HUMAN PAPILLOMA VIRUSES: REALITIES AND PERSPECTIVES

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ABSTRACT

Human papillomaviruses (HPVs) are the most common sexually transmitted viruses in the world. HPVs are responsible for a large spectrum of diseases, both benign and malignant. The use of the molecular virology methods to establish HPV infection and prospective epidemiologic studies have convincingly demonstrated that certain types of HPV are etiologically involved in the development of cervical cancer. Therefore, it is important to understand the natural history of HPV infection, the molecular mechanisms of viral regulation, the factors that may influence viral spread, persistence and/or progression to neoplasia. This review brings together some molecular aspects of HPV as well as the status of the specific viral diagnosis, treatment and prevention of HPV infection. Currently, many studies focus on the HPV life cycle and intimate pathogenic mechanism(s) of HPV-produced diseases. Nevertheless, prospective studies are needed to gain more relevant knowledge, which can be used to combat the infection more effectively. At the same time, the advent of modern molecular techniques has led to rapid advances in the HPV diagnostic and prognostic capabilities.

Key words: HPV, virus-induced carcinogenesis, HPV molecular diagnosis; therapy, HPV vaccination

Introduction

Certain types of human papillomavirus (HPV) account for an estimated 11% incidence of global cancer in woman (40). Depending on the kind of lesions where HPV is isolated, one can be them divided in “low” and “high” risk HPVs (57). “Low risk” HPV types, such as HPV 1 and 2, cause proliferative epithelial lesions commonly called warts. Attention in HPVs, however, has been increased greatly in recent years because molecular biological and epidemiological studies provide evidence that infection with “high risk” HPV is etiologically linked to the development of precancerous lesions of the cervix and the final progression to cervical cancer (53, 55). Over 150 different HPV types have been identified up to now. Since these viruses cannot be propagated in vitro and in turn not purified for direct biochemical and antigenic characterization, HPVs are classified as genotypes and not as serotypes (3). Analysis of different isolates led to the recognition of multiple HPV genotypes (e.g. the most prevalent HPV 16/18) associated with different lesions of the uterine cervix, called cervical intraepithelial neoplasia (CIN I-III). These premalignant lesions can finally proceed to cervical carcinoma, the second most common cause of cancer among women worldwide (3).

In the meantime it is generally accepted that HPV infection is a high risk factor for cervical cancer. This was further substantiated by biological data demonstrating the oncogenic potential of particular HPV types both in vitro and in animal experiments (3). Current studies show that HPV infection is highly prevalent in the general population. Indeed, a recent cross-sectional study demonstrated a 46% prevalence of HPV among sexually active university students (1).

A consistently effective and safe treatment for HPV infections is currently not yet available. Present therapeutic options are more directed at surgical eradication and/or by destroying malignant lesions via physical or chemotherapeutical intervention. A majority of these treatments have been developed empirically, few have been thoroughly tested, but none of them are completely satisfactory. Fortunately, modern molecular techniques are well established and these methods are most useful for detection and HPV typing. HPV testing should be obligatory to be implemented in national screening programs, thereby reducing the incidence of cervical cancer.

Genome organization

Human papillomaviruses belong to the Papillomavirus genus of the family Papillomaviridae. The viruses have double-stranded circular DNA genomes (Fig. 1). The icosahedral capsid is non-enveloped. HPV consists of approximately 8,000 bp (3) which can be divided into three different sections: early (E) genes, late (L) genes and the long control region (LCR).

All papillomaviruses possess only one coding DNA strand. The late open reading frames (ORFs) encode the structural proteins which are required for viral assembly and maturation of infectious progeny particles (major capsid protein L1 and minor capsid protein L2). The early ORFs encode non-structural regulatory proteins responsible for viral DNA replication (E1/E2), transcriptional self-regulation (E2) and cellular
transformation/ immortalization (E5, E6 and E7, referred as viral oncogenes). Once the viruses have been penetrated basal cells, they can latently persist as non-integrated episomes in a defined copy number or can induce benign tumors such as papillomas by finalizing the permissive cycle.

Fig. 1. Schematic representation of the HPV-16 genome. The long control region (LCR) harbors all regulatory elements necessary for transcription. The open reading frames (ORFs) encode the early (E) and late (L) viral proteins (for details, see text)

During progression to cervical cancer, however, HPV becomes integrated into the host genome, thereby disrupting the negative feedback loop of the E2 protein on its own expression and preserving only the E6/E7 oncogenes expression (43). HPV integration in turn results in up-regulation of HPV oncogene expression by increasing the E6/E7 mRNA half-life due to generation of viral-cellular fusion transcripts (25). Although E4 is classified as an early gene, it can be considered as a late accessory protein, involved in the destruction of the host cell cytoskeleton, enabling the release of infectious progeny viruses (11). The oncoproteins E5, E6, and E7 interrupt cellular homeostasis, thereby favoring cell transformation (8). E5 is apparently involved in general growth stimulation by interfering with the down-regulation of the EGF and PDGF receptor and has transforming activity in rodent cells. E6 and E7 are obligatory oncoproteins involved in immortalize primary keratinocytes of human foreskin or cervical epithelium cells (56). Moreover, continuous E6/E7 expression is required to maintain the malignant and proliferative phenotype both under in vivo and in vitro conditions (7, 51). E6 for instance, binds to the tumor suppression protein p53. In normal cells, p53 controls cell growth, proliferation as well as chromosomal stability. Wild type p53 suppresses cell growth while mutants favor cell proliferation (52). When p53 is bound to E6, p53 is destroyed via an ubiquitin-dependent mechanism favoring the accumulation and outgrowth of cells with unscheduled DNA synthesis. Similarly, E7 binds to retinoblastoma (Rb) and Rb-related pocket proteins by also enhancing their degradation via ubiquitin pathway. This event releases transcription factors of the E2F family, activating transcription of genes regulating the S-phase and cell proliferation. Moreover, E7 inactivates cyclin-dependent kinase inhibitors leading to growth stimulation (for review see ref. 56).

The long control region (LCR) of HPV comprises approximately 800-1000 bp and contains the cis-regulatory elements (enhancer, promoter) involved in viral transcription and replication. From here, transcription is initiated and genes are transcribed in the form of polycistronic mRNAs which become differentially spliced. Functionally, the HPV16/18 LCR can be divided in 3 parts: 5’-terminal portion of unknown function, which only marginally contributes to the activity of the promoter, central 230-bp constitutive enhancer essential for the promoter activity and promoter proximal region containing basically the promoter region at the 3’-terminus of the URR (20).

Besides binding of many cellular transcription factors (e.g. NF-1, SP-1, Oct-1), the LCR also contains a progesterone response element (PRE). Progesterone is present in oral contraceptives and is found in women in varying levels during the ovulation cycle. Since progesterone is also present during pregnancy, this could be one explanation why malignant HPV lesions occurring more frequently in women that in men. For instance, the target cells of HPV-16 infection and the epithelia of the squamous-columnar junction of the cervix express progesterone receptors (8). Progesterone may increase the transcription of E6 and E7, thereby increasing the tendency of cell transformation. The glucocorticoid response element (GRE) can also function as cis-regulatory element in cooperation with other transcription factors. The transcription factor AP-1 is the main regulator determining the efficiency of the HPV expression and in turn the intracellular net amount of the viral oncoproteins E6/E7. Moreover, has been demonstrated that the AP-1 composition differ considerably between immortalize and malignant HPV-positive cells (45). Intriguingly, non-malignant HPV-positive cells revealed an AP-1 composition characteristically for uninfected normal human fibroblast or keratinocytes, while this pattern is changed in malignant counterparts (45, 46). Notably, AP-1 seems to regulate negatively the HPV transcription under certain circumstances in which the AP-1 complex bound to the LCR is preferentially formed by c-Jun/JunB and Fra-1 (38, 47) (see below).

HPV types are distinct if their genomes have less than 90% homology in the DNA sequences of the L1 ORF, which encodes for the major capsid protein (3). Infections with different HPV types may cause local cell proliferation, which can develop into common warts, condylomas or other genital and oral lesions. The majority of these lesions regress spontaneously.
in immunocompetent individuals. However, in those with inherited or pharmacologically induced immune deficiencies, there is a strong tendency for the infections to persist, with a probability of malignancy in the case of some infection with high-risk HPV types (Table 1).

**HPV life cycle**

HPV gains entry through microabrasions and enters basal cells by direct binding to cell surface receptors (Fig. 2). The characteristics of the specific receptor have not been identified, although there is evidence to suggest that both the α6-integrin family and heparin sulphate may play a part (14).

![Fig. 2. Schematic representation of the HPV life cycle](image)

**Fig. 2.** Schematic representation of the HPV life cycle

![Fig. 3. Progression from a benign cervical lesion to invasive cervical cancer](image)

**Fig. 3.** Progression from a benign cervical lesion to invasive cervical cancer (according to ref. 33). After exposure to HPV, the development of a productive infection (low-grade squamous intraepithelial lesion, LSL or cervical intraepithelial neoplasia, CIN I) and the progression to neoplastic status (high-grade SIL, HSIL/CIN II-III and invasive carcinoma) depend on host and virus factors.

The HPV life cycle is tightly linked to the differentiation state of the keratinocyte and shows both non-productive and productive stages (Fig. 3). Non-productive stages involve establishment of the viral genome as a low copy number nuclear plasmid. This occurs in the proliferating basal layer of the epithelium where HPV replicates its DNA to force cell division of basal and parabasal cells and to establish a steady-state level of viral genomes (9). The productive step of the viral life cycle occurs in the terminally differentiated layers of epithelium (9). During this stage, HPV amplifies its genome to a higher copy number and expresses its late genes and produces viral progeny particles. Regulation of viral gene expression is controlled by a variety of transcription factors, including activator-protein-1 (AP-1), yin-yang-1 (YY-1), octamer binding factor family members (Oct-1) and nuclear factor-1 (NF-1). HPV does not induce cell lysis and further cycles of infection occur by shedding of virus-containing epithelial cells.

**Genital HPV infections and disease**

Recent advances in molecular virology have shown a strong association between infection with certain HPV types and dysplastic and neoplastic lesions of the cervix uteri and other anogenital sites (36). The primary mode of transmission is through direct sexual contact (55). Oral-genital contact may result in HPV infection of the oral cavity. Mothers may infect their babies at delivery. This mode of transmission results in laryngeal papillomatosis or genital warts in newborn.

![Fig. 2. Schematic representation of the HPV life cycle](image)

**Fig. 2.** Schematic representation of the HPV life cycle

Very strong evidence indicates that HPV infection causes the vast majority of cervical cancers cases. The evidence can be summarised as follows: (a) HPV DNA is consistently present in over 93% of cervical intraepithelial neoplasias, squamous cell carcinomas, or adenocarcinoma specimens, and specific genotypes (mostly 16, 18, 31 and 45) are responsible for this association (4, 27); (b) The prevalence of these cancer-associated HPV types increases with the grade of squamous intraepithelial lesions (41); (c) Present data indicates that the development of high-grade cervical carcinoma is usually preceded within 2 years by an HPV-16 or HPV-18 cervical infection (25).

HPV infection affects the genital skin and mucosa, including vaginal tract, cervix and anal canal. Cervical cancer is the third most common cancer among women worldwide, with about 400,000 newly diagnosed cases each year. Cervical cancer is the most common cancer of women in most developing countries, where it may account for as many as one fourth of female cancers. Many studies have concluded that this cancer does not occur in virgins, is most common among prostitutes, and is correlated with number of lifetime sexual partners; therefore cervical cancer has been recognized for decades to behave as a sexually transmitted disease.

Lesions that are destined to become malignant squamous cell carcinomas typically undergo a series of dysplastic changes over time span of many years (Fig. 3). More than 25 HPV types can infect the genital tract and be associated with cervical dysplasia in some infected women. Most dysplasias do not progress with likelihood of resolution decreasing with the severity of the dysplasia. However, the more severe dysplasias generally arise form less dysplastic lesions after several years,
although some high-grade dysplasias may develop rapidly without passing through a low-grade stage.

**Host cell control during HPV-induced cancer**

Progression to cervical cancer is a multi-step process. The long latency period between primary infection with “high-risk” HPVs and tumor development clearly indicate that viral infection is not sufficient to induce malignant transformation. It has been postulated that the long control region (LCR) is a direct target of an intracellular regulatory pathway, which negatively interferes both with viral gene expression and cell proliferation. Consequently, progression to malignancy is accompanied by the loss of intracellular surveillance, which correlates with abundant viral gene expression and tumorigenicity (54).

As aforementioned stated, activator protein AP-1 seems to be an important key regulatory molecule in the modulation of HPV gene expression. AP-1 acts as a junction point for many regulatory pathways associated with proliferation, apoptosis, differentiation and neoplastic transformation (for review, see ref. 13). The decision which cellular or viral target genes were finally turned on/off is mainly determined by AP-1 composition (48). Between two and three AP-1 binding sites are found within the LCR of “high-risk” HPVs, all of them are indispensable for viral oncogene expression (7).

Although AP-1 was hitherto considered as a positive regulatory protein in all HPV types investigated so far, recent experiments demonstrated that AP-1 is also a central key element within an intracellular surveillance network negatively controlling HPV transcription and in turn cell proliferation (15, 45, 46; for review, see also ref. 57). Using non-tumorigenic and tumorigenic somatic cell hybrids as well as primary human fibroblasts or keratinocytes as experimental model system, AP-1 composition was found to vary considerably between these different cells. In primary cells and non-tumorigenic HPV-positive cells, jun-family members were mainly associated with the fos-related antigen fra-1, a protein, which can block the trans-activating activity of AP-1 under certain experimental conditions. In contrast, fra-1 concentration is low in extracts from tumorigenic cells. The potential involvement of fra-1 in the context of HPV negative regulation could be of functional relevance, since fra-1 is located on chromosome 11, a chromosome, which can completely suppress the tumorigenic phenotype of cervical carcinoma cells (39). Intriguingly, restriction enzyme-fragment-length-polymorphisms analyses have revealed that fra-1 is within a region (11q13) (44), often found to be rearranged or deleted in cervical carcinomas (26). Conversely, c-fos, the canonical dimerization partner of jun proteins is expressed in substantial amount in malignant HPV-positive cells, but is absent in AP-1 complexes from non-tumorigenic hybrids.

Alteration of AP-1 composition has profound biological effects on non-malignant cells. c-fos overexpression under the control of a heterologous promoter in non-malignant cells induces tumorigenicity, which is preceded by a change of the jun/fra-1 ratio towards a constellation initially detected in the malignant counterparts (45). Furthermore, conversion to tumorigenicity is accompanied by a resistance against TNF-α, a cytokine, capable to selectively suppress HPV transcription in formerly non-malignant cells. c-fos-induced malignancy also abrogates the transcription of particular chemokines (MCP-1).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequent Association</th>
<th>Less-Frequent Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common warts</td>
<td>1,2,4,26,27,29,41,57,65,77</td>
<td></td>
</tr>
<tr>
<td>Deep planar warts</td>
<td>1,2,4,63</td>
<td></td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis</td>
<td>2,3,5,8,10,12,14,15,17,19-25,36-38,47,50</td>
<td></td>
</tr>
<tr>
<td>Condylomata acuminata</td>
<td>6,11</td>
<td></td>
</tr>
<tr>
<td>Cervical intraepithelial neoplasia:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>6,11,16,18,31,33,35,39,42,45,51,52,74</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>6,11,16,18,31,33,35,39,42,44,45,51,52,58,66</td>
<td></td>
</tr>
<tr>
<td>Cervical carcinoma</td>
<td>16,18,31,33,35,39,42,45,51,52,56,58,59,66</td>
<td></td>
</tr>
<tr>
<td>Recurrent respiratory papillomatosis</td>
<td>6,11</td>
<td></td>
</tr>
<tr>
<td>Focal epithelial hyperplasia</td>
<td>13,32</td>
<td></td>
</tr>
<tr>
<td>Conjunctival papillomas and carcinomas</td>
<td>6,11,16</td>
<td></td>
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* According to W. Bonnez, 1997 (3)
which regulate the network of infiltrating immunological effector cells necessary to control persisting viral infections (for review, see ref. 35).

Hence, AP-1 is apparently a key regulatory factor of intracellular surveillance mechanism (45), which controls viral gene expression and the phenotype of cells in vivo upon heterotransplantation into immunocompromized animals.

**Epidemiology**

HPV infections are endemic. No sporadic epidemic patterns of HPV infection have been recognized. The prevalence of genital warts can vary from 0.6% to 3% (40). The prevalence of the HPV types in cervical cancer infection is presented in the **Fig. 4.** Of the 25 genital HPVs tested, HPV-16 is the most prevalent type (50% overall), followed by HPV-18 (14%), HPV-45 (8%), and HPV-31 (5%) (4). Our recent results for the prevalence of HPV types in Bulgaria are in accordance with those reported worldwide (27).

**Fig. 4.** Worldwide prevalence of HPV types in cervical cancer (4)

The prevalence of cervical HPV infection varies according to the method of detection. By cytology, rates vary between 0.9% and 4.8% depending on the criteria and age, and decrease after age 24 (50). When using PCR assays, the rates of HPV infection are higher, but also decline with age (30). In one study, 49% of women aged 20 to 25 years were positive for HPV by PCR, compared to 34% aged 26 to 50 years (30). This decline with age is also seen with HPV vaginal infections. Most HPV infections limited to HPV DNA detection are transient (22).

Genital HPV infection occurs primarily through sexual intercourse. Factors that may influence the acquisition of disease include the number of sexual partners, the presence of genital warts on sexual partner (about 2/3 of sexual partners of persons with anogenital warts will develop the disease within 2 years), a history of sexually transmitted disease, and smoking (3). Other factors that may contribute to cell transformation are the use of oral contraceptives and immunosuppression.

Little is known about the prevalence of laryngeal warts or recurrent respiratory papillomatosis. Epidemiologic data are lacking for other HPV diseases such as very rare epidermodysplasia verruciformis. Focal epithelial hyperplasia (Heck’s disease) is also a relatively uncommon disease.

**Laboratory (virology) diagnosis of HPV infection**

The diagnosis of HPV infection remains problematic. Reliable serological tests for infection are not available. Attempts to culture HPV with use of routine techniques have been unsuccessful. Therefore, infection has been variably defined in epidemiological studies by clinical evidence of warts or colposcopically visualized lesions, by cellular cytological or histopathologic changes suggestive of HPV infection, or by the presence of HPV DNA in human tissues. Cytologic and histopathologic diagnostic techniques are subject to sampling error and variability in interpretation (23) and limit the cohort to those individuals who manifest evidence of viral cytopathic effects.

The availability of modern molecular diagnostic techniques has led to rapid advances in our HPV diagnostic capabilities. Over 130 different HPVs have been identified and classified on the basis of differences in DNA structure. This genotyping classification has demonstrated clinical relevance (24). It is now well established that some HPV types carry a low risk of progression to cancer (types 6, 11, 42, 43, 44) whereas others

<table>
<thead>
<tr>
<th>Type of wart or lesion</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condylomata acuminata</td>
<td>Podofilox, Cryotherapy, Trichloracetic acid, Podophyllin, Scissor excision,</td>
</tr>
<tr>
<td></td>
<td>Electrosurgery, Laser surgery, Interferon</td>
</tr>
<tr>
<td>Anal warts</td>
<td>Imiquimod, Cold-blade surgery, Cryotherapy, Electrosurgery, Laser surgery</td>
</tr>
<tr>
<td>Vaginal warts</td>
<td>Cryotherapy, Laser surgery, 5-Fluorouracil, Bi/Trichloracetic acid, Imiquimod</td>
</tr>
<tr>
<td>Cervical warts</td>
<td>Imiquimod, Electrosurgery, Cryotherapy, Laser surgery, Interferon</td>
</tr>
<tr>
<td>Anal intraepithelial neoplasia</td>
<td>Cryotherapy, Trichloracetic acid, Podophyllin, Laser surgery, Cold-blade surgery,</td>
</tr>
<tr>
<td></td>
<td>Electrosurgery</td>
</tr>
<tr>
<td>Vaginal intraepithelial neoplasia</td>
<td>Laser surgery, 5-Fluorouracil, Interferon, Imiquimod</td>
</tr>
<tr>
<td>Cervical intraepithelial neoplasia</td>
<td>Electrosurgery, Cryotherapy, Laser surgery, Interferon</td>
</tr>
<tr>
<td>Recurrent respiratory papillomatosis</td>
<td>Microsurgery, Laser surgery</td>
</tr>
<tr>
<td>Oral papillomas</td>
<td>Cold-blade surgery, Cryotherapy, Podophyllin, Interferon</td>
</tr>
</tbody>
</table>

**TABLE 2**
are associated with “intermediate” (types 31, 33, 35, 51, 58) to “high risk” (types 16, 18, 45, 56) of progression to cancer (32).

Nucleic acid detection assays such as the Hybrid Capture System (Digene Diagnostics Inc.) and Polymerase Chain Reaction (PCR) permit rapid and relatively low-cost HPV detecting and typing. They can also quantitate the amount of HPV DNA present, important information since for low-risk HPV type the higher the DNA load, the greater the chance that CIN or cancer is present. These observations are the primary rationale for HPV testing and typing to identify women with CIN or at risk of progression (10, 34, 42).

Treatment
A consistently effective and safe treatment for HPV infections is not available. Present therapeutic options are directed at eradicating the disease, not the infection, by destroying the lesions with physical or chemical means. Some common treatment modalities of HPV lesions are shown in Table 2. In attempts to find additional drugs in the treatment of cervical cancer, inhibitors of the histone deacetylases have received much attention due to their low cytotoxic profiles (see below).

The effect of histone deacetylase inhibitors on cervical carcinoma cells
Modulation of histone acetylation is a regulatory process, which controls the nucleosomal organization of bulk cellular DNA and in turn gene expression. Changes in the chromatin architecture is coordinated by a concerted interplay between histone acetylases (HAT) and deacetylases (HDAC), which are also targets of the viral oncogenes E6 and E7 (5, 37). De novo DNA methylation and histone modification act functionally together in a dynamic and reversible fashion, leading to the conceptional idea that cancer can be considered as an epigenetic disease. Hence, an integrated epigenetic approach to understand the role of such mitotic heritable changes in gene expression that are not encoded within the DNA sequence is of fundamental importance, because epigenetic alterations are potentially reversible (12).

Recent studies were directed to investigate the molecular effects of HDAC inhibition on cervical carcinoma cells as well as on primary human foreskin keratinocytes, separately immortalized with amphotropic retroviruses separately carrying the open reading frames of HPV 16 E6, E7 or E6/E7. In these experiments one could show that E6/E7 oncogene function of human papillomavirus can be completely bypassed by HDAC inhibition. Both malignant and immortalized HPV16/18-positive cells became blocked in G1/S transition despite ongoing viral gene expression. G1 arrest was accompanied by a down-regulation of cyclin D and cyclin A and a concomitant up-regulation of the cyclin kinase inhibitors (CKI) p21 and p27. Binding of both CKIs led to a complete block of the cyclin-dependent kinase (cdk2) activity and in turn prevented binding of E7. This was intriguing with respect to the reversibility of HPV transformation process, since it is thought that the abrogation of the growth inhibitory function of p21 and p27 through E7 represents a key event in HPV-induced carcinogenesis (for review, see ref. 19). HDAC inhibitors also trigger pRb degradation, while E2F expression remained unaffected. pRb degradation is an E7-specific phenomenon, since in E6-positive cells pRb only became hypophosphorylated. The presence of E2F under cell cycle arrest led to a classical “conflict situation” which finally induced apoptosis. Hence, the knowledge how the transforming potential of HPV can be bypassed without switching off viral transcription could open new therapeutical perspectives for the treatment of cervical cancer (16, 17, 18).

Prevention
True chemoprophylaxis (podofilox; 5-fluorouracil) or passive immunoprophylaxis (hyperimmune globulins) is not available in clinical practice (2, 6, 29). Nevertheless, the prospects for the successful development of an effective prophylactic HPV vaccine are excellent (3, 21, 31). HPV quadrivalent recombinant vaccine is a mixture of virus-like particles derived from the L1 capsid proteins of HPV types 6, 11, 16 and 18. It is administered intramuscularly in a three-dose regimen with the initial injection followed by subsequent doses at months 2 and 6. The vaccine is indicated for use in the prevention of cervical cancer, vulvar and vaginal precancer and cancers, precancerous lesions and genital warts associated with HPV types 6, 11, 16 and 18 infections in adolescent and young women. The quadrivalent vaccine has demonstrated good immunogenicity in young women (16-26 years) and male/female adolescents (aged 9-15 years), inducing high and persistent anti-HPV antibody titers (49). In randomized, double-blind, placebo-controlled trials in more than 20 000 young women the vaccine was highly effective in preventing cervical dysplasia of any grade and external genital lesions related to HPV types 6, 11, 16 and 18 infection. The vaccine was well tolerated, with injection-site reactions and fever being the most common vaccine-related adverse events.

Conclusions
The increased understanding of the natural history of HPV infection, a virus that appears to infect ultimately much of the world’s population, may enable us to intervene in viral transmission, to assess accurately the cancer risk of an HPV-infected individual, to identify and modify risk factors that adversely effect the outcome of infection, to target medical interventions appropriate to the state of infection, and to understand the host responses that control or eliminate the virus
in most individuals. The understanding of the host immune response in HPV infection in addition to the knowledge of the mechanisms of HPV replication, will allow the development of future strategies for HPV eradication. Pieces of the preventive HPV vaccination puzzle are on the table. The HPV quadrivalent vaccine is approved or being considered for approval around the world. While indications may vary slightly with countries, the vaccine is expected to prevent cervical cancer, vulvar and vaginal precancer and cancers and genital warts associated with HPV types 6, 11, 16 and 18 infections.

REFERENCES