

Human papillomavirus infection: Epidemiology and pathophysiology

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Received 24 July 2007

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.

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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.,

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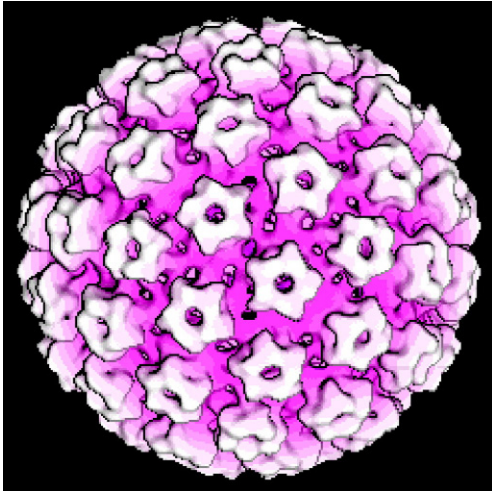


Fig. 1. Human papillomavirus. (Reprinted with permission from Elsevier [8].)

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.

Table 2
Estimated medical costs of 8 sexually transmitted diseases in Americans aged 15–24 years

STD	No. of new cases in 2000	Average lifetime cost per case (US\$)	Total direct medical costs (US\$)
HIV	15,000	199,800	3.0 billion
HPV	4.6 million	1,228 women 27 men	2.9 billion
Genital herpes	640,000	417 women 511 men	292.7 million
Hepatitis B	7,500	779	5.8 million
Chlamydia	1.5 million	244 women 20 men	248.4 million
Gonorrhea	431,000	266 women 53 men	77.0 million
Trichomoniasis	1.9 million	18	34.2 million
Syphilis	8,200	444	3.6 million
Total	9.1 million	NA	6.5 billion

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HIV=human immunodeficiency virus; HPV=human papillomavirus; NA=not applicable; STD=sexually transmitted disease.

with histologically confirmed squamous cell cervical cancer conducted in 9 different countries, HPV DNA could be detected in 90.7% of the cases by one detection method and in 96.6% by another; the proportion of control women testing positive were, respectively, 13.4% and 15.6%. This study tested either cytology smears or biopsied tissue and found that the most common types, in order of frequency, were HPV-16, -18, -45, -31, -33, -52, -58 and -35) [14].

Worldwide, cervical cancer is the second most common cancer in women and the most common cancer in women in developing countries [9,15]. In developed countries, cervical cancer accounts for 1.7% of all cancers while in developing countries this figure is 7% [16]. In 2000, the World Health Organisation estimated that there were 470,600 newly diagnosed cases of cervical cancer and this disease was associated with 233,400 deaths annually –80% of these deaths occur in developing countries [15]. The higher prevalence of cervical cancer in developing countries may be largely attributable to the limited access women in these countries have to screening programs combined with high-risk characteristics such as poor nutrition and high parity [15]. In the United States, prevalence and mortality rates vary according to ethnicity [17]. There is a 1.5-fold higher incidence of cervical cancer and a 2-fold higher cervical cancer-related mortality rate in Black compared with Caucasian women [18].

Burden of HPV infection

There is a substantial economic burden associated with sexually transmitted diseases (STDs). In the United States in 2000, there were an estimated 4.6 million new cases of HPV infection among 15–24 year olds; this accounted for 44% of the total estimated burden [19]. A recent review (2005) of available costing data indicated that, annually, the healthcare costs associated with HPV-related conditions range from US\$2.25 to \$4.6 billion [20]. A comparison of the direct medical costs of STDs among U.S. individuals aged 15–24 years demonstrated

that HPV infection was similar to HIV in terms of total direct medical costs (US\$2.9 vs. \$3.0 billion; Table 2). In contrast, total direct medical costs for all other STD such as *Chlamydia trachomatis*, genital herpes and hepatitis B were US\$292.7 and \$5.8 million, respectively.

A U.S.-based observational study (n=103,476) demonstrated that significant costs are also associated with the screening and treatment of cervical cancer [21]. Irrespective of age, cervical HPV-related disease resulted in annual healthcare costs of US\$26,415 per 1,000 women. Routine cervical cancer screening accounted for two-thirds of the annual cervical HPV-related healthcare costs, 17% of costs were attributed to the management of cervical precancers and only 10% to the treatment of invasive cervical cancer [21].

Summary

HPV infection is the most common sexually transmitted disease, and U.S. data indicate that it is particularly prevalent among women aged 20–24 years. HPV infection has been definitively linked with the development of both cervical cancer and genital warts. HPV types 6 and 11 are associated with 90% of cases of genital warts, and HPV infection with a high-risk type (in particular, types 16 and 18) is deemed as necessary cause of cervical cancer. While the majority of HPV infections appear to be transient and resolve within 2 years, in susceptible women and under certain conditions, cervical cancer can develop approximately 12–15 years after the initial infection. Pharmacoeconomic data indicate that there is a substantial healthcare burden associated with HPV-related conditions, including cervical cancer.

Questions and answers

Given the advent of HPV vaccination, should screening with the pap test be abolished?

Certainly not. Currently available vaccines protect against only 2 of the 15 high-risk HPV types; the others cause around 30% of cervical cancers and a number of other anogenital neoplasms. Also, it will be a number of years before all women at risk are protected by vaccination. And women already infected are not protected from cancer from the types they are already infected with. In addition, vaccination programs should be implemented as part of universal coverage; otherwise, there will be no gains in curbing cervical cancer disease burden because this is a disease of the underserved and if vaccination is offered only to those who have access to screening programs, vaccination programs will be costly but not cost-effective.

Which types of HPV virus are the most prevalent among women with cervical cancer?

This study tested either cytology smears or biopsied tissue and found that the most common types, in order of frequency, were HPV-16, -18, -45, -31, -33, -52, -58, and -35.

Conflict of interest statement

MS has received grant/research support from Merck Frost/Merck Research Laboratories and GlaxoSmithKline, speaker fees from Merck Frost/Merck

Research Laboratories and Digene, consultant fees from Merck Frost/Merck Research Laboratories and Roche and serves on the Speaker's Bureau for Merck Frost/Merck Research Laboratories. ED-F declares that she has no conflict of interest.

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