. Decades of extensive research on human genetics leads to the discovery of single nucleotide polymorphism (SNPs) across individuals and interestingly SNP markers for specific diseases have been discovered. A variety of illnesses, including cervical cancer, have also been related to copy number variations, however they are less prevalent than SNPs but may involve the acquisition or deletion of genomic DNA segments in comparison to a reference human genome [26,27]. Advancement in biomedical research leads to identify individualized treatment for complicated ailments based on genetic variation has been facilitated. Over the past two years, more than 165 new DNA alterations in more than 100 new chromosomal regions have been found through genome-wide association study, which affects clinical characteristics and the likelihood of prevalent human diseases [28].

7. HLA POLYMORPHISM IN HOST

The highly polymorphic genes known as HLA, which encodes cell-surface proteins necessary for immunological regulation, are found on human chromosome 6. HLA gene variations have been connected to a number of human diseases, such as autoimmune disorders, cancer, degenerative diseases, and infections [29]. An individual's susceptibility of acquiring persistent HPV infections is significantly influenced by immune recognition of the virus by host. This immune recognition is modulated by polymorphisms in HLA genes which leads to production of altered proteins with varying resemblance (lower or higher) for different HPV antigens, thereby affecting the efficiency of antigen presentation and subsequent immune response necessary for viral clearance. Building on this, numerous gene association studies have investigated the impact of genetic variations within HLA genes [30]. A study by Ferguson et al. 2011 identified specific human leukocyte antigen-G (HLA-G) gene polymorphisms, namely HLA-G*01:03and HLA-G*01:01:02, as significant risk factors for persistent human papillomavirus (HPV) infection. This research indicates an association between these alleles and susceptibility to persistent HPV 16 infection. These HLA-G variants are also associated with a heightened risk of persistent infections from HPV types 2, 3, 4, and 15 [31]. HLA-G interaction with HPV is multidimensional, influencing susceptibility, disease progression, and transmission. Specific alleles such as HLA-G*01:01:05and HLA-G*01:01:03could raise the possibility of co-infections. Conversely, HLA-G*01:04:01, HLA-G*01:06, and HLA-G*01:01:02, have been linked to higher likelihood of developing more advanced lesions, though these particular associations haven't always reached statistical significance [32]. However, HLA-G genotype matches between mother and child, specifically for HLA-G* 01:01:01/01:04:01, can increase the probability that an infant will test positive for

HPV, highlighting HLA-G complex impact on HPV immunity and its clinical manifestations [33].

Several studies indicate a complex and varied association between HLA class II alleles and HPV infection, leading to cervical intraepithelial neoplasia (CIN) and cervical cancer across different populations. Certain alleles like DQB1* 03, DRB1* 04, and DRB1* 11, and specific haplotypes such as DRB1 * 1101-DQB1* 0301 and DRB1 * 0401-DQB1* 0301 are significantly related to heightened vulnerability to CIN. Conversely, DRB1* 0101-DQB1* 0501 often shows a protective effect [34].

On the other hand, polymorphism in alleles for cervical cancer, particularly in HPV-positive cases, include DQB1 * 05, DQB1 * 0402, DQB1 * 0602, DQB1 * 0601, DRB1 * 04, DRB1 * 11, DRB1 * 0401, DRB1 * 1101, DRB1 * 15, and their associated haplotypes like DQA1 * 0102 - DQB1 * 0602 and DQA1 * 0501 - DQB1 * 0301. Notably, in women infected with HPV16, the DRB1 * 15-DQB1 * 0602 haplotype and HLA-DRB1 * 15 are highly associated with cervical cancer [35].

Despite these observations, studies on the relationship between HLA polymorphism and the risk of cervical squamous cell carcinoma can often be not evident. According to some studies, the DRB1 * 1501 - DQB1 * 0602 haplotype and DQB1 * 03 alleles are strongly associated, while others report no association or even an inverse relationship. Conversely, DRB1 * 01 and DRB1 * 13 alleles/haplotypes are frequently associated with a decreased risk of squamous cell carcinoma of the cervical region. The exact mechanisms, specific contributing DRB1 * 13 or DQB1 * 0603 alleles, or their linkage to other MHC genes still require further investigation [36].

Beyond HLA-G and HLA class II polymorphisms, research also highlights the involvement of HLA class I polymorphisms in susceptibility to prolonged HPV-16 infection and cervical cancer. For instance, in South India in context of HLA-B * 44, there is a strong association between cervical cancer and persistent HPV-16. Conversely, HLA-B * 15 appears to offer a protective effect against cervical cancer, including CIN III and invasive cervical cancer, particularly in HPV52-positive cases. Though there is evidence linking HLA-B * 07 to a higher incidence of cervical squamous lesions, no HLA-B alleles have been independently linked to an increased risk of CIN. Other HLA class I alleles implicated in prolonged HPV infection and cervical cancer progression include HLA-A * 0301, HLA-A * 3101, HLA-A * 3303, HLA-A * 02, HLA-A * 0201, HLA-B * 3501, HLA-B * 37, HLA-B * 3701, HLA-B * 3901, HLA-B * 4402, HLA-B * 58, HLA-B * 5801, HLA-Cw * 0501, HLA-Cw * 0704, and HLA-C * 0702. These findings underscore the varied influence of HLA class I molecules on the immune response to HPV and subsequent disease progression [37-40] (Fig. 3).

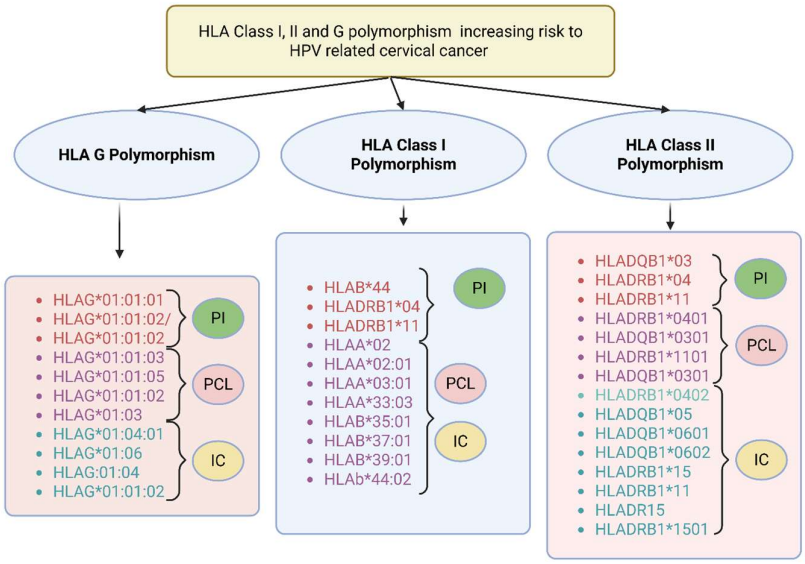

Fig. 3. HLA G, HLA Class I and HLA Class II polymorphism linkedto HPV persistence and development of cervical cancer

***PI- Persistent infection, PCL- Precancerous lesions, IC- Invasive cancer (**Created in BioRender. Padhi, S. (2025) https://BioRender.com/21xamkb)

Fig.3 shows the distribution of HLA Class I, II, and G Polymorphisms associated with increased risk of HPV-related cervical cancer. The schematic illustrates specific Human Leukocyte Antigen (HLA) alleles and their association with different stages of cervical carcinogenesis. Polymorphisms are categorized into three major groups: HLA-G, HLA Class I, and HLA Class II. Alleles are further grouped based on their clinical significance in the disease progression pathway. PI (Persistent Infection): Alleles associated with the inability

to clear Human Papillomavirus (HPV) infection. PCL (Pre-cancerous Lesions): Alleles linked to the development and maintenance of cervical intraepithelial neoplasia (CIN). IC (Invasive Carcinoma): Alleles specifically associated with the progression to malignant invasive cervical cancer.

Most research has concentrated to examine the relationships between HPV-induced malignancies, particularly cervical cancer, and HLA polymorphism. However, fewer studies have directly investigated how HLA genes influence an individual's susceptibility to, or ability to clear, initial HPV infections.

8. TP53 POLYMORPHISMS

TP53 gene is most commonly altered in human tumors, it is clear that it is crucial in halting the development of cancer. Somatic mutations in the TP53 gene cause over half of human malignancies [41]. Polymorphism in the TP53 gene occurs at codon 72, resulting in two variant proteins: one with proline (Pro72) and the other with arginine (Arg72). Both variants retain wild-type p53 functionality under normal conditions. However, emerging evidence suggests that these variants may alter in their susceptibility to degradation by the HPV E6 oncoprotein, potentially influencing cervical cancer risk. A study demonstrated that p53Arg (Arg72) is more efficiently degraded by high-risk HPV E6 proteins compared to p53Pro (Pro72) [42]. Inheritance of germline mutations in TP53 causes predisposition to early onset of cancer in early childhood, a disorder called Li Fraumeni's syndrome [43]. The somatic mutations are mainly missense and nonsense mutations which inactivate p53 and result in expression of mutant protein in 90% of the cases and in 10% of the cases, the protein is absent. The majority of the time, p53 mutations cause tumor suppressor activity to be lost and oncogenic function to be gained; as a result, mutant p53 becomes an oncoprotein in cancer cells that promotes the growth of carcinoma cells. Variation in p53 DNA binding domain typically cause p53 to malfunction and become inactive, which can contribute to the development of cancer [44]. Wild type p53 is unable to activate the downstream genes because mutant p53 with oligomerization domain mutations dimerize with it. Mutant p53 can be recruited by the cancer cells to acquire selective advantage and this will promote invasion, metastasis and chemoresistance [45]. Multiple lines of research have demonstrated that HPV E6 oncoproteins from both high-risk and low-risk HPV types have evolved diverse mechanisms to interfere with the tumor suppressor p53 (TP53), beyond the well-characterized pathway of E6-induced degradation via the ubiquitin-proteasome system. One mechanism by which E6 influences p53 involves its direct binding to the C-terminal region of p53, a process that's independent of E6AP, the ubiquitin ligase crucial for p53 degradation [46]. This binding occurs with both low-risk and high-risk HPV types, yet it doesn't result in p53 degradation. Instead, it likely alters p53's transcriptional regulation, potentially diminishing its ability to bind DNA and repress target gene transcription. This interaction may explain how low-risk HPV E6 proteins, despite not degrading p53, can still weaken its tumor suppressor functions through direct interaction (Fig. 4).

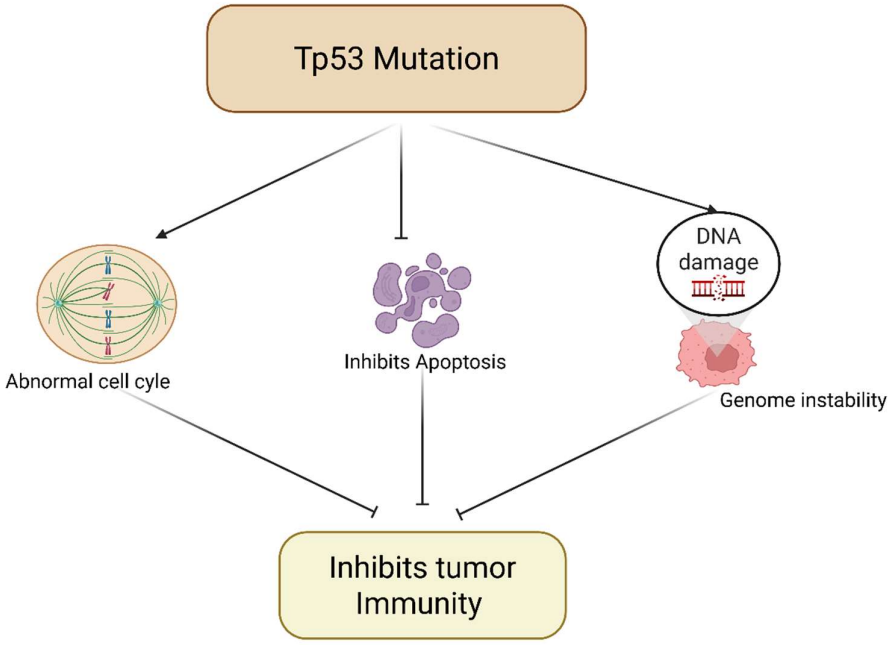

Fig. 4. TP53 polymorphisms linked to HPV related cervical cance (Created in BioRender. Padhi, S. (2025) https://BioRender.com/xk6z1kw)

Fig.4 illustrates the multifaceted role of TP53 mutations in driving oncogenesis and suppressing the host immune response. A mutation in the TP53 gene, a critical tumor suppressor, leads to three primary cellular consequences: the promotion of an abnormal cell cycle (characterized by unregulated proliferation), the inhibition of apoptosis (preventing programmed cell death of damaged cells), and the accumulation of DNA damage resulting in genomic instability. Collectively, these pathways converge to inhibit tumor immunity, creating an immunosuppressive environment that allows malignant cells to evade detection and destruction by the immune system, thereby facilitating tumor progression.

So, due to lack of study about TP53 and HLA polymorphisms in HPV-related cervical cancer that can plays a "dual role" by either synergistically promoting disease progression or by conferring protection, depending on the specific allelic combinations present in the individual may be primary area to focus.

9. INTEGRATED ANALYSIS OF HLA AND TP53 POLYMORPHISMS IN CERVICAL CARCINOGENESIS

The transition from a persistent hrHPV infection to invasive cervical carcinoma is not a random event but a genetically choreographed process. While the HPV E6 and E7 oncoproteins facilitates transformation, the host's Human HLA and TP53 polymorphisms acts as bridge by either facilitating or inhibit this progression. The synergistic mechanism of HLA and TP53 creates a multi-hit vulnerability in the host by immune evasion and tumor suppressor failure. Polymorphism in HLA Class I (A, B, C and Class II (DR, DQ) determine the efficiency of viral peptide presentation to T-cells. If a host carries alleles with low affinity for HPVE6/E7 epitopes, the virus remains invisible to the adaptive immune system resulting in viral persistence. Similarly, the E6 oncoprotein recruits the E6-associated protein to ubiquitinate p53. The Arg72Pro polymorphism (rs1042522) is the critical junction here. The Arg72 variant has been shown in multiple meta-analyses to be more susceptible to E6-mediated degradation compared to the Pro72 variant.

Several researches suggests that the risk of cervical cancer is significantly amplified when specific HLA risk alleles coexist with the TP53 Arg72 variant. This dual factor hypothesis has been supported by four fundamental aspects of genetic and molecular research:

- **P53 polymorphism and proteolysis:** Storey et al. (1998) first identified that the p53 Arg72 isoform is degraded by HPV E6 oncoprotein at a faster rate than Pro72 variant providing a biochemical basis of differential risk for cervical cancer [47].
- **Haplotype specific susceptibility:** Researches dated back to 1994 showed HLA DRB1*1501*-DQB10602 haplotype as the critical genetic determinant for HPV16 positive cervical cancer linking MHC class II alleles to viral outcomes [48].
- **Genome- wide association (GWAS):** GWAS 2013 confirms the dominance of MHC (HLA0 region on chromosome 6p21.3 making it the most significant site for cervical cancer risk on global scale [49].
- **Immune evasion and persistence:** Beyond classical HLA genes, polymorphism in HLA-G genes demonstrated that it impairs the host ability to clear high risk HPV (hrHPV) types 16 & 18 leading to chronicity [31].

10. GENOME-WIDE ASSOCIATIONS STUDIES AS A POWERFUL TECHNIQUE FOR DETECTION OF MUTATION

GWAS have been effectively used in cancer research and are useful tool for locating common susceptibility changes within a group [50]. Using programs like Regenie, or PLINK, association analysis is carried out following genotyping and imputation [51]. Once relevant variations have been identified, new loci are validated by meta-analyses and replication studies in different cohorts. The causative SNP can be distinguished from many sets of correlated, highly associated variants with the use of colocalization, bioinformatic annotations, and fine-mapping approaches. In order to test for gene and pathway enrichment using in silico predictions, variants are annotated for known chromatin marks and adjacent genes [52]. These expectations become crucial for understanding the function of the noncoding genome, which accounts for the majority of the susceptibility variations that have been found. To investigate the biological function of lead variants, several functional assays have been designed and assessed. These include quantitative trait loci (QTL), analyses for expression (eQTL), methylation (metQTL), splicing (sQTL), and protein levels (pQTL), as well as chromosome conformation capture and chromatin immune precipitation (ChIP).

11. CONCLUSION

Chronic infections with high-risk HPV strains, including HPV 16 and 18, are the usual cause of cervical cancer, while not all HPV infections result in cervical cancer. The development of cervical cancer is largely impacted by host genetic variables, specifically TP53 and HLA polymorphisms. HLA variants can dysregulate the immune response against HPV, while TP53 polymorphisms impact a crucial tumor suppressor pathway. This variations of genetic factor in host can either combinedly increase susceptibility by compromising immune clearance and tumor suppression, or confer protection. In depth analysis of these genetic factors, often population-specific, genetic predispositions is vital for advancing personalized risk assessment and developing more targeted prevention and treatment strategies for HPV-related cervical cancer. In summary, cervical carcinogenesis is a multi-hit process where viral persistence is facilitated by an individual's genetic predisposition. Future research must focus on the

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functional synergy between these host markers to refine early detection strategies and improve the global survival rates of women battling this preventable disease.

Declaration of Interest Statement:
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this review article

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SKP, SRN, SPJ, GV, SSM have equally contributed in all stages of preparing, drafting, reviewing and writing this review article. All authors read and approved the final version of this manuscript.

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