Bharti G, et al., J Infect Non Infect Dis 2022, 6: 032
DOI: 10.24966/INID-8654/100032

HSOA Journal of Infectious & Non Infectious Diseases

Research Article

A comprehensive Review on Cervical Cancer; HPV Infection to Prevention

Bharti Gupta, Lokeswara Balakrishna, Siva Palepu, Nuthangi Maniteja, Akanksha Kumari, and Parikipandla Sridevi*

Department of Biotechnology, Faculty of Science, Indira Gandhi National Tribal University, India

Abstract

Cervical cancer is the third most common cancer in women worldwide, more than half a million women are being diagnosed with cervical cancer, and resulting in 0.3 million deaths worldwide. About 95% cervical cancer are caused by a persistent Human Papillomavirus (HPV) infection. High-risk subtypes of the HPV are responsible for 99% cervical cancer cases. It is largely preventable, as early detection and treatment of precancerous lesions can avert its progression to tumour. Thus, improving triage, treatment, and follow-up in infected patients. A combination of HPV vaccination and screening could almost eradicate cervical cancer and reduce the burden of other tumours and diseases related to HPV.

The aim of this review article is to summarize current understanding along with updated information concerning the afore known aspects of role of HPV infection in cervical cancer, also including discussion about its molecular biology, and carcinogenesis. This review also focuses on the expanding knowledge of the diagnosis and preventive strategies to maximize reductions in cervical cancer cases worldwide.

Keywords: Awareness; Cervical cancer; Diagnosis; Human Papillomavirus (HPV); Prevention; Treatment

Background

Human Papilloma Virus (HPV) infection causes cervical cancer, it is one of the fourth top most cancer in the world, with an estimated 5,70,000 cases in 2018, with 90% of the 3,11,000 deaths worldwide [1]. The acquisition/incidence rate is very high among the sexually active young adults, and infection rate is more in the patients affected with oncogenic HPV types, than the non-oncogenic types [2]. HPV infection also causes anogenital warts and malignant diseases in both males and females. These warts are the major clinical symptoms of the HPV infection. The anogenital warts are considered as benign and also been associated with the increased risk factor [3], furthermore, they cause itching, bleeding and pain. Anogenital warts are highly infectious, however approx. 20-30% of anogenital warts regress spontaneously. The risk of anogenital warts increases with the increased number of active sexual partners in the course of one's lifetime [4]. Papillomaviruses are ubiquitous in nature and have been detected in a wide variety of animals as well as in humans and they are also specific for their respective hosts.

Understanding that HPV is a necessary factor of most cervical cancers has led to two important developments for cervical cancer prevention, primary and secondary prevention methods, primary being the vaccination, diagnosis, and awareness, secondary includes the treatment.

This review aims at systematically covering the HPV infection, its progression into cancer, current status of diagnosis and treatments along with future prospects in development for the prevention and awareness of HPV-associated lesions and cancers.

Clinical perspective and natural history of Human Papillomavirus (HPV)

Genital contact is the major leading risk factor for the acquisition of the HPV [5]. Approximately, 85%-95% of sexually active individuals get HPV infection during their lifetime, and risk factors plays a major role in persistent infection and development of cancer. There are a number of risk factors which has shown effect on the development of cervical cancer from a transient HPV infection.

- Immunity of the patient: patients with weaken immune system, and those already with HIV are more likely to be having a persistent HPV infection leading to pre-cancer and cancer.
- Smoking: Smoking has been shown a direct association with the HPV infection, and increased risk of cervical cancer. It influences persistence HPV infection by increasing the cell proliferation, cell cycle up regulation of pro inflammatory factors, and also suppress the host immune function [6].
- Multiple Sex partners: The major risk factor for HPV infection is the number of sexual partners. There is a strong association between the acquisition of HPV infection and number of sexual partners [7].

Other factors for the development of risk include sex at an early age, in one of our previous report on HPV infection [8], marriage and sexual activity at early age have also shown a significant increase in HPV cases. Unprotected sex and multiple pregnancies also contribute as major risk factors in persistent HPV infections [9].

Pathogenesis of HPV

HPV and Cervical cancer burden: The prevalence and types of HPV infection varies with geographical region and also within a population. The global predominance of HPV infection is approximately 12% with significant regional variation [10].

***Corresponding author:** Parikipandla Sridevi, Department of Biotechnology, Faculty of Science, Indira Gandhi National Tribal University, India, Tel: +91-9630036673; E-mail Id: psridevi@igntu.ac.in, psridevi.igntu@gmail.com

Citation: Gupta B, Balakridhna L, Palepu S, Maniteja N, Kumari A, et al. (2022) A comprehensive review on cervical cancer; HPV infection to Prevention. J Infect Non Infect Dis 6: 032.

Received: Jun 20, 2022; **Accepted:** Jun 29, 2022; **Published:** July 06, 2022

Throughout the world, HPV is accountable for 51% load of the cancer [11], nearly in 100% of cervical tumours, 88% and 50% in anal, and penile tumour respectively [12]. It has been shown that HPV-16 is the predominantly found genotype in head and neck squamous cell carcinoma with a prevalence of 26%. In Brazil, the prevalence of HPV varies between anatomic sites and gender [13]. Whereas, the global HPV prevalence differs according to the socioeconomic development of the region and the population analysed [12]. According to Veronica Colpani [10], the Brazilian population have a high prevalence of HPV infection comparatively to the women with normal cytology in the distinct zone of the world; for example, Central America (13%), North Africa (9.2%), Western Europe (9%) and Southern Asia (7.1%) [9,14]. As per a meta-analysis of 1 million women, the approximate global HPV prevalence in women with normal cytological was 11.4% with the exception of 16.1% in Latin America [9].

HPV infection is usual among sexually active young adults with an estimated prevalence ranging in between 20% and 46% [15]. It has been seen that the changes in hormonal milieu and immune response during pregnancy might favours the endurance of HPV infection [16]. This causes a large variation in the prevalence of HPV in pregnant women from 5.5% to 65%. In Africa, the prevalence of HPV infection among pregnant women was 33.3% in which 62% positive women were infected with high-risk or intermediate risk HPV types [16].

HPV Classification and Epidemiology

HPVs are heterogeneous group of circulars, double standard DNA viruses belonging to Papillomaviridae family [17]. HPV causes benign tumours (common warts, genital warts), premalignant, and malignant epithelial lesions [18].

- HPV genome can be divided into three parts;
- Early region: regulates the functions of viral protein in infected host cell:
- Upstream regulatory region: controls the viral replication and transcription, and
- Late region: encodes two capsid formation proteins (L1 and L2) [19].

Based on the nucleotide sequence difference between species, HPV classification can be done [20]. Furthermore, more than 180 types of HPVs are reported worldwide [21]. Characterization and classification of new genotypes in achieved by involving viral genome sequence and their comparison with known species. Major capsid protein L1 coding region is the most conserved region by differing 10% sequence difference in each genus. However, there are only five HPV genus which infect humans [22], alpha, beta, gamma, meu and nuHPV genera [17].

Mucosal HPV

Mucosal HPV or genital HPV types causes infection frequently at the anal and genital areas, and also infect at the mouth and throat lining. Mucosal HPVs also causes infection in other parts of the body rather than the mucosa surface; some species of the genus alpha HPV comes under this category. These alpha HPVs are conserved with E5 open reading frame in the ELR region [17]. The 12 mucosal HPV types of Alpha papilloma virus are classified as High-risk HPV (Hr-HPV) or Carcinogenic group by the International Agency for Research on Cancer 1(IARC group 1) based on the biological and epidemiological data of HPV 16,18,33,31,35,39,45,51,52,56,58, and 59 [23-24]. The remaining 8 mucosal HPV types as classified as possibly carcinogenic (IARC group 2A and 2B) i.e., HPV 26,53,66,67,68,73,70,82 [20]. The High-risk HPV (Hr-HPV) types are being called as the agents of the cervical cancers and others including vagina, anus, vulva, penis, head and neck cancers and or pharyngeal cancers particularly. Among all Hr-HPVs, HPV 16 and 18 strains causes about 70% cervical cancers. Hr-HPV 16 is the most studied and the low-risk HPVs (Lr-HPVs) includes HPV 6, and 11, causes benign lesions, condylomata acuminate, upper aero digestive tract and respiratory papillomatosis [17]. A list of alpha HPV types of mucosal sites is given in (Table 1).

Genus	HPV type	Other members	High/low risk	Genome organization
Alpha HPV	HPV 32	HPV 42	Low risk	3rd ORF in ELR
	HPV 61	HPV 81,83,84,62,86,87,89	Low risk	
	HPV 16	HPV 31,33,35,52,58,67	High risk	
	HPV 6	HPV 11,13,44,74	Low risk	
	HPV 2	HPV 27,57		ORF of E5 is having different biological property
	HPV 18	HPV 39, 45,59,68,70	High risk	
	HPV 26	HPV 51, 69, 82	High risk	
	HPV 53	HPV 30, 56, 66	High risk	
	HPV 32	HPV 42	Low risk	

Table 1: List of Alpha HPV types infecting mucosal site.

Cutaneous HPV

Cutaneous HPV types infect the skin causing the lesions, common warts, cutaneous papillomas, and planar warts. This cutaneous group includes genus beta, gamma, meu, nu, and some species from the genus Alpha papilloma virus. The genus beta includes more than 54 HPV types which are again classified into five species as β1,2,3,4,5 and the gamma genus includes 98 types divided into 27 species [25]. Few of cutaneous HPV types from alpha papilloma virus includes HPV 2,3,7,10,27,28,57. Beta HPVs contains no E5 ORF and these infections exists in the latent form in population and activates under the patients of immune suppression [17]. Gamma having the large number of species. A list of Beta and Gamma HPV types of mucosal sites is given in (Table 2).

Genus Name	Type Species	Other members	High/low risk	Genome Organization
Beta HPV	HPV 5	HPV 36, 47, 93, 8,12,14,19,20,21,25		E5 ORF is absent, ELR is less than 100 nucleotides in length
	HPV 9	HPV 15, 17, 22,23,37,38,80		
	HPV 49	HPV 75,76		
	HPV 92,96			

Gamma HPV	HPV 4	HPV 65, 95		E5 ORF is absent, ELR is less than 100 nucleotides in length
				Type species are dividable by inclusion bodies
	HPV 60,50,48,88			

Table 2: List of Beta and Gamma HPV types infecting cutaneous site.

Mucosal and cutaneous HPV types

These includes only alpha papillomavirus types. A list of alpha HPV types of both mucosal and cutaneous sites is given in (Table 3).

Genus Name	Type species	Other members	High/low risk	Genome Organization
Alpha HPV	HPV 10	HPV 3,28,29,78,94	Low risk	
	HPV 7	HPV 40,43,91	Low risk	

Table 3: List of Alpha HPV types infecting both mucosal and cutaneous cutaneous site.

HPV life cycle

HPVs infect basal cells of epithelial tissue [26]. The virus growth is mainly based on the differentiation of keratinocytes, however, till now no evidence available of its expression in other than keratinocytes. The high amount of viral protein expression occurs only in the upper layers of the epithelium. In many lower layers of stratified epithelium [21], the presence of micro wounds provides the access to virions into the basal lamina. HPV shows two types of life cycles: productive or active, and latent life cycle [19]. The completion of productive life cycle depends upon the nature of the site of infection, presence of hormones, and external factors.

Productive Infection of HPV

Virus attachment and entry: HPVs can get entry into the epithelial cells through micro abrasions or wounds [19]. It infects the epithelial cells or transit amplifying stem cells of the stratified epithelium. HPV virions contain two major proteins (L1 and L2) which plays major role in the attachment and entry of the virus to the host cell. HPV gets entry into host cell by binding to the L1 capsid protein to the cellular receptors on the basal membrane [27]. The primary cellular receptor is Heparin Sulphate Proteoglycans (HSPGs), aubiquitous polysaccharide and also laminin on the surface of basal cellular layers. After binding of L1 protein to the primary receptor, some structural conformational changes occur in the N terminus of the L2 component (Cyclophilin B mediated) by cleaving the L2 viral protein by furin PROTEASES or PC5 or PC 6 [26]. This Structural conformation process achieves the transfer of viral capsid to the secondary receptor (alpha 6 integrin) and for the necessary transfer of the viral genome to the nucleus and internalization of the virus. In addition to alpha 6 integrin, epidermal growth factor, tetraspanin enriched membrane microdomains, syndecan 1, annexin A2 heterotetramer and vimentin serves as the entry receptors for HPVs [28]. The selection of receptor is mainly based on the genotype of HPV, and cell of infection. The infected basal epithelial cell produces daughter cells. One daughter cell migrates away from the basal cell layer and commits to the differentiation process while another remains in the same location (Where infection occurs) but rapidly divides in the basal layer and acts as a reservoir for the viral DNAs for upcoming cell divisions.

The internalization of the virus or endocytosis occurs by the mechanism of clathrin dependent and lipid raft independent process similar to macro pinocytosis [29]. Later virions underwent some structural changes results in viral partial uncoating where virions are trafficked by endosomal system. Through the process of uncoating of virions in endosomes (acidified) the disassociating of the L1 protein from the L2/viral genome complex is mediated by Cyclophilin B, and the dissociated L1 will be targeted for degradation to lysosomes. L2 protein aids in the transfer of viral genome from the early endosome to the golgi complex (trans) with the help of sorting nexin 17 which allows escaping of L2 genome of viral complex from the compartments of the late endosomes [29]. Virus moves from the cytoplasm to the nucleus with the help of microtubules, association of vesicles, motor protein dynein light chains, and also requires the process mitosis thus, L2 mediates the process. Finally for the establishment and activation of the infection, transcription of the viral genome, and L2 protein should colocalize at ND10 domains [30].

Gene amplification and expression: After entry of the HPV genome into nucleus of dividing cells, the early transcription is initiated to encode the viral proteins E1, and E2 which are useful to carry out the initial replication of incoming viral genome for its stability and these two are first viral proteins to be expressed, however, sometimes E1 may not be needed if viral copy numbers reached a level of 50-100 copies [29]. E1 protein is only protein coded by the virus, which acts as ATP dependent helicase and binds to the AT rich region with a less affinity at ori C. E2 protein binds to E1 for stabilization by interacting with ACCN6GGt sequences adjacent to the ori C for a higher affinity as a dimer of hexamers, also it recruits replication machinery [31]. E2 oncoprotein forms a dimer which binds to four palindromic sites of LCR, out of these, three are adjacent to Origin of replication required for replication of viral genome [32]. Initial viral genome replication generates 50-100 copies per nucleus. The viral genome amplification limitation can be controlled by the E8/E2 via the NcoR/Smrt complex [32]. HPV do not code enzymes for replication other than E1 and it should be modifying the cellular environment for the replication of the viral genome [29].

In the basal layer the viral genome replicates at the stage of S phase with the cellular DNA, and the replicated genomes partitioned equally during the process of cell division. The E2 protein role in the basal cells is very crucial for the correct segregation [32]. In addition to replication and segregation, it also acts as transcriptional factor and regulates the early promoter for the virus and also controls the viral oncogene expression (E6 and E7). At low levels, it acts as transcriptional activator, while in high levels E2 acts as a repressor of the oncogenic expression by displacing SP1 transcription activator from a site adjacent to the early promoter. The bovine papillomavirus genomic maintenance suggested that viral episome may be maintained with 10 to 200 copies in basal cells [33].

This increasement or stimulation of the cell proliferation is mediated by E6 and E7 proteins in basal cells and suprabasal cells. E6 and E7 proteins capacity to enter S phase is very crucial along with E1, E2 replication proteins. In the suprabasal cells the terminal differentiation occurs only after exiting the cell cycle to

produce protective barrier [34]. E7 binds with the pRb protein and pocket family members (p107 and p130), this binding and triggering the pocket proteins for degradation causes E7 to release E2F transcriptional factors which results in constitutive activation of E2F gene expression which controls the cell proliferation and DNA synthesis such as Cyclin A and E. The other components helpful in cell proliferation are cyclin dependent kinase inhibitors p21 and p27, Histone deacetylases. The E7 mediated cell proliferation activation is depending upon the levels of p21 and p27 inhibitor [32].

The primary role of high risk E6 protein is inactivation of p53 tumor suppressor and its degradation and ubiquitination through the associated ubiquitin ligase UBE3A which prevents the apoptosis in upper epithelial layers and E6 expression up regulates the activity of telomerase while low risk HPV E6 protein do not able to bind directly with p53 but it may target transcriptional activity of p53 indirectly by binding p300 and/or TIP 60 [35]. High risk E6 protein also plays a major role in suprabasal epithelial cell proliferation through its PDZ ligand domain C terminal and also develops metastatic tumours by interrupting normal cell adhesion. However Low risk HPV E6 proteins lack the PDZ ligand domain and lacking the telomerase activity also [29].

Packaging and release of virions: The last stage of the HPVs productive cycle requires the expression of capsid proteins; L2 is minor protein, which requires the exit of cell from cell cycle and L1 is a major protein allows the genome packaging and expression occurs preceding the L2 expression [36]. Virions assembly occurs in the terminally differentiating nuclei, requires the splicing in the mRNA splicing and the transcript generation at the polyadenylation of the ate promoter, this mediates by the E2 protein expression level at high amount. For packaging of genome, E2 also requires for the encapsulation of the genome in addition to L1 and L2 [30]. Viral maturation process occurs in the upper layers of differentiated keratinocytes where the particles are being starts exposure of Oxidizing environment from a reducing environment and the disulphide bond accumulation occurs between the L1 proteins, results in the capsid condensation which gives stability to capsid and becomes resistant to proteolytic digestion [29]. The assembled virion contains 360 molecules of L1 proteins arranged into 72 capsomers which are pentameric with a variable number of L2 proteins of 5-fold axis of symmetry [37]. HPVs are non-lytic; virions release requires efficient escape from the cornified envelope which can mediated by E4 in the upper epithelial layers. E4 disrupts the structure of the keratin and affects the cornified envelope integrity [38].

Non-productive Infection

The non-productive infection of HPV is associated with the Hr-HPVs, leading to the cervical cancers. Here the lesions of the cervix is identified as the Low grade Squamous Intraepithelial Lesion (LSIL) or High grade Squamous Intraepithelial Lesion (HSIL) or as flat condylamn. The Hr-HPV associated with cervical cancers are more frequently from alpha 7 and 9 with Hr-HPV 16, and 18 as the most prevalent types.

LSIL or Grade 1 CIN comes under low grade cervical lesions which are almost equal to the productive infections in the terms of viral gene expression and viral coat proteins, it can be found in the cells of the epithelial surface. High grade lesions: HSIL or Grade 2,3 CINs are fallen into high grade lesions with occurrence of the closer viral amplification to the epithelial surface than LSIL and condylomas having an enough proliferative phase [39]. It has been evaluated that 20% of CIN1 lead to CIN2, 30% of CIN2 grade lesions lead to severe neoplasia and approximately 40% of CIN 3 can leads to cancer [40].

The molecular changes for the non-productive infection are not yet fully understood. Viral gene deregulation can be done by viral genome integration, epigenetic modifications such as methylation of viral DNA, results in changes in cellular signalling [41]. The genome integration results in two viral gene expression E6 and E7, this causes the E2 Open reading frame deletion which in turn codes for a transcriptional repressor of E6/E7 expression. The mRNAs of the E6/E7 of integrated genomes are more stable than episomal genomes. P16 INK4A expression is appraised as the biomarker for E7 elevated levels of expression in CIN1, CIN 2 and CIN 3 as the integration of the viral genome disrupts the viral sequences encoding E2, E4, and E1. E2 having the negative role on the cell proliferation by URR regulation and arrests the cell cycle at the G2 phase. HPV E4 protein also inhibits the cell cycle division by cyclin B/cdk 1. Integration of the genome can also lead to the 3' end of the early transcripts of virus loss and suppress the viral mRNA species production which encodes for E6 and E7, contributes to the deregulation of the expression of the viral oncogenes [42]. In addition to all, the exposure to glucocorticoids and progesterone's also influences the development of precancerous changes effecting expression of viral genes.

Even though many types of the HPVs infect the cervix, only the Hr-HPV associated with cervical cancers because of the specific activities of the genes produced by them. The E7 proteins of Hr-HPV promotes the centrosomal abnormalities in the cell culture and acts as mutator to increase the errors in the cell cycle [43]. The E7 proteins of Hr-HPV mediates the Rb degradation through a proteasomal dependent crucial for the cell transformation by E7 but all above functions are lacked in E7 proteins of the Lr-HPVs. High risk E6 proteins forms the tripartite complex with p53 and E6AP (Cellular ubiquitin ligase) which gives the p53 degradation, this loss of p53 mediated DNA damage led to accumulation of the secondary changes in the chromosome of host, this step is the most important for the progression of the cancer while Lr-HPVs E6 protein binds with weak affinity and has no ability to bind E6AP. Even Hr-HPV E6 proteins are plays a role in activating the telomerase subunit which adds hexamers to the chromosome's telomeric end, because telomeres shorten the cell divisions and eventually cell senescence occurs. This mechanism is not found in the E6 proteins of Lr-HPVs. However, high risk oncogenes also need the much expression of the oncogenes for the development of the cervical cancer, alone expression can't be sufficient for disease.

Molecular biology of HPV infection

This is one of the complex process in HPV infection; viral regulatory proteins interact with each other and express its genome in host for initiation and progression of cervical cancer.

HPV genome structure

HPV is a double stand circular DNA with non-enveloped in nature, among double strand single strand used as a template for transcription, this template strand contains three genomic regions.

- **Open reading frame:** Nearly 10 small open reading frames are present, among first 7 Open Reading Frame (ORF) called early ORF, codes for viral regulatory proteins responsible for the damage of the cell cycle and helps in initiation and progression of

cancer in the host cell [32]. The remaining last 3 ORF regions are called late ORF regions, codes for capsid proteins that are L1 and L2. L1 and L2 proteins help in the primary and secondary binding of HPV to the host cell. L1 ORF is most commonly conserved among Papillomavirus, helps in the classification of HPV and their phylogenetic organization; L1 spontaneously packed into virus particles.

- The second region of the genome called the Long Control Region (LCR) which regulates the transcription and replication of HPV genes.
- The third region is called the upstream regulatory region or non-coding region.

HPV binding to host cell

This is a multistep process this contains HPV attachment to the host cell, changes taking place afterwards are shown below.

- Human Papillomavirus contains L1 (late protein 1), and L2 (late protein 2) capsid proteins; L1 is major capsid protein and L2 is minor capsid protein.
- Whenever HPV enters the body, L1 capsid protein binds to the receptor heparin sulfate proteoglycans (HSPGs) present on the surface of the basal membrane.
- Immediately after binding to the host cell conformational changes happen in the capsid proteins with the help of cyclophilin B.
- After conformational changes in capsid the affinity of L1 reduced or lowers, immediately after conformational change expression of N-terminus of L2 protein expressed on the surface of the virus particle.

Up to this step primary binding of HPV to host cell is completed, now expressed N- terminus of L2 protein needs to bind to the complementary region in host cell this can happen after cleavage of N- terminus region of L2 protein by furin thus allows binding of HPV to the plasma membrane of host cell known as secondary binding of HPV to host cell, this attachment plays a major role in initiation of cancer in the host cells [26,44].

Based on the genotype of HPV it uses different cell receptors for binding to the host cell, several HPVs may also use Epidermal Growth Factor Receptors (EGFRs), integrins, laminins, etc. as receptors for HPV binding to the host cell.

Internalization of HPV and entry into the host cell

This step explains how HPV reaches from the plasma membrane to the targeted cell's nucleus. Generally, any cargo transportation in cell form outside of the cell to the inside of cell done by endocytosis. Transportation of HPV from the plasma membrane to Trans Golgi Network (TGN) can take place by endocytosis/endocytic tubulation methods. This endocytosis will take place by two methods; one is clathrin-mediated, and another one is caveolar mediated endocytosis. During trafficking of HPV from the plasma membrane to the final target; host nucleus, many sorting factors will help to reach desired location to discharge cargo. The major step present in this trafficking and transportation was the separation of L1 genome from L2 genome and finally, L2 genome only transported into the nucleus of the cell.

- **Endocytic tubulation:** Tube-like structure will form from endosome when the size of transport material is large and it needs to transport more quantity from plasma membrane to trans-golgi network, this tube contains transmembrane receptors and other sorting proteins for cargo transportation and recycling to target location modulated by the BAR (Bin, Amphiphysin, Rvs) domain containing proteins.
- **HPV genome intracellular trafficking into targeted cells:** Immediately after reaching HPV to the plasma membrane clatherin-mediated endocytosis occurs by the Rab GTPase, it takes incoming HPV into the cytosol and transfer it to the target region via involvement of different organelles. This happens with the help of tetraspanins.

Before transferring to the desired location endosome with HPV genome, it becomes mature and link with lysosomes and develops into late endosomes, the endosome and lysosome complex determine what to degrade and what to transfer to the target region. During this step endosomal acidification and uncoating of HPV happens, and the only degradation of L1 protein happen by the presence of host chaperones CyPs. These chaperones also help in the disintegration of the viral capsid, and tyrosine kinase PyK2, play an important role in the disintegration of the viral capsid. Now only the L2 viral genome present in the late endosome will enter into the TGN. The entry of the viral genome into the TGN is done by the retromer where several changes take place in L2 HPV Genome, The following retromer complexes help in transportation are sorting nexin-17 (snx17) and snx27, in this retromer complex many cargo recognition complexes are present which helps in exact binding of cargo carrier to the exact location. This entire process is completed by the presence of another receptor is the endosomal sorting complex receptor for transportation (ESCRT) This interaction between ESCRT and the L2 genome helps in the entry of the viral genome in to host cell nucleus which favours the viral infection.

HPV genome integration into host cell

Trafficking of the viral DNA to the nucleus of a target cell is a critical stage in the infectious pathway of HPVs [44]. After internalization and trafficking of the incoming HPV genome only the L2 HPV genome enters into the nucleus with the help of retromer complexes which helps in the transportation of the viral genome into the TGN to the nucleus. The E2 ORF has been identified as the preferential site of integration because it is more commonly disrupted or deleted than any other site, E2 protein deregulates the expression of E6 and E7 protein this cause the loss of ORF at integration time and increases the expression of E6 and E7 proteins, deregulate the normal cell cycle or cell program, L2 genome coming to nucleus from golgi complex wait for some time to enters into the nucleus during the mitotic division of host cell, in prophase, nucleus membrane breakdown favours the entry of HPV genome into host cell after entry into host cell, it remains in endosome until nucleus envelope form in telophase, later it fuses with the nuclear membrane and become part of host genome, after that it increase its genome along the host genome by host cell division. Immediately integration of HPV genome into the host translation of its genome and expression of proteins resulting in cancer progression. Later with help of many proteins, HPV causes the progression of cancer generally HPV genome integrates into the host chromosomes, this regulatory mechanism lies in the E1 and E2 Genes of HPV [45], function of early proteins role is given in (Table 4)

Protein	Function
E6	Activates telomerase function Works as a integrin associated protein Blocks the cell cycle of the normal host cell
E7	Binding of the Rb family of proteins Ensures the continuity of survival of Infected cells with HPV Inactivation of cyclin inhibitors (p21, p27) these regulate the cell progression and proliferation
E1	Helicase activity, Initiates the viral replication
E2	Replication, viral genome segregation

Table 4: Functions of HPV early proteins.

Inflammation induced genome integration

This is also one of the methods used by HPV to integrate its genome into the host cell. Immediately after infection of HPV, a small lesion appears on the cervix due to inflammation known as Cervical Intraepithelial Neoplasia (CIN1) due to this inflammation production of Reactive Oxygen Species (ROS), and Reactive Nitrogen Species (RNS) occurs leading to cell damage and favours the entry of HPV genome into the host cell via the formation of Double-Strand Breaks (DSBs), and hyperplasia. Some deregulation of protein production and external factors helps in transformation of (CIN1) into (CIN2) by cell proliferation, later the deregulation of E6 and E7 proteins helps it to transform into (CIN3) and finally into the carcinoma [45].

HPV oncogenesis and cell cycle progression

- Now the integrated genome in the host nucleus needs to maintain for the progression of cancer, this contains the following steps:
- **Initial amplification:** This is maintained by E1 and E2 proteins.
- **Establishment:** This step contains escaping of HPV from the immune system, and persistent infection in host cell, a number of regulatory proteins helps in the HPV establishment [46].
- **Maintenance and vegetative amplification:** Vegetative amplification occurs only in differentiated cells and generates a high number of virus genomes. It is achieved by the over production of E6 and E7 Proteins.

Origin of initial replication

After infection, initial genome amplification occurs before the maintenance of the viral genome in the nuclei of infected basal epithelial cells, it takes place with the help of E1 and E2 proteins initiating the replication of integrated viral genome in the host cell. E1 is the only virally encoded enzyme and function as an ATP dependent helicase, E1 binds with AT-rich sequences at the Origin of Replication (ORI) with weak affinity and is required for the initiation and elongation of viral DNA synthesis.

E2 stabilizes E1 binding to the origin of replication, via ACCN6GGT sequences, this interaction resulting in high-affinity binding of the E1/E2 complex to the origin of replication. E1 and E2 proteins are attached and forms as dimer then these both proteins complex attached to ORI of HPV and initiate cell replication, it is also essential to maintain genetic content of HPV in the host cell. Here along with cellular DNA, HPV DNA will also replicate and distribute daughter cells by this process, each cell maintains 50-100 episomal copies of the HPV genome in the host cells.

At this stage viral protein expression is low, to avoid immune system activation, E2 protein plays a crucial role in suppressing the p97 promoter, thus avoiding the chromatin conformation, due to which the immune system remains inactive, and E2 protein regulates the viral transcription [26].

The role of other proteins: E6, E7, and E5 are essential, as they are oncoproteins for the development of cancer. Immediately after internalization of HPV genome and initial replication of HPV genome expression production of E6 and E7 proteins takes place, which helps in de-regulation of cell program and helps in the progression of cancer by continuous division of cells. E6 protein interacts with many host cell proteins and deregulate essential cellular function and leads to the development of cancer via attachment of E6 proteins to tumor suppression protein p53, E6 proteins can also help in escaping the cell death by degradation of ubiquitin-protein ligase (e3a), This (e3a) helps in degradation of mutated protein in the host cell, another role of the E6 protein is to maintain the episomal genome in the host cell [47].

E7 protein helps in the inactivation of cyclin-dependent kinase inhibitors p21, and p27. These proteins strictly check the cell proliferation, and cell progression. E7 protein helps in overcoming the G1/S checkpoint of the cell cycle by inactivating CDK2 inhibitors. E7 proteins show a target on the pocket protein that release E2F proteins, thus changing gene expression. E4 proteins helps in post-translation modification of viral genome expression, and in restructuring the cytokeratin filament to release the progeny virions in late replication. Only E1 and E2 proteins help in initiation of replication but remaining proteins helps in deregulation of the cell cycle by interacting oncoproteins.

The E5 protein is a transmembrane endoplasmic reticulum resident protein that can regulate and stimulate the mitogen-activated protein kinase (MAPK), it can regulate the cell division pathway and also E5 protein helps in evading the immune response by suppressing the MHC in the host cell.

Types and stages of cervical cancer

Cervical cancers are named after the type of cells they infect; mainly two types of cervical cancers are present these are as follows and the third type of cancer happens rarely, different stages if cervical cancer are given in (Table 5).

Stages	Definition
Stage 0	Cancer only on the surface of the cervix and do not grown into the deeper parts.
Stage 1	Cancer cells have grown from the surface of the cervix to deeper tissues, tissue samples can be used to determine the stage, based on the tissue size.
Stage 1A	The cancerous area is less than 3mm in depth.
Stage 1A1	The cancerous area is between 3mm to 5mm in depth.
Stage 1A2	Tumor is grown into a large size and is still confined to the cervix's lower tissues.
Stage 1B	The tumor is 5mm or more in-depth and less than 2 centimeters in depth.
Stage 1B1	The tumor is 2centimeter or more in-depth and less than 4cm wide.
Stage 1B2	The tumor is 4 centimeters or more in width.
Stage II	Cancer has spread beyond the uterus and surrounded area; the tumor is limited to the vagina which does not spread to the perimetrical area.

Stage 2A	The tumor is less than 4cm wide.
Stage 2B	The tumor is 4cm or more in width.
Stage 2A2	Cancer spread to the perimetrical area.
Stage 3	Cancer has spread to the lower parts of the vagina and start affecting kidneys and internal organs.
Stage 3A	Cancer spreads to the lower part of the vagina and still does not infect the pelvic wall.
Stage 3B	Cancer spread to the pelvic wall.
Stage 3C	Cancer causes an effect on lymph nodes in the pelvic region.
Stage 4A	Cancer spread to the bladder (or) rectum.
Stage 4B	Cancer spreads to other parts of the body and damages several internal organs also.

Table 5: Different stages of cancer

Squamous carcinoma

Cervix is made up of two types of cells outer cervix is made with squamous cells if these cells become cancerous that type of cervical cancer is called squamous cervical cancer. The most common type of cervical cancer is found around 66% in women.

Adenocarcinoma

The inner cervix is made up of glandular cells that produce mucous if these cells become cancerous this type of cervical cancer is called adenocarcinoma. This type of cancer is found in nearly 28% of women.

Mixed carcinoma

Sometimes both squamous and glandular cells become cancerous at the same time, this type of cancer is called adeno-squamous carcinoma. This is the rarest cancer condition this type of cancer present only 6% in women.

Above mentioned classification is based on the histopathology of cancer [48].

Diagnosis

The main interest in HPV diagnosis relates to its causative role in cervical cancer, which is among one of the most common cancers in women, with an annual incidence of nearly half a million and a mortality rate of approximately 50% [49].

Direct visual inspection

This is an alternative strategy for the detection of early-stage cervical carcinoma, in this speculum is used for the direct inspection of the cervix. This strategy was proposed by World Health Organization (WHO) to detect asymptomatic women with cervical lesions at a curable stage. The efficacy of this technique is less in comparison with cytological screening, and hence, it has been shown to perform poorly [50].

Visual inspection with acetic acid: Visual inspection with acetic acid is a simple. Reliable, inexpensive procedure. This is done with the application of 3-5% of acetic acid on the cervix, and then visualization cervix in a good light source. This procedure is also known as cervicoscopy. This procedure is mainly based on the presence of protein amount on the surface of epithelial tissue of the cervix. In normal epithelial tissue, the protein is present in low amounts, when compared to pre-cancers cells of infected epithelial tissue of the cervix. After applying the acetic acid (dilute), the normal epithelial cells give no acetowhite area, while in infected patients it gives opaque distinct acetowhite area with well-defined margins. Although in the suspected patients there may not be visibility of acetowhite patches because of bleeding, obvious growth ulcers on the cervix. The presence of proteins is inversely proportional to the density of the Acetowhite area, visual inspection test for HPV detection and its outcomes are given in (Table 6).

VIA test outcome	Criteria
Negative (-)	• No acetowhite lesions • Aceto-whitening on endocervical polyps, Nabothian cysts • Prominent white line-like aceto-whiteninng of the squamoco-lumnar junction
Single positive (+)	• Faint, translucent, ill defined, irregular acetowhite lesions on the cervix • Definite, angular, geographic acetowhite lesions far away from the squamocolumnar junction
Double positive (++)	• Opaque, dense, dull, definite, well-defined acetowhite lesions touching the squamocolumnar junction or close to the external. • Large, circumorificial, well-defined, thick, dense acetowhite lesions • Growth on the cervix turns acetowhite

Table 6: Visual inspection test for HPV detection and its outcomes.

Visual inspection with Lugol's solution: In this method, Lugol's iodine is used instead of acetic acid for visual inspection. The method is also known as Schiller's test. The procedure is based on the staining of squamous epithelium by iodine which is glycophilic and gives mahogany brown or black colour. Glycogen is absent in precancerous lesions; thus, it cannot be stained with iodine and gives a thick, saffron yellow or mustard appearance. Therefore, it can be said that it depends on the interaction between iodine and glycogen. In the 1930s, when there was no other method to screen the women for cervical cancer precursors, schiller iodine was highly regarded by gynaecologist in developed countries [51-52]. But, when this test became widely used then its false positive outcomes became obvious, and hence, its used was largely discontinued [53], visual inspection test results and its criteria are given in (Table 7).

VILI test result	Criteria
Negative (-)	Normal cervix where squamous epithelium turns mahogany brown or black & the columnar epithelium does not change colour& remains pale Patchy, indistinct, ill-defined, colorless or partially brown areas in the transformation zone Leopard skin appearance Scattered, irregular, ill-defined non-iodine uptake areas on the cervix, with or without extension to the vagina Thin, yellow, non-iodine uptake areas with angular, or digitating margins, resembling geographical areas, located far away from the columnar junction
Positive (+)	Growth on the cervix turns yellow Well defined, dense, thick, bright, mustard or saffron-yellow, iodine non-uptake areas touching the squamocolumnar junction Circumorificial, well defined, thick, dense, yellow lesion, occupying large portion of the cervix

Table 7: Visual inspection test results and its criteria.

Cytology

Cytology test is used to examine the cells from the body under a microscope. It is used to look for morphological changes in the cells. The cytological screening for cervical cancer has been effective in reducing the incidence as well as mortality of cervical cancer worldwide. It is particularly an organized program that has good-quality screening, adequate coverage, and optimal frequency. A high-quality cytology test is a highly specific screening test, with estimates specificity of 98-99% [54]. Whereas, the sensitivity of this test suggested by the cross-sectional studies was comparatively low in the order of 50% in some circumstances but, studies that have been able to assess sensitivity longitudinally have produced sensitivity in order of 75%. The different types of cytology are described below: -

- **Conventional Pap smear:** This method is being used for more than 50 years worldwide and has been associated with an impressive reduction in cervical cancer burden. In this test, the cells are lightly scraped from the ectocervix or endocervix with the help of a spatula or brush and further collected for the preparation of smears. The smears are then examined under the microscope by a cytotechnologist or specially trained doctors. The method has overall low sensitivity and high specificity with an average of 64.5%, and a mean of 92.3% respectively [52]. However, the main concern related to this is its false-negative rates, which include the misdiagnosis of premalignant and malignant cells as normal cells. The screening method is frequently repeated at an interval of 1-5 years for an effective result [52].
- **Liquid-based cytology:** In this method, a brush is used instead of a spatula for the collection of cells from the ectocervix or endocervix. The head of the brush is then shaken vigorously, and kept in a small pot or vial containing a preservative solution. In the laboratory, it is followed by sample filtration or centrifugation. The smeared prepared for liquid-based cytology is a uniform monolayer, uneven manual smearing is avoided. This makes the LBC method easy to read. The process averts drying artifacts and eliminates most bacteria, yeast, red blood cells, proteins, and contaminating mucous [55].

HPV DNA testing

When it is used appropriately as an adjunct to cytology, it can maximize the detection of high-grade cervical lesions and, reduced the incidence of cervical cancer [56]. There are various methods for the testing of HPV DNA which include in-situ hybridization, nucleic acid amplification via Polymerase Chain Reaction (PCR), Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR), etc. To detect the HPV DNA, DNA should be isolated first from the cervical samples or scrapes, only a portion of it is used for the DNA isolation thus, if the number of HPV DNA copies present is a limited number in a specimen, sampling error may occur and can result in inconsistencies. During the transport of viral nucleic DNA, it must be preserved to maintain it and to avoid false-negative results. Adequate controls like sample spiking and the amplification of the β-globin gene are crucial to assess the genomic DNA integrity of the specimen with known positive material [49]. According to Sherman et al. [57], several commercially available molecular kits like; Cytyc Corp and PreservCyt should be used to preserve nucleic acid for molecular diagnosis, it can preserve the viral nucleic acid after prolonged storage at room temperature.

Low-risk HPV detection: Lr-HPV includes HPV 6, 11, 42, 43, and 44. It can be detected by using 5'-TET-3'-DABCYL-labelled molecular beacons. This molecular beacon is based on one-step multiplex real-time PCR. For Lr-HPV detection, the fluorescent data is taken at 560nm and the reaction internal control is taken at 610nm on a Rocher Light Cycler 2.0 instrument [58].

High-risk HPV detection: Hr-HPVs includes HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 70. Molecular beacons detecting 15 high-risk types are 5'-FAM-3'-DABCYL-labelled. The fluorescent data for Hr-HPV detection are taken at 530nm while the reaction internal control is detected at 610nm on a Rocher Light Cycler 2.0 instrument [58].

Prevention and treatment of cervical cancer

Prevention is the best strategy to control disease among a population. Avoiding risk factors and increasing protective methods can be considered as a measure prevention method.

Primary prevention

The main aim of primary prevention is to reduce and prevent the initial incidence of infection within a population.

HPV vaccination: HPV vaccination is one of the primary preventive measures. Both therapeutic and prophylactic vaccines can be used for HPV vaccination. The therapeutic vaccine is used for the elimination of residual cancer and prevents the growth of low-risk infection into high-risk disease [59]. It mainly targets the early oncoproteins E6 and E7. It generates cell-mediated immunity against transformed cells, while prophylactic vaccines neutralize antibodies and are based on L1 capsid proteins [60]. According to Garbuglia et al., [60], several studies have suggested that after surgical treatment of high-grade CIN2-3, the administered HPV prophylactic vaccine can prevent reinfection of HPV and can be considered adjuvant. Nowadays, three prophylactic vaccines are available: Cervarix, Gardasil4, and Gardasil9 which are prepared from purified L1 protein via recombinant DNA technology (RDT) and are composed of virus-like particles (VLPs). The first global recommendation for the vaccination of HPV was proposed by the Strategic Advisory Group's Experts on Immunization of WHO in October 2008 [61].

According to Dobson SR et al., [62] and Meites E et al., [63], the Advisory Committee on Immunization Practice (ACIP) declared that for girls those under 15 years of age, only two-dose of vaccination is needed yet 3-dose vaccination is recommended for the female who started vaccination between the age of 15, and 45. If a person is immunocompromised then regardless of their age and gender, they must follow the 3-dose schedule of vaccination [64].

- **Cervarix (bivalent HPV vaccine):** It was approved in 2007 and acts against HPV 16 and 18. This bivalent vaccine is composed of VLPs from HPV16 and HPV 18. The efficacy of the Cervarix vaccine against high-grade precancerous lesions is 92.9% [65].
- **Gardasil (Quadrivalent HPV vaccine):** It acts against HPV 6, 11, 16, and 18. It is a tetravalent vaccine, and was approved in 2006. It has 98% efficacy against high-grade precancerous lesions [65].
- **Limitation of vaccines:** The vaccines cover two types of Hr-HPV only. Thus, it could not prevent all HPV-related cancers. Therefore, routine screening is vital for preventing cervical cancer.

The vaccines do not treat existing HPV-related infections or protect against other sexually transmitted infections. Most people are not aware of HPV vaccination, even some providers do not feel comfortable about giving a clear recommendation of HPV vaccination [66].

Awareness of HPV infection and cervical cancer: Cervical cancer is a major public health issue all over the world which necessarily initiates the need to spread awareness regarding its risk factor and preventive method among the population especially in females belonging to rural areas [67]. It has been seen that in Arab communities, there is limited awareness about HPV infection, its correlation to cervical cancer, and the vaccines regarding cervical cancer [68]. Awareness program like National educational campaign, community screening for cervical cancer, sex education is essential to reduce the risk of cervical cancer.

Management of cervical cancer risk factors: The risk factor increases the chance of getting a disease like cancer. Although, several risk factors increase the chance of getting cervical cancer and odds of developing cervical cancer in women, still many women among them may not develop this disease. Risk factors for cervical cancer include an irregular screening history, smoking; in the cervical mucus of women who usually smokes, the by-products of tobacco have been found, HPV infection; it is the most important risk factor of cervical cancer, HIV infection; weakens the immune system and hence cause a higher risk of HPV infection, chlamydia infection; it is caused by chlamydia bacteria and spread through sexual contact which often has no symptoms but it can cause a higher risk of cervical cancer in women, sexual history like first sexual intercourse before the age of 15 or 16, multiple sexual partners, having sexual intercourse with one partner who has many sexual partners, low education, deprivation, lack of balanced diet, immune status and socioeconomic factors. It can be managed by giving information and warning about tobacco use, regular screening, male circumcision, provision and promotion of condoms for those engaged in sexual activity, sex education customized to age and culture, the intrauterine device can be used to lower the risk of cervical cancer. When a woman suffers from symptoms like irregular blood spotting or light bleeding between periods, postmenopausal spotting or bleeding, bleeding after sexual intercourse, and increased vaginal discharge with foul-smelling, she must go for further evaluation and diagnosis followed by treatment.

Secondary prevention

If a disease has already started, then secondary prevention measures are used to stop the progression of the disease [69].

Screening for precancerous lesions to prevent their development into invasive cancer: Various methods are used for the secondary screening of precancerous lesion to prevent their development into invasive cancer which includes: cytology method like Pap cytology, Liquid-based cytology, and automated cytology is also available now. In 2004, it has been mentioned on International Agency for Research on Cancer that pap cytology tests of high grade can reduce the mortality of cervical cancer to 80% in developed countries [69]. Visual inspection with acetic acid and Lugol's iodine is also used to detect precancerous lesions with naked eyes. VIA is a comparatively inexpensive and easy to learn method [70]. The visual inspection follows the 'screen and treats' method which is very convenient as it requires a single visit at once and has high compliance with treatment of screened positive women [71-72].

Methods of detection or screening for cervical cancer: In the past few years, HPV detection has moderately become the screening method for cervical cancer, as tenacious infection with High-Risk Human Papilloma Virus (HR HPV) is a mandatory condition for cervical carcinogenesis [69]. At present, there are at least 193 different methods for the detection of cervical cancer yet only 69 tests have been clinically assessed in publication [73]. Different methods used to detect cervical cancer are Hybrid Capture II, Cervista HPV high-risk test, Cobas 4800 HPV test, PCR-based MY09/11, and CPI/II systems [69,74], SPF LiPA method, etc. The Hybrid Capture II uses chemiluminescence for the approximate detection of the presence of HPV [55]. Cervista HPV HR test which was approved in 2009 by FDA could precisely detect high-risk HPV type in compared with HC II [75-76].

Limitations of secondary prevention: Though secondary prevention is playing an important role in the screening of cervical cancer, it still has its limitations. The limitations comprise of lack of awareness about screening program among populations, the availability of trained health workers for screening is not sufficient, the long lag between screening and treatment, women with low socioeconomic status do not afford regular screening and they lack ready access to adequate healthcare services; thus, they are at high risk of developing cervical cancer.

Treatment of cervical cancer: Distinct types of treatment are used for the patients suffering from cervical cancer which involves a standard method and clinical trial method. In clinical trials, new types of treatment are tested and mostly open to patients who have not started any treatment till that date. The clinical trial is a research study that aims to develop the current treatment strategy and method or new treatment. When a clinical trial is completed, then it can be considered as standard treatment. The treatment may cause side effects to the patient. There are five types of standard treatment for cervical cancer which are described below:

- **Surgery:** It is used to remove precancerous tissue or cancerous cells near the cervix. Most of the surgical methods such as cryotherapy, Loop Electrosurgical Excision Procedure (LEEP), laser surgery and cold-knife conization do not remove the uterus so that women can conceive later. In cryotherapy, a supercooled probe like liquid nitrogen is used to freeze the abnormal tissue. This process requires freezing gas to destroy the precancerous cells on the cervix and takes about only 15 minutes for the treatment. The main advantage of this treatment is that it can be performed at the same time as positive visual inspection by acetic acid, while the patient should be advised that they may have an ample, watery discharge after the treatment; therefore, they need precaution during sexual intercourse or avoid it until this watery discharge stops [77]. In laser surgery, a carbon dioxide laser beam is used for the ablation of tissue and the tissue suffers from less distortion, consequently, it can heal faster but the process is quite expensive. A small electrical wire loop is used in LEEP to remove abnormal cells from the cervix. It serves a dual purpose and helps in preserving the excised tissue for histologic examination of margin status and it is comparatively less expensive than laser therapy [55]. Surgery that goes through the removal of the uterus, includes: total hysterectomy, radical hysterectomy, radical trachelectomy, pelvic exenteration, bilateral salpingo-oophorectomy.
- **Radiation therapy:** This therapy uses radiation or high-energy x-ray beams to kill the cancer cells to prevent their further growth.

External radiation therapy and internal radiation therapy are the two types of radiation therapy. In external radiation therapy, the machine is used outside of the body that sends radiation towards cancer while in internal radiation therapy, radioactive substances sealed in wires, needles, catheters, or seeds are used which are placed near or into cancer. Radiation therapy depends on the type and stage of cervical cancer. However, radiation therapy causes both short and long-term side effects. Tiredness, nausea, diarrhoea, vaginal pain, menstrual pain, radiation cystitis is some of the short-term side effects of radiation therapy. The long-term side effects of radiation therapy include: vaginal dryness and painful sex, vaginal stenosis, urinary problems, rectal bleeding, etc.

- **Therapies using medication:** Medications are used to treat a medical condition. Cidofovir and podophyllin in combination with vidarabine are few examples of medications for HPV. Cidofovir is derived from an acyclic nucleoside phosphonate which has wide-range activity against DNA viruses. When human carcinoma cell lines containing HPV-16 or HPV-18 and human cervical keratinocytes immortalized by HPV-33 are exposed to cidofovir then it causes the inhibition of cell proliferation [55,78]. Podophyllin is a cytotoxic agent which is used to treat genital warts. It arrests mitosis in metaphase.

- **Chemotherapy:** It involves the use of drugs like; cisplatin, carboplatin, paclitaxel, topotecan to prevent the growth of cancer cells by killing the cells or by ceasing the cell division. It can be taken by mouth or injection (intramuscular or intravenous). The side effect of chemotherapy is followed by damages to some normal cells. Mouth soreness, hair loss, loss of appetite, fatigue, and vomiting are the common short-term side effects. Long-term side effects involve neuropathy, nephrotoxicity, and menstrual problem [79].

- **Targeted therapy:** Drugs are used to identify and attack specific cancer cells in targeted therapy without harming normal cells. It includes monoclonal antibodies therapy, which uses antibodies to identify substances on cancer cells. These antibodies are then attached to cancer-causing substances that kill and blocks the growth of cancer cells or stops them from spreading. It is given by infusion. An example of the monoclonal antibody used is Bevacizumab.

- **Immunotherapy :** Immunotherapy is based on the immune system. It uses the immune system of the patient to fight cancer. Immunotherapy with clinical trials undergoing or accomplished includes therapeutic vaccines, an immune checkpoint inhibitor, targeted antibodies, and adoptive T-cell transfer [69]. Pembrolizumab is a T-cell immune checkpoint inhibitor that targets the Programmed cell Death 1 (PD-1) and Programmed Death-Ligand 1 (PDL-1) proteins was found unbiased and encouraging in PDL-1 positive recurrent or metastatic cervical squamous cell cancer [80]. Pembrolizumab can be used for cervical cancer that has started growing again after chemotherapy. This drug is given as an intravenous infusion every three weeks. The disadvantage of this therapy is that it causes side effects like constipation, muscle pain, fever, etc. At times the immune system even starts attacking other parts of the body, which further causes life-threatening problems in the liver, kidney, intestines, lungs, or other organs [81].

Future directions and conclusions

With the emerging new concepts and technologies for cancer interventions, the precise prevention, diagnosis, and treatment of cervical are not only necessary, but now. The clarification of the molecular mechanism underlying HPV persistence and related cervical cancer will help us to predict the prognosis of patients with HPV infections at an earlier stage. Molecular classification based on HPV integration and genetic profiling may also translate into the precision medicine that allows clinicians to focus medical recourses more on high-risk patients whose diseases are genuinely progressing, greatly reducing the psychological and economic burdens of the cervical screening programs and HPV vaccination programs in the future.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: Not applicable

Competing interests: Not applicable

Funding: Not applicable

Author's contribution

Bharti Gupta contributed to the conceptualization, data curation, investigation, methodology, resources, validation, visualization, and writing of manuscript with input from all the authors, reviewing and editing of manuscript. siva palepu, nut hangi Maniteja, and akanksha kumari contributed to data curation, methodology, resources, visualization and writing of the manuscript. Lokeswara Balakrishna Sunnam contributed to the conceptualization, resources, supervision, planning, review and editing of the manuscript. Parikipandla Sridevi contributed to the conceptualization, project administration, resources, supervision, review and editing of the original draft.

Acknowledgement

Authors are thankful to all faculty members of the Department of Biotechnology, Indira Gandhi National Tribal University, Amarkantak, M.P., India for their constant support. Special thanks to Hon'ble Vice-chancellor, IGNTU, Amarkantak for providing financial assistance.

Conflict of interest

The authors declare no potential conflict of interest.

References

1. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, et al. (2018) Global Cancer Observatory: Cancer Today. Lyon, France International Agency for Research on Cancer IARC Cancer Base no 15.

2. Franco EL, Villa LL, Sobrinho JP, Prado JM, Rousseau MC, et al. (1999). Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. J Infect Dis.180:1415-23.

3. Blomberg M, Friis S, Munk C, Bautz A, Kjaer SK (2012) Genital warts and risk of cancer: a Danish study of nearly 50 000 patients with genital warts. J Infect Dis 205: 1544-1553.

4. Wiley DJ, Douglas J, Beutner K, Cox T, Fife K, et al. (2002) External genital warts: diagnosis, treatment, and prevention. Clin Infect Dis 35: S210-224.

5. Winer RL, Hughes JP, Feng Q, Reilly OS, Kiviat NB et al. (2006) Condom use and the risk of genital human papillomavirus infection in young women. N Engl J Med 354: 2645–2654.

6. Vashisht S, Mishra H, Mishra PK, Ekielski A, Talegaonkar S (2019) Structure, Genome, Infection Cycle and Clinical Manifestations Associated with Human Papillomavirus Curr Pharm Biotechnol. 20:1260-1280.

7. Baseman JG, Koutsky LA (2005) The epidemiology of human papillomavirus infections. J Clin Virol 32: S16-24.

8. Gupta B, Sunnam LB, Kumar A, Parikipandla S (2021) Prevalence of human papillomavirus 16 genotype in Anuppur district, Madhya Pradesh. Molecular biology reports 48: 503-511.

9. Kabekkodu SP, Bhat S, Pandey D, Varghese VK, Shukla V, et al. (2016) Prevalence and distribution of high-risk human papilloma virus (HPV) types in invasive squamous cell carcinoma of the cervix and in normal women in Andhra Pradesh, India. Asian Pacific Journal of Cancer Prevention 16: 1-7

10. Martel DC, Plummer M, Vignat J, Franceschi S, (2019). Technical data sheet Technical data sheet.7: 664-670.

11. Parkin DM, Bray F (2006). Chapter 2: The burden of HPV-related cancers. Vaccine 24:11-25.

12. Chan PKSS, Chang AR, Yu MY, Li WH, Chan MY, et al. (2015). High Incidence of Human Papillomavirus Types 16 and 18 in Cervical Carcinoma Patients in a Tertiary Care Unit, Jabalpur, MP, India. International Journal of Health & Allied Sciences 7: 52-55.

13. Akagi K, Li J, Broutian TR, Padilla NH, Xiao W, et al. (2014) Genome-wide analysis of HPV integration in human cancers reveals recurrent, focal genomic instability. Genome Research 24: 185-199.

14. Formana D, Martel DC, Lacey CJ, Soerjomatarama I, Lortet TJ, et al. (2012) Global burden of human papillomavirus and related diseases. Vaccine 30: F12-F23.

15. Edna OV, Orvalho A, Nália I, Kaliff M, Lillsunde LG, et al.(2017) Human papillomavirus prevalence and genotype distribution among young women and men in Maputo city, Mozambique. BMJ Open 7: 1-14.

16. Kabekkodu SP, Bhat S, Pandey D, Varghese VK, Shukla V, et al. (2016) Prevalence and distribution of high-risk human papilloma virus (HPV) types in invasive squamous cell carcinoma of the cervix and in normal women in Andhra Pradesh, India. Asian Pacific Journal of Cancer Prevention 16: 1-7.

17. Villiers EM, Fauquet C, Broker TR, Bernard HU, Hausen ZH (2004) Classification of papillomaviruses. Virology 324: 17-27.

18. Herald ZH, Francoise BS (2008) The discoveries of human papilloma viruses that cause cervical cancer and of human immunodeficiency virus. The Nobel Prize 8: 1-26.

19. Doorbar J (2005) The papillomavirus life cycle. Journal of Clinical Virology 32: 7-15.

20. Bernard HU, Burk RD, Chen Z, Doorslaer VK, Hausen HZ, (2010) Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology 401: 70-79.

21. Woodman CBJ, Collins SI, Young LS (2007) The natural history of cervical HPV infection: Unresolved issues. Nature Reviews Cancer 7: 11-22.

22. Braaten KP, Laufer MR (2008) Human Papillomavirus (HPV), HPV-Related Disease, and the HPV Vaccine. Reviews in Obstetrics & Gynecology 1: 2-10.

23. Sharma K, Kathait A, Jain A, Kujur K, Raghuwanshi S, et al. (2009) Co-infections of HPV16/18 with other high-risk HPV types and the risk of cervical carcinogenesis: A large population-based study. Gynecologic Oncology 9: 1-9.

24. Vaccarella S, Franceschi S, Snijders PJF, Herrero R, Meijer CJLM, et al. (2010) Concurrent infection with multiple human papillomavirus types: Pooled analysis of the IARC HPV prevalence surveys. Cancer Epidemiology Biomarkers and Prevention 19: 503-510.

25. Gheit T, Vaccarella S, Schmitt M, Pawlita M, Franceschi S, et al. (2009) Prevalence of human papillomavirus types in cervical and oral cancers in central India. Vaccine 27: 636-639.

26. Graham SV (2017) The human papillomavirus replication cycle, and its links to cancer progression: a comprehensive review. Clinical Science 131: 2201-2221.

27. Brianti P, De Flammineis E, Mercuri SR (2017) Review of HPV-related diseases and cancers. New Microbiologica 40: 80-85.

28. Abban CY, Meneses PI (2010) Usage of heparan sulfate, integrins, and FAK in HPV16 infection. Virology 403:1-16.

29. Harden ME, Munger K (2017) Human papillomavirus molecular biology. Mutation research Rev in mut res 772: 3-12.

30. Day PM, Baker CC, Lowy DR, Schiller JT (2004) Establishment of papillomavirus infection is enhanced by promyelocytic leukemia protein (PML) expression. Proc Natl Acad Sci 101: 14252-14257

31. Bergvall M, Melendy T, Archambault J (2013) The E1 proteins. Virology 445: 35-56.

32. Doorbar J (2006) Molecular biology of human papillomavirus infection and cervical cancer. Clin Sci (Lond) 110: 525-541.

33. Bechtold V, Beard P, Raj K (2003) Human papillomavirus type 16 E2 protein has no effect on transcription from episomal viral DNA. J Virol. 77: 2021-2028.

34. Brehm A, Nielsen SJ, Miska EA, McCance DJ, Reid JL, et al. (1999) The E7 oncoprotein associates with Mi2 and histone deacetylase activity to promote cell growth. EMBO J 18: 2449-2458.

35. Sierra H, Cordova M, Chen CSJ, Rajadhyaksha M (2019) Confocal Imaging–Guided Laser Ablation of Basal Cell Carcinomas: An Ex Vivo Study. Journal of Investigative Dermatology 135: 612-615.

36. Doorbar J, Egawa N, Griffin H, Kranjec C, Murakami I (2015) Human papillomavirus molecular biology and disease association. Reviews in medical virology 25: 2-23.

37. Buck CB, Cheng N, Thompson CD, Lowy DR, Steven AC, et al (2008) Arrangement of L2 within the papillomavirus capsid. J Virol 82: 5190-5197.

38. Doorbar J (2013). The E4 protein; Structure, function and patterns of expression. Virology 445: 80-98.

39. Mühr LSA, Eklund C, Dillner J (2018) Towards quality and order in human papillomavirus research. Virology 519: 74-76.

40. Peto J, Gilham C, Fletcher O, Matthews FE (2004) The cervical cancer epidemic that screening has prevented in the UK. Lancet 364: 249-256.

41. Ding DC, Chiang MH, Lai HC, Hsiung CA, Hsieh CY, et al. (2009) Methylation of the long control region of HPV16 is related to the severity of cervical neoplasia. Eur J Obstet Gynecol Reprod Biol 147: 215–220.

42. Frattini MG, Hurst SD, Lim HB, Swaminathan S, Laimins L (1997) Abrogation of a mitotic checkpoint by E2 proteins from oncogenic human papillomaviruses correlates with increased turnover of the p53 tumour suppressor protein. EMBO J 16: 318-331.

43. Duensing S, Duensing A, Flores ER, Do A, Lambert PF, et al. (2001) Centrosome abnormalities and genomic instability by episomal expression of human papillomavirus type 16 in raft cultures of human keratinocytes. J Virol 75: 7712-7716.

44. Williams VM, Maria F, Ubaldo S, Penelope JD (2011) HPV-DNA Integration and Carcinogenesis: Putative Roles for Inflammation and Oxidative Stress. Future Virology 6: 45-57.

45. Kozlov Sv (2009) Inflammation and Cancer. Methods and Protocols. Volume 1: Experimental Models and Practical Approaches Preface. Methods in Molecular Biology 511: 378.

46. McBride AA (2017) Mechanisms and strategies of papillomavirus replication. Biological chemistry 398: 919-927.

47. Diogo E, Natália RC, Rui MGC, Rui M (2019) Hallmarks of HPV Carcinogenesis: The Role of E6, E7 and E5 Oncoproteins in Cellular Malignancy. Biochimica et Biophysica Acta - Gene Regulatory Mechanisms 1862: 153-62.

48. Waggoner SE (2003) Cervical cancer. The Lancet 361: 2217-25.

49. Molijn A, Berhard K, Wim Q, Leen JVD (2005) Molecular Diagnosis of Human Papillomavirus (HPV) Infections 32: 43-51.

50. Mishra GA, Sharmila AP, Surendra SS (2016) Prevention of Cervix Cancer in India. Oncology 91: 1-7.

51. Schiller J, Lowy D (2018) Explanations for the high potency of HPV prophylactic vaccines. Vaccine 36: 4768-4773.

52. Sankaranarayanan R, Ramani W, Somanathan T, Namrata D, Bharathykutty C, et al. (2003) Test Characteristics of Visual Inspection with 4% Acetic Acid (VIA) and Lugol's Iodine (VILI) in Cervical Cancer Screening in Kerala, India. International Journal of Cancer 106: 404-408.

53. Aswathy S, Reshma J, Avani D (2015) Epidemiology of cervical cancer with special focus on India. International Journal of Women's Health 2015: 405-414.

54. Menzo S, Ciavattini A, Bagnarelli P, Marinelli K, Sisti S, et al. (2008) Molecular epidemiology and pathogenic potential of underdiagnosed human papillomavirus types. BMC Microbiology 8: 1-7.

55. Burd EM (2003) Human Papillomavirus and Cervical Cancer 16: 1-17.

56. Jiang G, Cruz Y, Jen Chang C, F Ho GY, Klein RS, et al. (1997) PCR detection of human papillomavirus: Comparison between MY09/MY11 and GP5/GP6 Primer Systems. Journal of Clinical Microbiology 35: 1304-1310.

57. Sherman L, Jackman A, Itzhaki H, Stoppler M, Koval D, et al. (1997) Inhibition of Serum- and Calcium-Induced Differentiation of Human Keratinocytes by HPV16 E6 Oncoprotein: Role of p53 Inactivation. Virology 237: 296-306.

58. Takacs T, Jeney C, Kovacs L, Mozes J, Sebe A, et al. (2008) Molecular beacon-based real-time PCR method for detection of 15 high-risk and 5 low-risk HPV types. J. Virol. Methods 149: 153-162.

59. Cartmell KB, Young-pierce J, Shannon Mcgue, Alberg AJ, Luque JS, et al. (2018) Barriers, facilitators and potential strategies for increasing hpv vaccination : A statewide assessment to inform action. Papillomavirus.

60. Garbuglia AR, Lapa D, Sias C, Capobianchi MR, Porto PD (2020) The Use of Both Therapeutic and Prophylactic Vaccines in the Therapy of Papillomavirus Disease. Fron. in Immuno 11: 188.

61. World Health Organization. (2016)" Guide to introducing HPV vaccine into national immunization programmes. World Health Organization. Portuguese, Portugal Pg no. 104.

62. Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, et al. (2013) Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: A randomized clinical trial. JAMA 309: 1793-802.

63. Meites E, Kempe A, Markowitz LE (2016) Use of a 2-dose schedule for human papillomavirus vaccination - updated recommendations of the advisory committee on immunization practices. mmwr. Morbidity and mortality weekly report 65: 1405-1408.

64. Markowitz LE, Dunne EF, Saraiya M, Chesson HW, Curtis CR, et al. (2014) Human papillomavirus vaccination: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and mortality weekly report. Centers for Disease Control and prevention. Recommendations and reports 63: 1-30.

65. Armstrong EP (2010) Prophylaxis of cervical cancer and related cervical disease: a review of the cost-effectiveness of vaccination against oncogenic HPV types. Journal of managed care pharmacy: JMCP, 16: 217-230.

66. Hong AM, Dobbins TA, Lee CS, Jones D, Harnett GB, et al. (2010) Human papillomavirus predicts outcome in oropharyngeal cancer in patients treated primarily with surgery or radiation therapy. British journal of cancer 103: 1510-1517.

67. Chauhan AS, Prinja S, Srinivasan R, Rai B, Malliga JS, et al. (2020) Cost effectiveness of strategies for cervical cancer prevention in India. PloS one 15: e0238291.

68. Alsous MM, Ali A, Al-Azzam S, Karasneh R, Amawi H (2021) Knowledge about cervical cancer and awareness about human papillomavirus vaccination among medical students in Jordan. Peer J 9: e11611.

69. Hu Z, MA D (2018) The precision prevention and therapy of HPV-related cervical cancer: New concepts and clinical implications. Cancer Medicine 5217-5236.

70. Basu P, Mittal S, Vale DB, Kharaji YC (2018) Secondary prevention of cervical cancer. Best Practice and Research: Clinical Obstetrics and Gynaecology 47: 73-85.

71. Kunckler M, Schumacher F, Kenfack B, Catarino R, Viviano M, et al. (2017) Cervical cancer screening in a low-resource setting: a pilot study on an HPV-based screen-and-treat approach. Cancer medicine 6: 1752-1761.

72. Denny LA, Wright TC, (2005) Human papillomavirus testing and screening. Best practice & research Clinical obstetrics & gynaecology 19: 501-515.

73. Poljak M, Kocjan B J, Oštrbenk A, Seme K (2016) Commercially available molecular tests for human papillomaviruses (HPV): 2015 update. Journal of clinical virology 76: 3-13.

74. Kleter B, van Doorn LJ, Schrauwen L, Molijn A, Sastrowijoto S, et al. (1999) Development and clinical evaluation of a highly sensitive PCR-reverse hybridization line probe assay for detection and identification of anogenital human papillomavirus. Journal of clinical microbiology 37: 2508-2517.

75. Ginocchio CC, Barth D, Zhang F (2008) Comparison of the Third Wave Invader human papillomavirus (HPV) assay and the digene HPV hybrid capture 2 assay for detection of high-risk HPV DNA. Journal of clinical microbiology 46: 1641-1646.

76. Stillman MJ, Day SP, Schutzbank TE (2009) A comparative review of laboratory-developed tests utilizing Invader HPV analyte-specific reagents for the detection of high-risk human papillomavirus. Journal of clinical virology 45: 73-77.

77. Bailey HH, Chuang LT, DuPont NC, Eng C, Foxhall LE, et al. (2016) American Society of Clinical Oncology Statement: Human Papillomavirus Vaccination for Cancer Prevention. Journal of clinical oncology: Official journal of the American Society of Clinical Oncology 34: 1803-1812.

78. Andrei G, Snoeck R, Piette J, Delvenne P, De Clercq E (1998) Antiproliferative effects of acyclic nucleoside phosphonates on human papillomavirus (HPV)-harboring cell lines compared with HPV-negative cell lines. Oncology research 10: 523-531.

79. Stern PL, van der Burg SH, Hampson IN, Broker TR, Fiander A, et al. (2012) Therapy of human papillomavirus-related disease. Vaccine 30: 71-82.

80. Juhl ME, Seferovic V, Antonijevic S, Krunic A (2016) Combined treatment of anogenital HPV infection with cryodestruction, podophyllin 25% and post-ablation immunomodulation with sinecatechins 15% ointment - a retrospective analysis. International journal of STD & AIDS 27: 1071-1078.

81. Garland SM, Kjaer SK, Munoz N, Block SL, Brown DR, et al. (2016) Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience. Clinical infectious diseases: An official publication of the Infectious Diseases Society of America 63: 519-527.

HERALD

Advances In Industrial Biotechnology | ISSN: 2639-5665

Advances In Microbiology Research | ISSN: 2689-694X

Archives Of Surgery And Surgical Education | ISSN: 2689-3126

Archives Of Urology

Archives Of Zoological Studies | ISSN: 2640-7779

Current Trends Medical And Biological Engineering

International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X

Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276

Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292

Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370

Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594

Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X

Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562

Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608

Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879

Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397

Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751

Journal Of Aquaculture & Fisheries | ISSN: 2576-5523

Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780

Journal Of Biotech Research & Biochemistry

Journal Of Brain & Neuroscience Research

Journal Of Cancer Biology & Treatment | ISSN: 2470-7546

Journal Of Cardiology Study & Research | ISSN: 2640-768X

Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943

Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771

Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844

Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801

Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978

Journal Of Cytology & Tissue Biology | ISSN: 2378-9107

Journal Of Dairy Research & Technology | ISSN: 2688-9315

Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783

Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X

Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798

Journal Of Environmental Science Current Research | ISSN: 2643-5020

Journal Of Food Science & Nutrition | ISSN: 2470-1076

Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X

Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566

Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485

Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662

Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999

Journal Of Hospice & Palliative Medical Care

Journal Of Human Endocrinology | ISSN: 2572-9640

Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654

Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493

Journal Of Light & Laser Current Trends

Journal Of Medicine Study & Research | ISSN: 2639-5657

Journal Of Modern Chemical Sciences

Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044

Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X

Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313

Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400

Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419

Journal Of Obesity & Weight Loss | ISSN: 2473-7372

Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887

Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052

Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X

Journal Of Pathology Clinical & Medical Research

Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649

Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670

Journal Of Plant Science Current Research | ISSN: 2639-3743

Journal Of Practical & Professional Nursing | ISSN: 2639-5681

Journal Of Protein Research & Bioinformatics

Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150

Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177

Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574

Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060

Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284

Journal Of Toxicology Current Research | ISSN: 2639-3735

Journal Of Translational Science And Research

Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193

Journal Of Virology & Antivirals

Sports Medicine And Injury Care Journal | ISSN: 2689-8829

Trends In Anatomy & Physiology | ISSN: 2640-7752

Submit Your Manuscript: https://www.heraldopenaccess.us/submit-manuscript

Herald Scholarly Open Access, 2561 Cornelia Rd, #205, Herndon, VA 20171, USA.
Tel: +1 202-499-9679; E-mail: info@heraldsopenaccess.us
http://www.heraldopenaccess.us/