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Topic: *Genomic characterization of Human Papillomavirus and pathogenesis leading to cervical cancer.*

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Abstract:

Human papillomaviruses cause cervical and another anogenital carcinoma. This double-stranded virus initially starts with the invasion of stratified epithelia in order to differentiate during its life cycle. Some human papillomavirus associated proteins target cellular components, especially those involved in DNA damage repair. The epigenetic regulation of host and viral transcription is also involved during this process. Human papillomavirus (HPV) infections are prevalent and spread through physical contact. If not managed immunologically or by screening, HPV16 can cause almost all cervical cancers globally. The oncoproteins E6 and E7, which disrupt growth regulatory mechanisms, are largely responsible for the carcinogenicity of certain HPV strains. The high risk of human papillomavirus can result in virion producing infection and continues with abortive and transforming infection. The onset of cancer can develop due to the gradual accumulation of host genetic abnormalities. The most harmful HPV is found in the genus Alpha papillomavirus. Based on genetic distances across viral genomes, they may be categorized into species and types. Current circulating infectious HPVs are a collection of viral genomes that have developed in tandem with the fast growth of the human population. E1 and E2 proteins cause cellular replication of the viral origin in the URR and enter the stable maintenance phase, where viral genome copies are made and chromosomal replication is synchronized. In sub-linages, D2/D4 variants were prevalent in glandular cervical lesions, whereas A1/A2 variations were detected in the great majority of cervix squamous cell carcinomas.

Key words: Carcinoma, Cervical cancer, Human Papillomavirus, Genetic variation, Epithelial cells, Transcription factor.

Introduction:

Papillomaviruses are the most abundant DNA viruses that infect the skin and mucosa of animal species with direct physical contact as the route of transmission, causing protruding warts and sometimes benign flats that result in cancer. Small double stranded DNA viruses with a length of 8kb are the main cause for cervical cancer. In the studies, a total of 400 types of human papillomavirus were found, of which 200 have been approved by the International Committee on Taxonomy of Viruses (ICTV). Somehow, ten types which are from the alpha genus are at greater risk of causing this disease and cancer, among which HPV 16,18,31,33,35,45 are the most serious and prominent. There are more than 200 human papillomavirus genotypes which show that HPV is coevolved with human host species [1][2]. The genotypes are characterized by Alpha, Beta, Gamma, Mu, and Nu and numbered species like Alpha 1, BOX 1, termed as phylogenetic genera. Human papillomavirus has evolved to be specifically adapted to epithelial tissues such as human skin and mucosa. The higher risk of Alpha genus (BOX1) is due to sexual contact but requires one to two years to get in control by immunological strategies mostly advantaged due to the reason this virus remains undetected by DNA and RNA assays [3]. Untreated viruses can cause cervical cancer in females and lead to non-keratinized mucosa and skin cancer as well as cancer of the lower genital tract, which includes the vagina, penis, and anus [4]. The high-risk HPV types are aimed at predicting the progression of cancer in accordance with guideline cancer-preventive treatment. The treatment related to this deadly virus has not been significantly noticeable in recent years. HPV16 is the most common cause of invasive cervical cancer (60%), thus it is rare to be detected and, after this, comes the HPV18 stain of human papillomavirus. (15%) [5]. Furthermore, HPV16 causes HPV-related, non-cervical cancers (85%) in females. The carcinogenicity concerning HPV16 in contrast to other high-risk HPV types makes it almost necessary to include some of the almost necessary ethnical carcinogens. High quality cervical cancer screening is a possibility. Indeed, for more than 50 years, cervical cytological screening applications have significantly reduced mortality, despite the difficulty of preparing and preserving them. Approximately 90% of squamous anal cancers and cervical cancers are caused by HPV and less than 50% include penis and vulva cancers [6,7]. In addition, gender differences in the incidence of HPV-related cancers have been minimized among HIV-infected people in high-income countries due to the high incidence of anal cancer in men [8]. More recent evidence

suggests that oropharyngeal cancer has two main types: one is caused by HPV and the other is caused by the use of tobacco and alcohol [9,10]. The discovery of HPV as the primary cause of obtrusive cervical cancer came after a century of epidemiological studies that established a link between the disease and sexual activity [11,12]. Precise serological estimation of aggregate HPV disease would be alluring in epidemiological examinations. Yet, tragically, accessible serological measures are restricted. There is no serological test can delicately gauge the combined lifetime occurrence of different kinds of HPV which makes it hard to relate serological estimations of this virus and severity of the disease. The recognition of HPV16 which is early protein E6 that is connected with oropharyngeal malignancy is used for the testing [13]. As needs be, epidemiological estimations depend essentially on HPV DNA testing. Although delicate, a positive DNA result can once in a while show the presence or affidavit of infection particles instead of genuine disease. The supported presence of viral records (mRNA) can be taken as a more certain marker of disease [14]. An extra intricacy of HPV, the study of disease transmission as characterized by HPV tests, should be thought of. The predominance of HPV relies upon the affectability of the HPV examiner and the recurrence of testing.

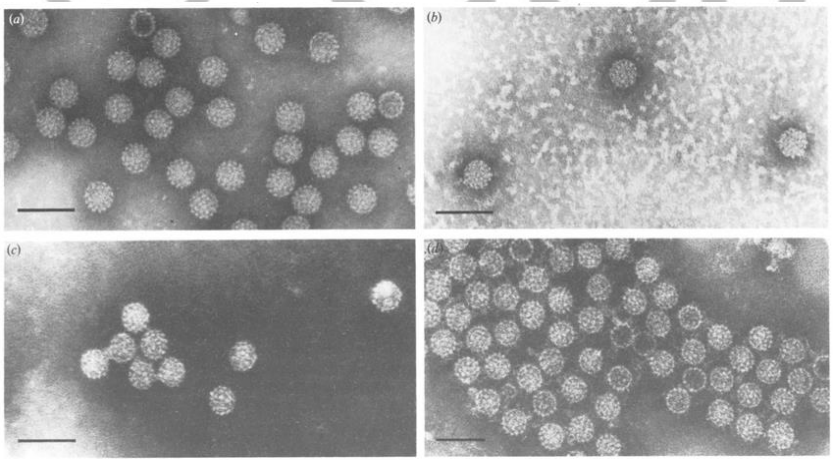

Figure:1 Electron micrograph of negatively stained Human and its particle suspension treated with antibody-negative serum. DOI:10.1099/0022-1317-71-2-419

Human Papillomavirus Life Cycle:

The human papillomavirus infection starts when the virions in the basal layer of epithelial cells are exposed to wounding. HPV virions always infect basal cells when they become exposed, resulting in low copies of episomes in the undifferentiated cells and then reaching the daughter cells for further differentiation and genome amplification, which is induced by late promoter activation after virionic assembly and release. The human papillomavirus genome migrates to the nucleus in vesicles to form low copies of episomes, and the protein involved in this process is L2 protein, making 10-2000 copies of its genome and only the early viral promoter is transcriptionally active during this phase, resulting in the expression of HPV early proteins such as E1 and E2, as well as E6 and E7. [15][16]. Infected basal cells replicate HPV genomes in synchrony with chromosomal DNA replication during the S phase, and the newly replicated genomes are distributed equally to the two daughter cells. One daughter cell stays in the basal layer to proliferate, while the other daughter cells migrate to the suprabasal layers to differentiate [17]. With increased levels of E1 and E2 expression, viral genome replication switches to a productive mode, resulting in the synthesis of thousands of genome copies. The L1 and L2 capsid proteins are expressed in the terminally differentiated layer of the epithelium under the control of the late promoter, and the mature viral particle is assembled. Virions are shed along with the dead squamous cells of the epithelium's outermost layer for further transmission [16].

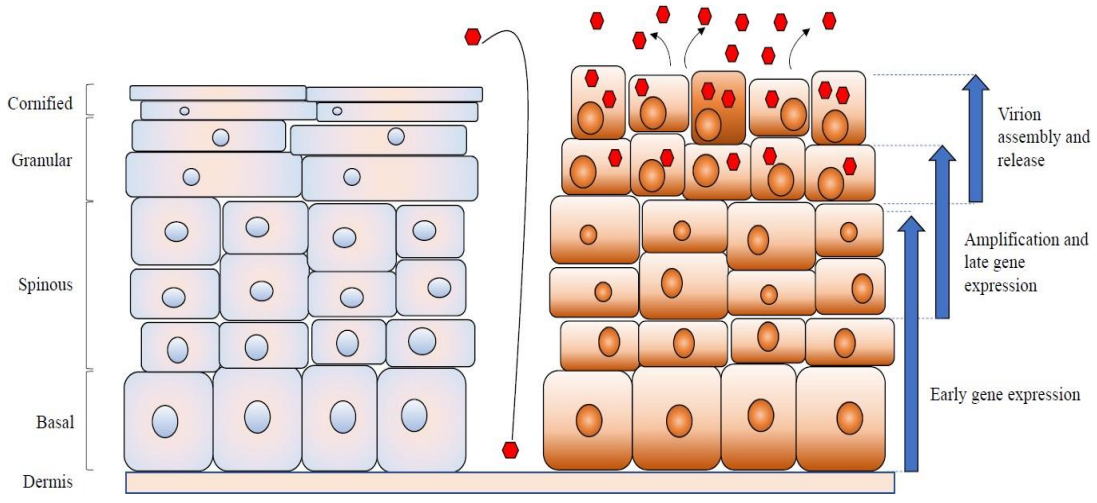

Figure 2: Early gene expression and amplification by virions for genome replication.

Regulation of the Human Papillomavirus Life Cycle:

The genomes of HR-HPV are found as extrachromosomal episomes in precancerous lesions. In contrast, HR-HPV DNA is frequently found integrated into the human genome in cervical squamous cell carcinomas. In general, there is a link between cancer progression and the physical state of the viral genome, with episomes being more common in early stages and integrated viral genomes being more common in high-grade lesions and carcinomas. HR-HPV integration is thought to be an early event in carcinogenesis and is mechanistically linked to virus-induced cancer [17,18,19]. Increased expression of E6 and E7 results in malignant progression resulting in cancer. The integration of viral genome occurs in E2 ORF. Three different modes of replication occur during the life cycle of HPV in the stratified epithelia [20,21]. In the initial and very first phase the viral entry in nucleus results in increase of DNA viral genomic replication increasing the episomes copy numbers showing dependency on E1 and E2 proteins. These proteins results in cellular replication of the viral origin in URR and enters in the second phase called stable maintenance phase as well. in this phase the viral genomes copies are being through the replication of viral episomes showing synchronism with chromosol replication in maintenance phase [22]. This second phase categorized by circular molecules that contain bi-directional replication forks proceeding in the opposite direction initiating ORI with help of E1 and E2 proteins. The vegetative amplification usually the third phase indicating fast production of large numbers of viral genomes showing recombinant dependent replication for both bi-directional theta replication [21]. The viral replication mechanism which particular ORI sequences absent is called showing recombinant dependent replication. This can initiate replication process in different HPV genome regions. The viral DNA along with its replication intermediates are detected and sensed as damaged DNA in the body. This results in the onset of DNA damage processes operated by virus for its genomic replication program in G2/M rather than s phase [23]. Expression of E6, E7, or E1 by themselves can activate these pathways by inducing replication stress [21,24]. Human papillomaviruses (HPV) viral proteins have their own functions like translation and transcription, which is related to the E1 protein, but the apoptosis and viral DNA replication associated proteins are E2 and E4, but they help specifically with viral DNA replication only. It also acts as a transcription repressor E6/E7. The female immune system is recognized by the E5 protein, which deals with the major histocompatibility complex. P53 degradation and alternation of the cell cycle are associated with the E5 protein,

which shows apoptosis resistance as well. There is another E7 protein which results in retinoblastoma na dp16 overexpression during the pathogenesis of this virus inside the body and helps the viral re-entry into S phase. The final two L1 and L2 proteins are known as major and minor viral capsid proteins, respectively. In Electron microscopy of extracellular vesicles from HeLa cells shows the typical morphology of HPV18 DNA that is shown in the diagram. The graphical representation of the unnormalized abundance of VPH in terms of number of reads.

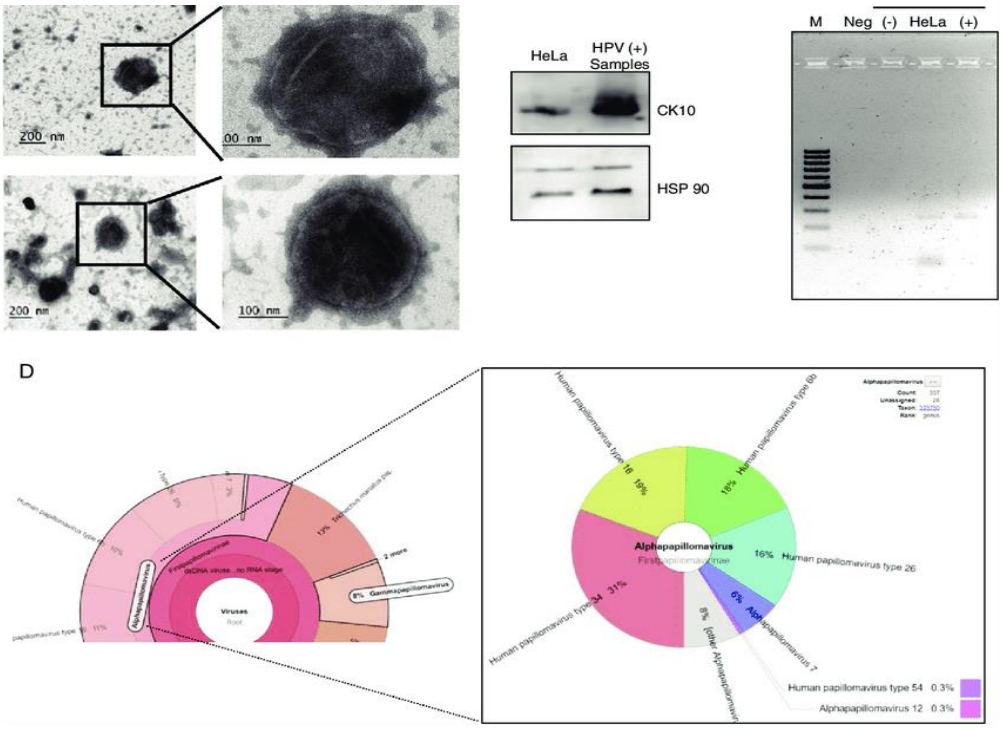

Figure 3: Presence of HPV DNA in extracellular vesicles from HeLa cells and cervical samples.

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HPV structure and genome organization:

The particles of the human papilloma virus are 55nm. HPV16 as described the most viral and deadly related to alpha HPV group. In the diagram two types of promoters are shown with arrows P97 and late 670 promoters. The ORFs shown as six open edges in red used to communicate at different stages pf epithelial cell separation with help of promoters are specific to E1, E2, E4, and E5 in green and E6 and E7. Two L1 and L2 ORFs are shown as yellow in color are used during joining in uper epithelial layer normally transferred by P670. The viral gene expression results after the non-coding region of viral genome contributes the post-transcriptional regulation sequences and binding sites for the viral gene products E1 and E2 and SP1 transcription factor, are shown in the diagram. The virus-related proteins are represented by an asterisk (*) are necessary for genome replication, viral assembly during the viral replication process, and release. The are some accessory proteins shown by a double dagger (‡) have roles in cell cycle entrance and immune evasion.

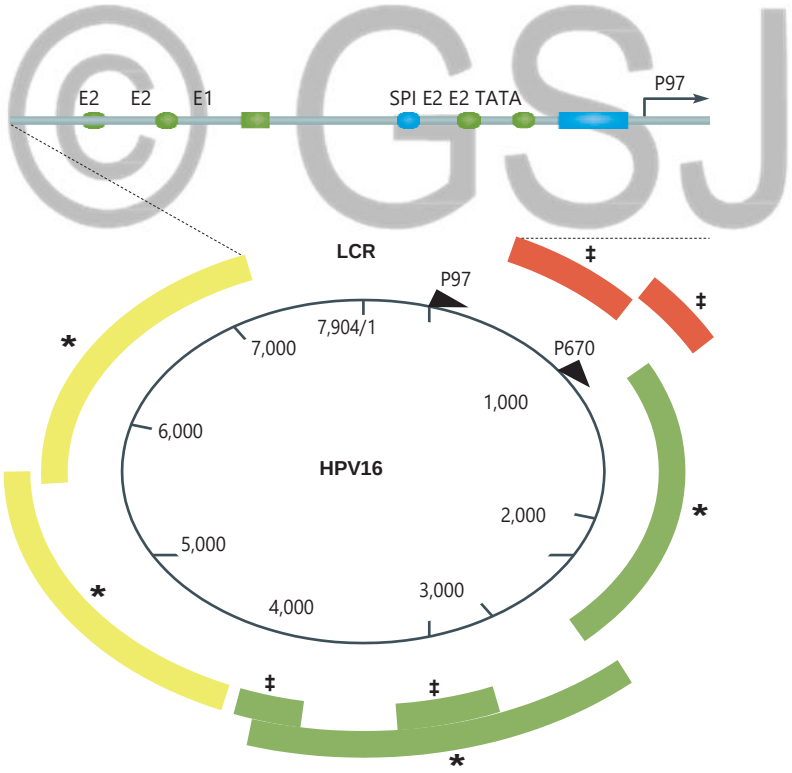

Figure 4: Genomic organization of human papilloma virus

Molecular biology of papillomaviruses:

Human papillomaviruses share a common genome association, and for the completion of their productive cycle, they depend on differentiating epithelium. Human papillomavirus is 800 base pairs long and has an icosahedral capsid made up of 360 copies of the L1 gene product with double-stranded DNA [25], eight to nine open reading frames, and multiple promoters that control viral gene expression. The open reading frames are always encoded on one strand of the viral genome, and complex patterns are used to splice the mRNA after the onset of infection. In this way, viral genes are expressed at different stages of the human papillomavirus [26,27,28]. Maintenance replication in the epithelial basal layer may be dependent on host cell replication factors due to the joint action of numerous viral gene products, including E6, E7, E2, and the virally encoded helicase E1. Post-translational modifications which include phosphorylation and proteolytic cleavage are controlled by viral proteins by expressing and being tightly regulated [27]. The gene expression of HPV depends on basal epithelial cells, especially those that show specific characteristics after the virus infects those cells. In some cases, external stimuli, hormones and some growth factors are equally responsible. The transformation zone and the adjacent endocervix region are responsible for the onset of cervical cancer. A cervix area that consists of columnar epithelium but later undergoes metaplasia, particularly after puberty, to produce a completely differentiated squamous epithelial layer is adjacent to the endocervix. The ectocervix's stratified layers are considered to be maintained by 'conventional' epithelial stem cells situated in the bottom layer. According to current understanding, productive high-risk HPV infection is preferred at the ectocervix, and lesion development begins with infection of an epithelial stem cell at the transformation zone or endocervix.

Human papillomavirus-mediated carcinogenesis:

The major role of E6 and E7 early proteins in the carcinogenic process is to inhibit the tumors suppressors p53 and pRB [29,30]. E6 roles also include the stimulation of telomerase activity and the dysregulation of immune system response, epithelial differentiation, cell proliferation, and survival signalling pathways. E7 increases genomic instability and the accumulation of chromosomal aberrations in addition to cell cycle dysregulation and proliferation. The dysregulation of the cell cycle, stimulation of telomerase activity, and genomic instability all contribute to an environment conducive for epithelial cell transformation. Because of the viral

sequence insertion, HPV integration can further promote the carcinogenic process by inactivating E2 expression, the major inhibitor of E6 and E7, and disrupting host genes. The carcinogenic process, which begins with the activation of E6 and E7 [31], must be supplemented by the accumulation of other changes in the host genes to result in the invasive cancer phenotype. The Cancer Genome Atlas Consortium's comprehensive genomic analysis found genes that were substantially mutated in cervical and head and neck HPV-associated cancers [32,33]. Surprisingly, a large majority of the discovered mutations follow a pattern consistent with the action of APOBEC, an innate immune mechanism that may bind and modify viral DNA, limiting viral infection. APOBEC3B can then be triggered by E6 and E7 oncoproteins. As a result, as has been documented in a number of human malignancies, APOBEC might be a significant source of mutagenesis in HPV-associated tumors [34,35,36]. HPV isolates of the same type that vary in the genome sequence by less than 10% are divided into variant lineages and sub lineages. These variations have been linked to an increased risk of cancer. Those with an HPV16 non-A variation B, C, and D, for example were consistently at a higher risk of cervical cancer than women with other variants. Furthermore, D2/D4 sub lineages were more common in glandular cervical lesions, whereas A1/A2 variations were found in the vast majority of cervix squamous cell carcinomas 75.4 percent. Growing data shows that epigenetic changes related to E6 and E7 activity are frequent throughout the early stages of epithelial malignancy and have been identified as possible biomarkers for cervical cancer [37,38].

Cofactors for persistence and progression and cervical cancer:

There are three types of co-factors for human papillomavirus which have viral, behavioral and host characteristics resulting in pre-cancer. For the progression of cervical cancer genetic and epigenetic variations are seen in human papillomavirus. In the studies the comparison between HPV16 infection is seen greater as compared to HPV51, HPV56 and HPV59 and important factor resulting in pre-cancer. Female immune system response is another significant outcome factor which includes a specific limited resistance against smoking, multiparity, and long-term use of hormonal contraceptives that increase the risk of HPV infections leading to precancer depending upon immune response totally [39,40]. The effect of behavioral HPV cofactors on clinical outcomes is limited when compared to viral and host variables. The development and chance of pre cancer increase 1.5-2-fold after onset of human papillomavirus in a host body [41].

Cervical cancer stages:

It has four different stages. Starting from stage I, carcinoma remains restricted to the cervix. Then comes stage IA, in which invasive cancer is recognized only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm. It leads to stage IA1 in which the stromal invasion measured is 3 mm in depth and <7 mm in extension. The stromal invasion is being measured in stage IA2, which is > 3 mm in depth and not >5 mm, and extension <7 mm. The stage IB, which is clinically visible for lesions limited to the cervix or preclinical cancers, The next stage, IB1, is clinically visible for tumors 4 cm in greatest dimension**.** Stage IB2 is clinically visible for tumors >4 cm in greatest dimension, parametrial involvement, but not in the pelvic sidewall. The worse stage starts in which cancer spreads beyond the cervix, named stage 2, but not to the pelvic sidewall or lower third of the vagina. Like stage 1, it further has sub stages; **s**tage IIA, which involves the upper 2/3rds of the vagina without parametrial invasion, and **s**tage IIA1, which **is** clinically visible for tumors 4 cm in greatest dimension. Involvement of up to the upper two thirds of the vagina following **s**tage IIA2 is clinically visible for tumors > 4 cm in greatest dimension, but not into the pelvic sidewall. In the last sub-stage, which **is s**tage IIB, the parametrial invasion takes place but not into the pelvic sidewall, leading to the most dangerous **s**tage III, in which the **c**ancer has extended into the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumour and the pelvic sidewall. The tumour involves the lower third of the vaginal All cases with hydronephrosis or a non-functioning kidney are Stage III cancers**.** Stage IIIa involves a tumour in the lower third of the vagina with no extension to the pelvic sidewall, which leads to extension of the pelvic sidewall leading to stage IIIb and causing obstructive uropathy. MR imaging findings that are suggestive of pelvic sidewall involvement include tumors within 3 mm of the abutment of the internal obturator, and pyriform muscles and the iliac vessel. In stage IV carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder, rectum extension beyond the pelvis, or biopsy proven to involve the mucosa of the bladder or the rectum, Stage IVa spreads the tumour into adjacent pelvic organs, extension beyond the pelvis, or rectal/bladder invasion, leaving distant organ spread in stage IVb.

Conclusion and future possibilities:

The human papillomavirus (HPV) is a leading cause of illness and death. The identification and categorization of the wide range of HPV types that contribute to illness has offered essential molecular tools for the medical community, leading in innovative diagnostic, screening, and preventive techniques. Current research shows a viral genetic foundation for pathogenicity resulting from the development of a common ancestor of all oncogenic HPV strains. Nonetheless, determining the precise genetic basis of HPV oncogenicity is a difficult task that will need the use of novel analytic techniques. HPV genomics research can serve as a paradigm for non-recombinant genome evolution, genetic drivers of pathogenicity, and genomics application. HPV proteins stimulate biological processes, allowing for viral replication. This includes those involved in the repair of DNA damage as well as the epigenetic regulation of host and viral transcription. The ATM and ATR DNA repair mechanisms are constitutively activated by HPVs, and these proteins are preferentially recruited to viral genomes. These mechanisms are necessary for viral replication. These pathways are particularly significant because they may serve as targets for pharmacological treatment to treat HPV-related illness. The Alpha, Beta, and Gamma genera are the primary evolutionary branches of human papillomaviruses; the viruses have evolved to infect particular epithelia with unique survival strategies. Many HPV strains in the Beta and Gamma genera are linked to non-visible skin infections that begin in childhood and can continue and generate virus particles for years. The Alpha genus primarily infects anogenital mucocutaneous surfaces and the mucosa of the upper aerodigestive tract. The Alpha genus contains viruses that may live without causing visible disease, as well as viruses that generate highly prolific warts and an important evolutionary branch including viruses with carcinogenic potential. Some HPV strains, particularly HPV16, have a significant ability to cause cancer in humans via two well-known oncogenes, E6 and E7. If these HPV infections continue, the most susceptible tissue is the cervix uteri. Aside from viral load and viral type, smoking, hormone usage, and HIV coinfections may all contribute to the development of HPV infections into human cancer. Prevention by vaccination and/or screening, as well as improved treatment, are critical to reducing the burden of HPV-related illness. The use of entire genomes for variant taxonomy allows HPV researchers to discuss the characteristics of HPV variant lineages without needing to explain sets of nucleotide alterations to identify a group of HPV variants.

This will be especially valuable in future research on carcinogenic HPV kinds. There is considerable evidence that various HPV16, HPV31, HPV52, and HPV58 variants have distinct carcinogenic properties. In the future, we will need a strategic plan in order to prevent cervical cancer in women by introducing human papillomavirus vaccines. For women over 50, who have been exposed to the virus and are unable to get vaccinated. The strategy also includes vaccinating young girls before they have any type of **s**exual intercourse.

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