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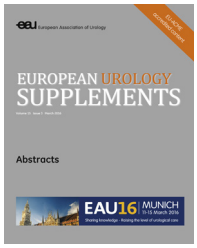

European Association of Urology

Infections of the Genital Tract: Human Papillomavirus–Related Infections

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Article info

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Abstract

Context: The human papillomaviruses (HPVs) are a major global health burden, playing a part in diseases ranging from genital warts to malignancies such as penile cancer in men and cervical cancer in women.
Objective: To explore the molecular biology and epidemiology of HPV infection; the diseases linked to it; and current prevention strategies, including the potential role of vaccination.
Evidence acquisition: The relevant papers, reviews, and guidelines pertaining to the topics were collected for the purpose of this review from PubMed and online guidelines resources including the European Association of Urology and the Centers for Disease Control and Prevention.
Evidence synthesis: The current knowledge on genital HPV in men is explained and summarised.
Conclusions: There is an urgent need for more data on the incidence and persistence of HPV at the different anatomic sites, the incidence of external genital lesions, and the types of HPV in these lesions. This will allow a more comprehensive understanding of the natural history of HPV infection and its progression to both benign and malignant disease in men and will help formulate the development and implementation of vaccination programs.
Patient summary: This review explores the molecular biology and epidemiology of human papillomavirus (HPV) infection; the diseases linked to it; and current prevention strategies, including the potential role of vaccination. There is an urgent need for more data on the incidence and persistence of HPV at the different anatomic sites, the incidence of external genital lesions, and the types of HPV in these lesions.
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1. What is human papillomavirus?

Human papillomaviruses (HPVs) are small nonenveloped viruses containing double-stranded DNA genomes of approximately 8000 base pairs within 55-nm-diameter icosahedral capsids [1]. More than 200 HPVs exist. These members of the papovaviruses infect various epithelial tissues, including the epidermis (cutaneous types) and the epithelial linings of the upper respiratory system and anogenital tract (mucosotropic types) (Fig. 1). They are

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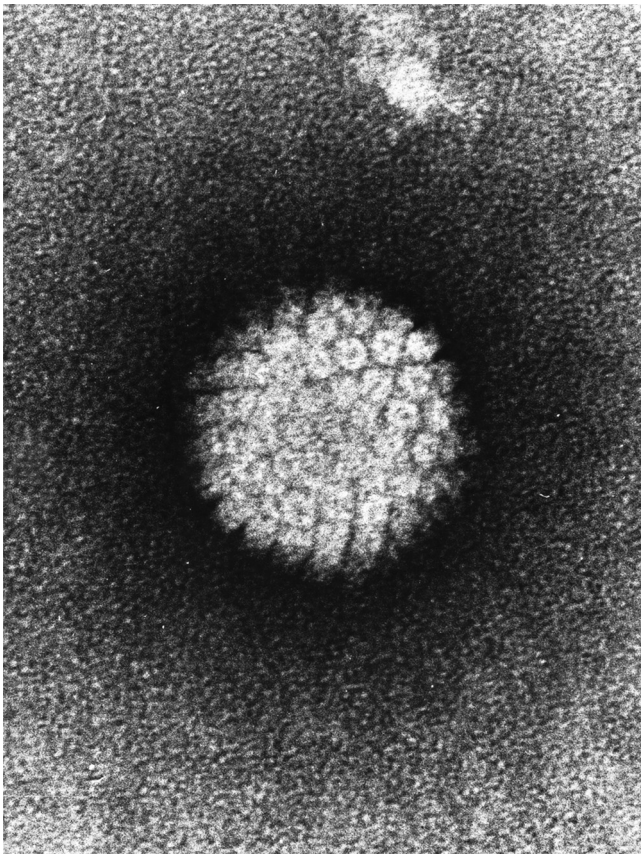

Fig. 1 – Transmission electron micrograph of the human papillomavirus structure. Reproduced from the Laboratory of Tumor Virus Biology with permission from the National Cancer Institute [125].

classified into low- and high-risk types based on their ability to promote malignant transformation (Table 1) [2].

Most HPVs are low risk in oncogenic potential and produce localised benign warts that do not undergo malignant progression even if left untreated. Low-risk mucosal HPVs such as HPV-6 and HPV-11 cause genital warts (condyloma acuminata), whereas the high-risk HPVs cause squamous intraepithelial lesions that can progress to invasive squamous cell carcinoma (SCC). HPV-16 is by far the most prevalent mucosal high-risk HPV type, followed by HPV-18 and HPV-31 [3].

The 2008 Nobel Prize in Physiology or Medicine was awarded to Harald zur Hausen for his discovery that high-risk HPV types are the causative agents of cervical cancer. Infection with high-risk HPVs is not enough and additional genetic alterations are needed for malignant progression, though [4]. The HPV oncoproteins E5, E6, and E7 are the primary viral factors responsible for development and growth of cancer, primarily via altering growth regulation by host proteins and by inducing genomic instability.

Table 1 – Human papillomavirus types and oncogenic potential

Classification	HPV types
High risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probably oncogenic	26, 53, 66, 68, 73, 82
Low risk	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81

HPV = human papillomavirus.
Adapted from Muñoz et al [2].

1.1. The human papillomavirus life cycle

Most viruses infect and produce progeny virus within a target cell. In HPV infections, though, new virion synthesis happens only after the infected cell has undergone mitosis and one of the infected daughter cells has differentiated [5]. HPVs infect cells in the basal layer of stratified squamous epithelium that becomes exposed as a result of microtrauma. These are the only proliferating cells in normal epithelia. Following infection, HPV genomes are established as extrachromosomal elements or episomes. These genomes do not encode enzymes necessary for viral replication and so rely on host cell replication proteins to mediate viral DNA synthesis. The suprabasal cells remain active in the cell cycle as they undergo differentiation, and a subset of cells re-enter S phase in the top epithelial layers to replicate HPV genomes in a process called amplification. This is followed by capsid protein synthesis, virion assembly, and release.

1.2. The molecular biology behind human papillomavirus–induced tumours

Chronic HPV infection can ultimately lead to cancer development [3]. In precancerous lesions, most HPV genomes persist in an episomal state, whereas in many high-grade lesions, genomes are integrated into host chromosomes [6]. The proapoptotic viral E2 protein represses transcription of early viral genes like the E6/E7 oncogenes [7].

Integration of viral DNA disrupts E2 expression and increases proliferative capacity, a crucial step in progression to cancer [8]. Integrated copies of E6/E7 messenger RNA are also more stable than episomal copies, and coexistence of HPV episomes with integrated copies may be crucial in HPV carcinogenesis [9]. E1 and E2 viral proteins from episomes can initiate DNA replication from integrated copies, resulting in their amplification, induction of chromosomal abnormalities, and activation of DNA repair systems, which can result in further genomic anomalies and ultimately malignant progression [6].

1.3. Role of E6/E7 viral proteins

The E6 and E7 oncoproteins act synergistically and are central to the development of HPV-induced cancers [10]. Both E6 and E7 are approximately 18- and 13-kDa nuclear proteins and have also been found in the cytoplasm [11,12]. E7 but not E6 protein expression can immortalise human keratinocytes. The combination of E6 and E7, however, can immortalise most types of primary cells [13,14]. Still, HPV-immortalised cells are not tumourigenic in nude mouse models and require extensive passaging in

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