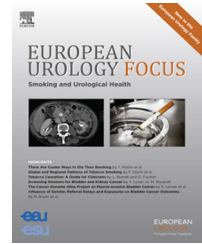


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Review – Andrology

## Human Papillomavirus Infection and Vaccination in Males

Eugenio Ventimiglia<sup>a,b,\*</sup>, Simon Horenblas<sup>c</sup>, Asif Muneer<sup>d</sup>, Andrea Salonia<sup>a,b</sup>

<sup>a</sup> Università Vita-Salute San Raffaele, Milan, Italy; <sup>b</sup> Division of Experimental Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy; <sup>c</sup> Department of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands; <sup>d</sup> Department of Urology and NIHR Biomedical Research Centre, University College London Hospital, London, UK

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### Abstract

**Context:** Human papillomavirus (HPV) is the commonest sexually transmitted pathogen in humans and is linked to the aetiopathogenesis for both benign and malignant disease in men.

**Objective:** To evaluate and summarise the evidence for HPV infection and vaccination in men.

**Evidence acquisition:** A search of Medline, PubMed, and Scopus was performed to identify articles published in English within the last 10 yr addressing HPV epidemiology, the natural history of HPV infection and its long-term consequences, and vaccination in men. Relevant studies were then screened, and the data were extracted, analysed, and summarised. The Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria were applied.

**Evidence synthesis:** HPV has an overall prevalence of >20% among men, although a minority of individuals develop external genital lesions (EGLs). The risk of acquiring a new HPV infection is robustly linked to sexual behaviour, with the most commonly infected sites being the prepuce, shaft, glans, corona, and scrotum. Of all cancer cases among men, 2% are attributable to HPV, and up to 50% of penile cancers are estimated to be either directly or indirectly driven by it, with HPV-16 the subtype most frequently isolated. Currently there are two different vaccines approved for men, with a good immunogenic profile and efficacy of up to 80% against EGLs; however, efficacy data regarding malignant lesions are still limited.

**Conclusions:** HPV, owing to its high prevalence and harmful consequences for men's health, has recently attracted considerable attention. Novel insights into the natural history of HPV infection, together with the successful development of several efficacious vaccines, have provided valuable tools in the prevention of HPV infections and their related consequences. HPV vaccination appears to be the only reliable method to provide protection against new HPV infections in men.

**Patient summary:** Human papillomavirus (HPV) infection is very common among sexually active men and can lead to more serious consequences, including cancer. Male vaccination is both a safe and efficacious option preventing both HPV infection and its long-term consequences.

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\* Corresponding author. Division of Experimental Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy. Tel. +39 02 26435506; Fax: +39 02 26437298.

E-mail address: [eugenio.ventimiglia@gmail.com](mailto:eugenio.ventimiglia@gmail.com) (E. Ventimiglia).

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## 1. Introduction

Human papillomavirus (HPV) is recognised in the aetio-pathogenesis of a number of conditions in men, including condylomata acuminata (also known as genital warts) as well as penile, oropharyngeal, and anal cancer [1]. More than 100 different HPV types have been described as being responsible for the broad range of diseases driven by HPV, with variable clinical manifestations and risk of tumourigenesis [1]. More specifically, approximately 40 different HPV types show a specific tropism for the anogenital region [2]; remarkably, they also represent the most common sexually transmitted pathogens among men and women in the USA, with an estimated 6.2 million new cases each year [3]. Although the main focus of HPV research was historically dedicated to cervical cancer in women, growing interest in the role of HPV in men has developed during the last two decades. Therefore, a better understanding of the natural history and possible treatment/preventive options for HPV-related anogenital disease are more important [4]. Since cervical cancer has been more extensively studied, the natural history has been translated to male HPV-related lesions, although the natural history of HPV is thought to differ between the two genders [5], as reflected in the epidemiology of HPV-related disease. In 2008, the incidence of anal cancers attributable to HPV was slightly higher among women than men, whereas the opposite trend was observed for oropharyngeal cancers [5]. Moreover, among men there is no such overwhelmingly prevalent clinical entity as cervical cancer, which accounts for more than five times all the incident cases of HPV-related cancer in men [5]. Nonetheless, HPV seroprevalence, which is usually higher in women than in men [6], decreases in women with increasing age, while it does not in men [7]. This again illustrates the need for different models to gain a general understanding of the whole disease pathway, which could lead to a different approach in terms of disease prevention and treatment. The advent of vaccines has revolutionised the paradigm of disease prevention in women, particularly in relation to cervical cancer, which has led to the view that the same concept can be used for men. Three highly effective and safe vaccines against HPV are currently available: a bivalent, a quadrivalent, and a nonavalent vaccine. There is increasing evidence supporting a rationale for using these vaccines to prevent both benign and malignant HPV-related lesions in both women and men [8]. HPV vaccines are not only able to elicit an effective immune response against HPV [9] but also appear to be effective against cervical, vaginal, vulvar, and anal dysplasia and against condyloma related to the specific HPV types covered by the vaccine in women [8]. In men, it has been shown that the quadrivalent vaccine reduces the onset of external genital lesions (EGLs), in particular condyloma [10], as well as rates of anal intraepithelial neoplasia among men who have sex with men [11]. Despite evidence suggesting that prevention of HPV infection will help to prevent or reduce anogenital and oropharyngeal cancers as well as virtually all HPV-related diseases, clinical studies specifically focusing on these areas are still lacking.

This review summarises the evidence currently available in terms of HPV infection in men, and analyses its prevalence, main clinical characteristics, natural history, and links to neoplasms. Moreover, a specific section is devoted to describing the state of the art of human vaccines against HPV.

## 2. Evidence acquisition

An initial search was carried out using the Medline, PubMed, and Scopus databases. We largely selected publications from the past 10 yr (2006–2016), but did not exclude commonly referenced and highly regarded older publications. Keywords included: *male human papilloma virus* OR *male HPV* AND *prevalence* OR *incidence* OR *natural history* OR *cancer* OR *vaccine* [Title/Abstract]. Abstracts were reviewed by the panel for relevance to the defined review question. If it was not clear from the abstract whether the paper might contain relevant data, the full paper was assessed. The references cited in all full-text articles were also assessed for additional relevant articles. Non-English articles were excluded from the analysis. With the consensus of the co-authors, the relevant studies were then selected and screened, and the data were extracted, analysed, and summarised after an interactive peer review process of the panel. The Preferred Reporting Items for Systematic Reviews and Meta-analysis flowchart was used to report the numbers of papers identified and included or excluded at each stage (Fig. 1).

## 3. Evidence synthesis

### 3.1. Epidemiology and natural history

HPV epidemiology gives a general overview of the magnitude and importance of the whole topic. Owing to the high rate of silent infections and asymptomatic carriers [6], a proper estimation of the prevalence is difficult to obtain. According to a systematic review by Dunne et al [6], HPV DNA can be detected in the anogenital region of 1.3–72.9% of men, depending on the individual study design, sampling method, and study population. Importantly, more than half of the studies they included reported an overall HPV prevalence >20%. A subanalysis for the site of action revealed that the prepuce, shaft, glans, corona, and scrotum were the anatomic locations more likely to harbour HPV DNA, whereas HPV prevalence in urine was <7%. More recently, a prospective cohort study including 290 US men aged 18–44 yr examined at baseline and every 6 mo (mean follow-up 15.5 mo) provided interesting insights into the natural history of HPV infection [12]. At baseline, the prevalence of any HPV type was 30%. Follow-up data led the authors to report a 12-mo incidence of new HPV infection of 29.2%, with a cumulative incidence of 42.3% (slightly higher for the oncogenic types). The median time to clearance (time necessary to determine complete regression in at least 50% of infected subjects) of any HPV infection was 5.9 mo, and at 12 mo approximately three men out of four initially positive no longer had any detectable HPV DNA.

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