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Human papillomavirus infection: Epidemiology and pathophysiology

Marc Steben [a,*], Eliane Duarte-Franco [a,b]

[a] *Direction Risques Biologiques, Environnementaux et Occupationnels, Institut National de Santé Publique du Québec, 190, boulevard Crémazie Est, Montréal, Québec, Canada H2P 1E2*
[b] *Department of Family Medicine, McGill University, 517 Pine Ave W, Montréal, Québec, Canada H2W 1S4*

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Abstract

More than 120 different types of the human papillomavirus (HPV) have been isolated; >40 of these types infect the epithelial lining of the anogenital tract and other mucosal areas. In the majority of individuals, HPV infections are transient and asymptomatic with most new infections resolving within 2 years. Epidemiological data from the U.S. National Health and Nutrition Examination Survey determined that the prevalence of HPV infection in a representative sample of women was highest in those aged 20–24 years (44.8%). HPV infection has been firmly established as the primary cause of cervical cancer. It is not clearly understood why HPV infections resolve in certain individuals and result in cervical intraepithelial neoplasias in others, but several factors are thought to play a role; including individual susceptibility, immune status and nutrition, endogenous and exogenous hormones, tobacco smoking, parity, co-infection with other sexually transmitted agents such as HIV, herpes simplex virus type 2 and *Chlamydia trachomatis* as well as viral characteristics such as HPV type, concomitant infection with other types, viral load, HPV variant and viral integration. Worldwide, pooled data from case–control studies indicated that HPV DNA could be detected in 99.7% of women with histologically confirmed squamous cell cervical cancer compared with 13.4% of control women. Both HPV infection and cervical cancer are associated with a substantial economic burden. Pharmacoeconomic data from the United States indicate that HPV infection and HIV were associated with similar total direct medical costs, and HPV infection was more costly than genital herpes and hepatitis B combined in the 15–25 age group. Furthermore, false-negative pap smears from women with precancerous lesions are among the most frequent reasons for medical malpractice litigation in the United States.

Keywords: Review; HPV infection; Epidemiology; Virology; Anogenital diseases; Cervical cancer; Prevalence; Disease burden

Human papillomavirus: pathophysiology

The human papillomavirus (HPV) is a non-enveloped double-stranded DNA virus that belongs to the Papillomaviridae family [1]. Over 100 different HPV genotypes (or types for short) have been isolated to date, and more than 40 of these types infect the epithelial and mucosal lining of the anogenital tract and other areas [2]. HPV strains can be practically classified by their risk of causing cervical cancer into low-risk (e.g. HPV-6 and -11) and high-risk (e.g. HPV-16 and -18) types. HPV-6 and -11 are associated with the majority of more benign lesions affecting the anogenital areas, such as genital warts (condylomata) and low-grade squamous intraepithelial lesions of the cervix (LSIL) and vulva (VIN 1) [3,4]. All cases of external genital warts are caused by HPV infection; 90% of cases are associated with HPV types 6 and 11 [5]. In the United States, available data indicate that about 1% of the sexually active population has visible genital warts and a further ≥15% have subclinical infection [4]. The highest rates of genital HPV infection have been reported in sexually active women aged <25 years. One in every two people will acquire a genital HPV infection in their lifetimes; by the age of 50, this proportion reaches 80% in women (http://www.cdc.gov/std/healthcomm/fact_sheets.htm).

In addition to anogenital warts, HPV infection may cause cervical cancer or be associated with anogenital and extra anogenital cancers and recurrent respiratory papillomatosis. HPV infection has been demonstrated to be a necessary step in the development of cervical cancer, although not sufficient, i.e.,

* Corresponding author. Fax: +1 514 864 7646.
E-mail address: marc.steben@inspq.qc.ca (M. Steben).

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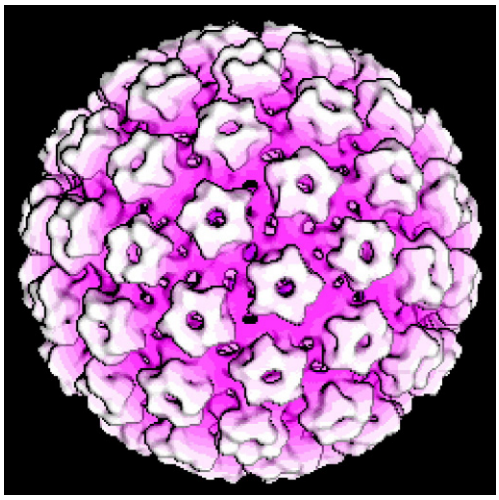

Fig. 1. Human papillomavirus. (Reprinted with permission from Elsevier [8].)

other factors must also be present. In all areas of the world, more than 70% of such neoplasias harbor HPV-16 or -18 and some type of HPV has been identified in over 99.7% [4,6].

The HPV virion contains an 8-kb circular genome that is enclosed in a capsid shell comprised of major (L1) and minor capsid proteins (L2). The genome not only encodes for late structural genes (L1 and L2), but also for several early genes (E1, E2, E4, E5, E6 and E7) that enable viral transcription and replication and interact with the host genome. (Fig. 1) [7,8].

In the majority of individuals, HPV infections are transient and asymptomatic; 70% of new infections resolve within 1 year and about 90% resolve within 2 years [3]. In a study of U.S. female college students, the median duration of new HPV infections was 8 months. A higher risk of infection was significantly associated with younger age, Hispanic or African American ethnicity, an increased number of sexual partners and an increased frequency of sexual intercourse, anal sex and alcohol consumption. In addition, persistence of HPV for periods ≥ 6 months was related to older age, to the presence of a high-risk HPV (i.e., one associated with a diagnosis of cervical cancer (-16 and -18)) and infection with multiple HPV types [3].

While in most cases HPV infection resolves spontaneously, in rare instances the infection persists, and eventually, cervical cancer develops over a period of approximately 12–15 years via a series of stages: low-grade (LSIL) and high-grade intraepithelial lesions (HSIL) as seen in cytologic examination or cervical intraepithelial neoplasia (CIN) grade I through III, in histologic specimens [9]. It is not clearly understood why HPV infections resolve in certain individuals and result in more severe lesions in others but individual susceptibility and other enabling factors may play a role. HPV-induced cervical carcinogenesis occurs as a multi-step process. It begins by primary infection of the proliferating basal cells of the squamous epithelium. If the infection is caused by a high-risk HPV type, and in presence of failure of the immune system to control and clear the infection plus the presence of some co-factors such as smoking, HPV infection persists accumulating, after time, enough genomic instability and leading to neoplastic transformation of the epithelium [9]. LSILs (or histologic equivalent CIN I), most likely the initial infective and potential progressive state, develop from the infected normal cervical epithelium in the vulnerable transformation zone and may still be controlled by the host's immune system and disappear without intervention. Squamous cell carcinomas are the most commonly occurring form of cervical cancer and develop from these CIN I/LSILs [9]. Current hypotheses suggest that HSILs or CIN-II/-III lesions may develop within 2–3 years of persistent HPV infection in susceptible individuals. Once HSILs have developed, it is thought that the viral oncogenes E6 and E7 abrogate cell cycle control and apoptosis mechanisms, signaling the transition from a viral infection to a malignant process. Further genetic alterations involving the loss of tumor suppressor genes and changes in growth modulating influences result in the progression from CIN II/II lesions to overt malignancy [9].

Prevalence of HPV infection

At present, HPV infections are the most commonly diagnosed sexually transmitted disease [10]; in the United States alone, it is estimated that 6.2 million new infections occur annually in individuals aged 14–44 years [10]. Within the general population, the prevalence of HPV infection in asymptomatic women is estimated to range from 2% to 44%. The U.S. National Health and Nutrition Examination Survey (NHANES) determined the overall prevalence of HPV infection in a representative sample of women (n = 1921) aged 14–59 years to be 26.8% [11]. The highest prevalence of HPV infection was reported in women aged 20–24 years (44.8%) compared with 24.5% for women aged 14–19 years and 27.4% among women aged 25–29 years (Table 1). HPV infection increased in prevalence with each year between the ages of 14–24 years ($p < 0.001$) and then declined through the age of 59 years.

HPV and cervical cancer

Overall HPV is responsible for 5.2% of all cancers. It is well established that HPV infection is the primary cause of virtually all cervical cancers and indeed deemed a necessary cause for the disease, without which, cervical cancer does not arise [6,12,13]. A landmark study has shown that HPV DNA can be found in 99.7% of cervical cancer specimens [6]. Worldwide, the plethora of HPV types causing cervical cancer varies from one country to another, however, over 70%, in any given country, are caused by only 2 types, HPV16 and HPV 18. In a pooled analyses of data from 11 case–control studies of women

Table 1
Prevalence of HPV infection among women in the United States

Age (years)	Prevalence (%)	95% CI
14–19	24.5	(19.6–30.5)
20–24	44.8	(36.3–55.3)
25–29	27.4	(21.9–34.2)
30–39	27.5	(20.8–36.4)
40–49	25.2	(19.7–32.2)
50–59	19.6	(14.3–26.8)

CI = confidence interval; HPV = human papillomavirus.